Médicaments antiviraux en cas de grippe saisonnière et pandémique. Revue de littérature et recommandations de bonne pratique

KCE reports vol. 49B

Federaal Kenniscentrum voor de gezondheidszorg
Centre fédéral d'expertise des soins de santé
2006

Le Centre fédéral d'expertise des soins de santé

Présentation : Le Centre fédéral d'expertise des soins de santé est un parastatal, créé le 24 décembre 2002 par la loi-programme (articles 262 à 266), sous tutelle du Ministre de la Santé publique et des Affaires sociales, qui est chargé de réaliser des études éclairant la décision politique dans le domaine des soins de santé et de l'assurance maladie.

Conseil d'administration

Membres effectifs : Gillet Pierre (Président), Cuypers Dirk (Vice-Président), Avontroodt Yolande, De Cock Jo (Vice-Président), De Meyere Frank, De Ridder Henri, Gillet Jean-Bernard, Godin Jean-Noël, Goyens Floris, Kesteloot Katrien, Maes Jef, Mertens Pascal, Mertens Raf, Moens Marc, Perl François Smiets Pierre, Van Massenhove Frank, Vandermeeren Philippe, Verertbruggen Patrick, Vermeyen Karel

Membres suppléants : Annemans Lieven, Boonen Carine, Collin Benoît, Cuypers Rita, Dercq Jean-Paul, Désir Daniel, Lemye Roland, Palsterman Paul, Ponce Annick, Pirlot Viviane, Praet Jean-Claude, Remacle Anne, Schoonjans Chris, Schrooten Renaat, Vanderstappen Anne,

Commissaire du gouvernement : Roger Yves

Direction

Directeur général : Dirk Ramaekers

Directeur général adjoint : Jean-Pierre Closon

Contact

Centre fédéral d'expertise des soins de santé (KCE).
Rue de la Loi 62
B-1040 Bruxelles
Belgium

Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85

Email : info@centredexpertise.fgov.be
Web : http://www.centredexpertise.fgov.be

Médicaments antiviraux en cas de grippe saisonnière et pandémique. Revue de littérature et recommandations de bonne pratique.

KCE reports vol. 49B

VAN DE VYVER NATHALIE, JANSSENS WIM, DE SUTTER ANN, MICHIELS BARBARA, GOVAERTS FRANS, HULSTAERT FRANK, LAMBERT MARIE-LAURENCE, PELEMAN RENAAT , RAMAEKERS DIRK

Federaal Kenniscentrum voor de gezondheidszorg
Centre fédéral d'expertise des soins de santé
2006

KCE reports vol.49B

Titre :	Médicaments antiviraux en cas de grippe saisonnière et pandémique. Revue de littérature et recommandations de bonne pratique.
Auteurs :	Van de Vyver Nathalie (Domus Medica), Janssens Wim (Internal Medicine, University Hospital Ghent), De Sutter Ann (General Practice, University Ghent), Michiels Barbara (UA), Govaerts Frans (Domus Medica), Hulstaert Frank (KCE), Peleman Renaat (Internal medicine, University Hospital Ghent, Lambert Marie-Laurence (KCE), Ramaekers Dirk (KCE)
Experts externes :	Bosmans Tia (IDEWE), Flamaing Johan (Geriatrics, University Hospital Leuven), Hanquet Germaine (IPH, Epidemiology, Brussels); Robays Hugo (Pharmacy, University Hospital Ghent), Schetgen Marco (SSMG); Van Damme Wim (Institute for Tropical Medicine, Antwerp), Van Ranst Marc (Virology, University Hospital Leuven), Vanhalewyn Michel (SSMG), Vanlaethem Yves (Infectious Diseases, Hospital St-Pierre, Brussels), Van Wijngaerden Eric (Infectious Diseases, University Hospital Leuven)
Validateurs :	Chevalier Pierre (RIZIV/INAMI, Brussels), Goubau Patrick (Virology, Clin. Univ. Saint-Luc, Brussels), Maes Sophie (Institute of Public Health, Brussels)
Conflict of interest :	Aucun conflit déclaré
Disclaimer:	Les experts externes et validateurs ont collaboré à la rédaction du rapport scientifique mais ne sont pas responsables des recommandations aux Autorités. Les recommandations aux Autorités ont été rédigées par le Centre d'Expertise (KCE).
Mise en Page :	Dimitri Bogaerts

Bruxelles, janvier 2007

Etude nr 2006-27-1
Domaine : Good Clinical practice (GCP)

MeSH : Influenza, Human; Antiviral Agents; Influenza A Virus, H5N1 Subtype, Enzyme Inhibitors [Pharmacological Action]
NLM classification : QV 268.5

Langue: français, anglais
Format : Adobe® PDF™ (A4)

Dépôt légal : D/2006/10.273/

La reproduction partielle de ce document est autorisée à condition que la source soit mentionnée. Ce document est disponible en téléchargement sur le site Web du Centre fédéral d'expertise des soins de santé.

Comment citer ce rapport ?
Van de Vyver N, Janssens W, De Sutter A, Michiels B, Govaerts F, Lambert M-L, et al. Médicaments antiviraux en cas de grippe saisonnière et pandémique. Revue de littérature et recommandations de bonne pratique. Good Clinical Practice (GCP). Bruxelles: Centre fédéral d'expertise des soins de santé (KCE); 2006. KCE reports 49 B (D/2006/10.273/66)

Préface

La grippe fait partie de notre vie. Chaque année nous sommes victimes de l'un ou l'autre syndrome grippal, parfois même d'une vraie grippe, causée par le virus de l'influenza. Pour les personnes en bonne santé, ce n'est pas bien grave. Pour les personnes plus faibles et les personnes âgées, cela peut être différent. Pour ces personnes à risque diverses interventions sont possibles, dont la vaccination qui est relativement bien entrée dans les mœurs.

Les conséquences économiques de la grippe et des problèmes apparentés ne sont pas insignifiantes, et des efforts pour identifier un médicament efficace sont en cours depuis plusieurs années. Une nouvelle classe de médicaments antiviraux est arrivée sur le marché européen il y a une dizaine d'années. En Europe, leur utilisation en cas de grippe saisonnière est restée limitée, principalement parce qu'ils ne guérissent pas la grippe et permettent seulement de raccourcir d'un jour la durée des symptômes. Ces médicaments peuvent cependant être envisagés non seulement pour le traitement, mais aussi pour la prévention de la grippe (avant, ou après, l'exposition au virus).

C'est la possibilité d'une pandémie de grippe qui a provoqué un regain d'intérêt pour ces médicaments. Rien n'est certain, mais l'évolution du virus de la grippe aviaire H5N1 est suivie avec attention tant par les scientifiques que par les décideurs politiques. A ce jour, les cas humains semblent résulter presque uniquement d'une contamination animale, et la létalité est élevée; on n'a pas mis en évidence de transmission soutenue d'homme à homme, condition nécessaire pour initier une épidémie humaine.

Les pays doivent se préparer à l'hypothèse d'une pandémie. Cependant il n'existe que peu ou pas d'éléments rationnels sur lesquels baser des décisions quant à l'utilisation des médicaments antiviraux dans ce contexte. Personne ne sait quand aura lieu cette pandémie, quelles seront les caractéristiques du virus en cause (virulence, capacité de transmission) – et encore moins si ce virus sera sensible aux médicaments. Les scientifiques arrivent à des avis contradictoires après parfois des discussions animées.

Beaucoup de pays ont établi un 'plan de pandémie', qui comprend entre autres stratégies l'utilisation des médicaments antiviraux. La plupart des pays, dont la Belgique, ont constitué un stock de médicaments antiviraux.

Plusieurs questions de recherche sont pertinentes. D'une part, quelle est l'efficacité des médicaments antiviraux actuels en cas de grippe saisonnière, en tenant compte du fait qu'un usage irresponsable pourrait favoriser le développement de résistance à ces médicaments, non seulement du virus de la grippe saisonnière, mais aussi peut-être du virus pandémique à venir? Quelles recommandations de bonne pratique peut-on formuler sur base des études de l'efficacité des médicaments antiviraux en cas de grippe saisonnière? Qui peut bénéficier d'un tel traitement? Y a- t-il des risques?

D'autre part se pose également la question de la meilleure utilisation possible de notre stock de médicaments antiviraux en cas de grippe pandémique. Notre stock est-il suffisant pour aider tout le monde? Quels choix ont fait les autres pays, en ce qui concerne l'utilisation de leur stock?

Il n'est pas possible de donner une réponse définitive à toutes ces questions. Mais vous trouverez dans ce rapport l'état actuel des connaissances scientifiques sur le sujet, et – sans doute encore plus important – vous pourrez mesurer l'étendue de ce que nous ne connaissons pas encore.

Jean-Pierre CLOSON
Directeur général adjoint

Dirk RAMAEKERS
Directeur général

Résumé

Introduction

L'objectif de ce projet KCE 2006 est de définir des recommandations de bonne pratique pour l'utilisation de médicaments antiviraux dans la prévention et le traitement de la grippe (influenza) saisonnière et en cas de pandémie, sur base de l'évidence disponible. Ce projet est une collaboration entre le KCE et, d'une part, l'organisation néerlandophone des médecins généralistes Domus Medica (pour la grippe saisonnière), et d'autre part l'Université de Gand – (départements de médecine générale, et département de médecine interne de l'hôpital universitaire) - pour la partie 'pandémie'.

La grippe (influenza) est due à un virus ARN qui se transmet de personne à personne par la toux ou les éternuements de personnes infectées. Chez les personnes à bas risque, la grippe saisonnière est une maladie non spécifique au décours spontanément favorable. Les personnes âgées, les patients diabétiques ou les personnes souffrant de maladies chroniques pulmonaires, cardio-vasculaires, ou rénales, ou encore de déficit immunitaire, présentent un risque plus élevé de complications sérieuses suite à une infection par le virus de l'influenza.

Les interventions possibles pour la prévention et le traitement de l'influenza incluent la vaccination et l'utilisation de médicaments antiviraux. Le matériel génétique du virus est instable et varie au cours du temps. Ces variantes génétiques peuvent éluder une immunité acquise suite à une vaccination ou une infection précédente. Certaines variantes peuvent être résistantes à un ou plusieurs médicaments antiviraux.

Certains virus de l'influenza infectent des animaux comme les oiseaux et les cochons. Ces virus normalement n'infectent pas les humains. Il peut arriver qu'émerge un virus aviaire génétiquement adapté aux humains qui se transmette facilement de personne à personne, avec la possibilité de causer une morbidité et une mortalité importante chez les humains. L'émergence et l'étendue d'une telle pandémie de grippe sont difficiles, sinon impossibles à prédire. Depuis 1997 plus de 200 cas confirmés d'infection humaine avec le virus de la grippe aviaire (influenza A H5N1) ont été rapportés. La plupart de ces cas semblaient résulter d'un contact direct avec des volailles infectées, ou avec des surfaces contaminées et ont eu lieu en Asie du Sud-Est. La mortalité chez les patients hospitalisés a été élevée. A ce jour, aucune infection humaine avec le virus de la grippe aviaire n'a donné lieu à une transmission soutenue de personne à personne. La surveillance des infections humaines avec des virus aviaires de type influenza A est importante, de même que la préparation à une possible pandémie de grippe. Dans ce contexte, les autorités ont préparé des plans de pandémie.

Il existe 2 classes de médicaments possédant une activité antivirale contre l'influenza. Les plus anciens de ces médicaments, les inhibiteurs des M2, n'étaient pas beaucoup utilisés du fait de leurs effets secondaires et de l'émergence de résistance. Le virus H5N1 est résistant aux inhibiteurs des M2. Depuis environ 10 ans il existe des médicaments qui inhibent la sortie de virus influenza des cellules : les inhibiteurs des neuraminidases (INAs). L'oseltamivir (TAMIFLU, Roche) et le zanamivir (RELENZA, GSK) sont des INAs. L'oseltamivir se prend par voie orale ; la poudre de zanamivir est inhalée au moyen d'un dispositif spécial. La prise d'oseltamivir est associée avec de légers effets gastro-intestinaux en fonction de la dose, et plus rarement, avec des problèmes au niveau du système nerveux central (ceux-ci ont été ajoutés récemment à la notice du produit). L'inhalation de zanamivir par des patients asthmatiques peut induire un bronchospasme.

Une résistance des virus influenza à été observée, plus fréquemment chez des enfants que chez des adultes, et la transmission de souches résistantes a été rapportée. Les souches résistantes à l'oseltamivir étaient sensibles au zanamivir.

Grippe saisonnière

Donnés en prophylaxie avant ou après exposition à la grippe saisonnière les INAs préviennent mieux l'influenza qu'un placebo dans la plupart des essais cliniques contrôlés (nombre à traiter : 25 en prophylaxie avant exposition ; 15 en prophylaxie après exposition). Quand les INAs sont utilisés pour le traitement de l'influenza saisonnière, les symptômes durent en moyenne environ un jour de moins que si un placebo est utilisé. Comme on pouvait s'y attendre, l'efficacité est limitée au sous-groupe de patients avec un diagnostic d'influenza confirmé par le laboratoire, ce qui limite l'extrapolation de ces résultats à la réalité de terrain.

Les INAs en prophylaxie de l'influenza ne sont pas un substitut à la vaccination. Les groupes à haut risque sont les mêmes que ceux définis comme cible pour la vaccination 1) maladies respiratoires chroniques (COPD = ou > stade II, asthme) ; 2) maladies cardio-vasculaires (à l'exception de l'hypertension sans complications) 3) maladies rénales chroniques 4) immunodéficience 5) diabète sucré 6) à partir de 65 ans.

Un problème est la confirmation rapide de l'influenza dans des conditions de terrain. Les tests antigéniques rapides utilisés à l'heure actuelle ne sont pas sensibles, en particulier au stade précoce de la maladie. Les tests de diagnostic moléculaires (PCR), plus sensibles, sont disponibles uniquement dans des laboratoires spécialisés.

L'utilisation de médicaments antiviraux, si elle est indiquée, doit commencer le plus tôt possible : en cas de traitement, dans les 48h après le début des symptômes ; en cas de prophylaxie endéans les 36-48h après le contact avec le cas index.

Les INAs ne dispensent en aucune façon des mesures d'hygiène visant à prévenir la transmission. Une résistance aux INAs peut se développer. Toute prescription ou usage inapproprié doivent être découragés. Ceci inclut le stockage préventif des INAs dans des habitations privées.

Les recommandations de bonne pratique sont d'application uniquement en cas de circulation de l'influenza A ou B dans la communauté. Nous avons évalué la force des recommandations (forte=1, faible=2) et la qualité des données scientifiques (élevée=A, modérée = B, faible ou très faible=C). Il est nécessaire de consulter la notice avant tout usage des INAs.

De manière générale l'utilisation des INAs pour la prophylaxie ou le traitement de l'influenza saisonnière ne peut être recommandée à l'heure actuelle car il n'y a à ce jour aucune évidence scientifique d'une efficacité cliniquement significative des médicaments antiviraux sur l'incidence des complications et la mortalité chez les sujets à haut risque. Bien que les groupes à risque classiques incluent les personnes de 65 ans et plus, les personnes agées en bonne santé encourent un risque de complications moindre que les personnes avec un risque réellement élevé (patients avec co-morbidités).

Enfants à haut risque : il n'existe pas de données spécifiques permettant de formuler des recommandations particulières.

Femmes enceintes: il n'existe pas de données suffisantes d'efficacité et d'innocuité; il n'est donc pas possible de formuler des recommandations

Utilisation des INAs à visée thérapeutique

Le traitement d'adultes et d'enfants présentant un syndrome grippal et par ailleurs en bonne santé n'est pas recommandé. Grade 1A.

Un traitement aux INAs peut seulement être envisagé au cas par cas chez des adultes à haut risque (avec co-morbidité), indépendamment de leur statut vaccinal, pour autant que le traitement puisse être initié endéans 48 heures après le début du syndrome grippal (*influenza like illness*). (Grade 2C). Il manque de données montrant une réduction des complications chez les adultes à haut risque.

Utilisation des INAs dans un but prophylactique

Dans un contexte non-institutionnel

L'efficacité des INAs est démontrée pour la prophylaxie avant exposition pendant 6 semaines des adultes sains. Cependant la prophylaxie avant exposition n'est pas recommandée dans ce groupe parce que le risque de complications liées à la grippe est faible et ne contrebalance pas les possibles effets secondaires des médicaments et le risque de développement de résistance. (Grade 1A).

Chez les enfants et les personnes à haut risque la prophylaxie avant exposition n'est pas recommandée car il n'existe pas d'études concluantes sur le sujet.

L'efficacité des INAs est démontréee pour la prophylaxie des adultes sains après contact avec un cas de grippe. Cependant la prophylaxie après exposition n'est pas recommandée dans ce groupe parce que le risque de complications liées à la grippe est faible et ne contrebalance pas les possibles effets secondaires des médicaments et le risque de développement de résistance. (Grade 2A).

En ce qui concerne les personnes fragiles à haut risque une utilisation prophylactique après exposition peut être envisagée au cas par cas pour celles vivant en contact étroit avec un cas probable d'influenza ET qui ne sont pas vaccinées, ou sont considérées comme étant insuffisamment protégées par la vaccination (par exemple en cas d'immunodéficience ou en cas de différence entre la souche vaccinale et la souche circulante confirmée au niveau national). Chez ces personnes, une vaccination de rattrapage, si appropriée, est nécessaire. Une confirmation de laboratoire du cas index est préférable (voir remarque sur les tests de laboratoire), mais la prophylaxie doit être initiée dans les plus brefs délais (36-48h après le contact avec le cas index). (Grade 2C).

Femmes enceintes à haut risque : il n'existe pas de données suffisantes d'efficacité et d'innocuité; il n'est donc pas possible de formuler des recommandations

Dans un contexte institutionnel

Toutes les institutions pour personnes âgées devraient avoir un plan détaillé pour la prévention et le contrôle des maladies transmissibles, y compris l'influenza. Pour l'influenza la vaccination des résidents et des travailleurs de santé est la mesure préventive la plus importante. En plus des mesures d'hygiène et autres, les recommandations qui suivent (concernant l'usage des NAIs) devraient faire partie du plan.

La vaccination des résidents et des travailleurs de santé est la mesure préventive la plus importante. Une prophylaxie avec des INAs n'est pas recommandée pour les travailleurs de santé.

Une prophylaxie avant exposition n'est pas recommandée dans ce contexte (grade 1B).

Une prophylaxie après exposition, avec l'oseltamivir, peut-être considérée après contact avec un cas possible d'influenza pour les résidents à haut risque, indépendamment de leur statut vaccinal (Grade 2C). La confirmation du cas index est recommandée mais la prophylaxie devrait être initiée aussitôt que possible (endéans 36-48h après le contact). Si le résultat du test est négatif (voir remarque sur les tests de laboratoire), la prophylaxie devrait être interrompue.

Une vaccination de rattrapage est recommandée si nécessaire.

A l'hôpital

Les recommandations suivantes devraient être inclues dans un plan détaillé de prévention et de contrôle des maladies transmissibles (y compris l'influenza), à l'hôpital.

La prophylaxie après exposition pour les personnes à risque hospitalisées peut être considérées au cas par cas. Le cas doit être confirmé (voir remarque sur les test de laboratoire) mais la prophylaxie doit commencer le plus tôt possible (endéans 36-48h après le contact avec le cas index). Si le résultat du test est négatif, la prophylaxie doit être interrompue. (Grade 2C).

Dans les services à haut risque tels que les unités de transplantation, il peut être envisagé de donner une prophylaxie antivirale à tous les patients du service, indépendamment de leur statut vaccinal. (Grade 2C).

Points clés

- **Le traitement de l'influenza avec les INAs diminue la durée des symptômes mais il n'existe pas d'évidence que ce traitement diminue significativement la mortalité ou les complications sévères comme la pneumonie.**
- **En utilisation prophylactique avant ou après exposition les INAs permettent de prévenir l'influenza (nombre à traiter pour prévenir un cas : 25, et 15 respectivement).**
- **De manière générale il n'est pas recommandé de traiter avec des INAs des adultes et des enfants présentant un syndrôme grippal.**
- **L'utilisation des INAs peut uniquement être recommandée au cas par cas dans la prophylaxie ou le traitement de l'influenza saisonnière chez les patients à haut risque présentant des co-morbidités.**
- **L'utilisation des INAs dans les résidences pour personnes âgées et dans les hôpitaux devrait être guidée par le plan institutionnel de contrôle des maladies infectieuses.**
- **L'utilité des tests de détection antigéniques utilisés en routine pour le diagnostic de l'influenza est limitée.**

Grippe pandémique

Au contraire de l'influenza saisonnière, Il n'existe pas d'essais cliniques contrôlés de l'usage prophylactique ou thérapeutique des INAs dans un contexte de grippe pandémique. Les recommandations cliniques sont donc basées principalement sur des critères non cliniques, des opinions, et priorités choisies par des preneurs de décision.

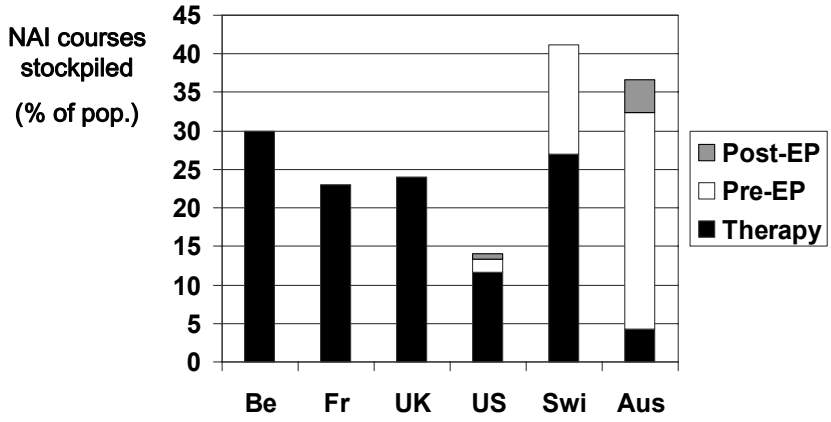
Des résultats sont rapportés dans 4 séries de cas pour un total de 40 patients infectes par le virus H5N1 mais ne permettent pas de tirer de conclusions. Quatorze patients sur 27 traités avec l'oseltamivir ont survécu, 9 patients sur 13 non traités sont décédés. Cependant le traitement avait été commencé tardivement (soit plus de 2 jours après le début de la maladie) chez presque tous les patients traités. Deux rapports concernant des virus H5N1 résistants à l'oseltamivir ont également été publiés. Un rapport mentionne que la souche virale restait résistante au zanamivir. Dans quelle mesure les résultats observés dans un contexte d'influenza saisonnière peuvent-ils être extrapolés à un contexte de pandémie avec un virus H5N1 reste incertain.

En l'absence d'évidence clinique tous les pays se basent sur différentes hypothèses pour décider quels médicaments antiviraux stocker, et en quelle quantité, en prévision d'une pandémie de grippe. Ces hypothèses concernent le taux d'attaque et l'efficacité des médicaments antiviraux pour diminuer la morbidité, la mortalité, et la transmission du virus en cas de pandémie. La capacité limitée de production des INAs au niveau mondial, et de possibles contraintes budgétaires sont des éléments supplémentaires à prendre en compte.

Nous avons analysé l'utilisation des médicaments antiviraux dans les plans de pandémie nationaux de différents pays. Dans les périodes pré-pandémiques (phases 3 à 5 de l'OMS), la plupart des plans prévoient de manière plus ou moins explicite le traitement de tous les cas et une prophylaxie post-exposition chez les contacts, dans l'espoir de contenir l'épidémie dans le pays. Ces besoins, quand ils sont estimés, varient de 0.3% (Suisse) à 10% (Australie) du stock total.

Pour la phase 6 de l'OMS (pandémie) nous avons mis en évidence une grande variation entre les pays en ce qui concerne les décisions quant à l'usage des médicaments antiviraux, ainsi que dans le degré de transparence dans l'allocation des ressources. Ceci est illustré par le graphe ci-dessous.

Stock de médicaments antiviraux dans certains pays sélectionnés. et stratégies prévues.



Be=Belgique, Fr=France, Swi=Suisse, Aus=Australie, Post-EP=prophylaxie après exposition, Pre-EP=prophylaxie après exposition, NAI= Inhibiteurs des neuraminidases, 1 traitement (course) = 5 jours de traitement ou 10 jours de prophylaxie.

La plupart des plans de préparation à la pandémie de grippe visent à réduire l'impact associé à un taux d'attaque constant, plutôt qu'à réduire la transmission. Tous les plans précisent qu'ils peuvent être modifiés lorsque plus d'information sera disponible sur la pandémie attendue. Les plus récentes recherches dans le domaine de l'utilisation des médicaments antiviraux sont à trouver dans le domaine des modèles mathématiques. Ces modèles essayent de calculer les effets de différentes interventions, et combinaisons d'interventions, sur une diminution de la transmission et donc du taux d'attaque. Ceci inclut par exemple différentes stratégies d'utilisation des antiviraux, telles que le traitement de tous les cas, en combinaison avec la prophylaxie après exposition de toutes les personnes vivant sous le même toit qu'un cas.

Les stocks de INAs sont constitués principalement d'oseltamivir. En Belgique le zanamivir représente 10% du stock de INAs et pourrait se révéler utile si le virus pandémique est résistant à l'oseltamivir. Plusieurs pays ont choisi de consacrer l'ensemble de leur stock de INAs au seul traitement des cas (Belgique, France, Royaume-Uni, les Pays-Bas). Certains pays tels que la Suisse, ou plus encore l'Australie, envisagent d'utiliser une grande partie de leurs ressources pour une prophylaxie avant exposition, dans un objectif de limiter la transmission de la maladie. Ces pays possèdent un stock important d'antiviraux (exprimé en nombre de traitements, par rapport à la population). Les Etats-Unis ont le stock le moins important de tous les pays analysés (14%), car seules certaines catégories de personnes clairement identifiées et quantifiées sont susceptibles de bénéficier de traitement ou de prophylaxie avant ou après exposition. Il s'agit là d'un choix de priorité clair et argumenté et d'une allocation transparente des ressources. Un tel choix de priorité implique des jugements de valeurs et devrait donc inclure des considérations éthiques.

Les autorités publiques disposent d'un certain nombre d'options. Elles peuvent décider de ne pas investir dans un stock de INAs en arguant du fait qu'il n'existe aucune preuve que les INAs soient utiles en cas d'influenza H5N1. Par mesure de précaution le gouvernement belge a cependant décidé de stocker des antiviraux, ainsi que l'ont fait beaucoup d'autres pays. La Belgique a aujourd'hui un stock correspondant à 2.7 millions de traitements d'oseltamivir et 0.3 millions de traitements de zanamivir (il est à noter que la dose journalière utilisée en prophylaxie est la moitié de la dose journalière utilisée en cas de traitement ; les besoins pour 5 jours de traitement sont donc équivalents aux besoins pour 10 jours de prophylaxie avant ou après exposition). Il n'existe pas d'évidence clinique soutenant l'utilisation des médicaments antiviraux en cas

de pandémie, et extrapoler à un contexte pandémique l'efficacité prophylactique des INAs observée dans un contexte de grippe saisonnière est sujet à caution.

Nous présentons un certain nombre d'options possibles quant à l'utilisation du stock d'INAs en Belgique en cas de pandémie de grippe (phase 6 de l'OMS). Il est important de souligner que la disponibilité et l'utilisation des médicaments antiviraux ne dispensent en aucune mesure d'autres mesures de contrôle de la pandémie.

Nous présentons les options possibles en cas de taux d'attaque modéré (15%) ou élevé (30%).

Scenario 1: taux d'attaque de 30%, traitement pour tous les malades

Si le taux d'attaque est de 30% le stock en Belgique suffit au traitement de tous les patients, ainsi que prévu dans le plan actuel de pandémie belge. Cette option de traitement pour tous respecte le principe d'équité; il est relativement simple à mettre en place. Dans ce scénario beaucoup de travailleurs de santé auront acquis une immunité quand la pandémie sera à son pic. Cependant aucune réduction significative de morbidité (pneumonie) ou de mortalité après traitement avec des INAs n'a été observée en cas de grippe saisonnière. Si le traitement pour tous les cas est la priorité et le taux d'attaque est de 30%, le stock existant ne permettra pas d'utiliser les INAs à d'autres fins.

Scenario 2: taux d'attaque de 15%

Si le taux d'attaque est de 15%, le traitement de tous les malades consommera seulement la moitié du stock existant. L'autre moitié, soit 1.5 millions, pourrait être utilisée à des fins de prophylaxie avant ou après exposition, ou pour une combinaison de ces 2 stratégies.

Scenario 2a : taux d'attaque 15%, traitement de tous les malades, avec prophylaxie avant exposition.

La prophylaxie avant exposition peut être prise pour une période plus ou moins longue notamment en fonction du délai nécessaire avant qu'un vaccin efficace ne devienne disponible. Un stock de 1.5 millions de traitements permettrait une prophylaxie avant exposition pendant 100 jours pour 150 000 personnes sélectionnées. Il pourrait s'agir de travailleurs de la santé, de personnes occupant des postes clés, ou encore de personnes à risque de complication en cas de grippe. Dans un contexte de grippe saisonnière, il faut donner des INAs à 25 personnes dans un but de prophylaxie avant exposition, pour prévenir un cas d'influenza. Ce scénario combine les avantages d'un traitement pour tous tout en garantissant le fonctionnement des services essentiels (santé et autres). Cependant il n'existe pas de données sur l'efficacité et sur l'innocuité de traitements prophylactiques pris pour plus de 6 semaines. Ce scénario demande que les autorités décident et communiquent en ce qui concerne la sélection des groupes prioritaires, ce qui représente un défi sur le plan de l'équité. Cela peut également poser des problèmes au niveau de la distribution. Enfin, débuter une prophylaxie avant exposition trop tôt (fausse alarme) pourrait aboutir à un épuisement rapide du stock.

Scenario 2b: taux d'attaque 15%, traitement pour tous les malades avec prophylaxie après exposition.

Une prophylaxie après exposition dure classiquement 10 jours. Cependant, si cette prophylaxie s'applique à des travailleurs de santé ou d'autres personnes entrant régulièrement en contact avec des cas d'influenza, il pourrait être nécessaire de calculer par personne-cible jusqu'à 5 épisodes de prophylaxie (10 jours) après exposition. Donc 1.5 millions de traitements pourraient permettre une prophylaxie après exposition pour 300 000 travailleurs de santé ou autres travailleurs soumis à une exposition répétée ; ou même une frange plus grande de la population soumise à des expositions moins fréquentes (personnes occupant des postes clés, ou des personnes à risque de complication, tels que définis dans les groupes cibles pour la vaccination.)

Dans un contexte de grippe saisonnière, il faut donner des INAs à 15 personnes ayant été exposées, pour prévenir un cas d'influenza. Cette option combine les avantages d'un traitement pour tous avec une garantie de maintien des services sélectionnés – services

de santé ou autres. Il revient aux autorités de décider quels sont les groupes prioritaires, un défi en termes d'équité. La distribution pourrait également poser des problèmes. Des prophylaxies après expositions répétées à domicile pourraient rapidement épuiser le stock. Si cette option est limitée à des groupes régulièrement exposés à des patients souffrant d'influenza, elle devient difficile à différencier d'une prophylaxie avant exposition.

Indépendamment du stock national, certaines instances privées (industries, ou autres organisations) peuvent décider de se constituer leur propre stock de INAs, à visée prophylactique, pour assurer la continuité de leurs activités pendant une pandémie. Dans certains endroits, la vaccination du personnel contre la grippe saisonnière s'inscrit dans cette logique.

D'autres variantes combinant les options sus-mentionnées et leurs caractéristiques sont possibles. Dans tous ces scénarios, à l'exception du premier, il est possible de faire une modélisation plus poussée, en fonction des choix faits par les preneurs de décision, ainsi que nous l'avons souligné.

Points clés

- **Il n'existe pas suffisamment d'évidence clinique que pour guider la décision en ce qui concerne l'utilisation des INAs pendant une pandémie d'influenza.**
- **La prise de décision est guidée par des critères non cliniques et un choix de priorités.**
- **La plupart des pays, y compris la Belgique, ont prévu des stocks de INAs, principalement d'oseltamivir.**
- **Les quantités de INAs stockés varient fortement d'un pays à l'autre.**
- **En fonction du taux d'attaque, il existe différentes options pour utiliser le stock existant en Belgique (traitement, prophylaxie avant ou après exposition dans certains groupes sélectionnés)**
- **L'absence de résistance à l'oseltamivir est une hypothèse de base importante**
- **Un avis éthique est nécessaire si il est nécessaire de limiter l'accès aux INAs à des groupes prioritaires, par exemple en fonction du risque pour la santé ou de la valeur économique.**

Scientific summary

Table of contents

1 INTRODUCTION 4

1.1 RESEARCH TOPICS 4

1.2 INFLUENZA 4

1.3 TESTING FOR INFLUENZA 5

1.4 ANTIVIRAL AGENTS 7

2 ANTIVIRAL AGENTS IN SEASONAL INFLUENZA 10

2.1 METHODS AND SOURCES OF EVIDENCE 10
- 2.1.1 Literature search for seasonal influenza 10
- 2.1.2 Selection of the literature 10
- 2.1.3 Quality appraisal, data extraction and grading recommendations 10

2.2 DISCUSSION ON RCTS AND META-ANALYSES 13
- 2.2.1 Treatment 14
- 2.2.2 Prevention 18

2.3 DISCUSSION ON GUIDELINES 18
- 2.3.1 Treatment 19
- 2.3.2 Prevention 20

2.4 PRACTICE GUIDELINES 21
- 2.4.1 Treatment 22
- 2.4.2 Prevention 22

3 ANTIVIRAL AGENTS IN PANDEMIC INFLUENZA 24

3.1 LITERATURE REVIEW 24
- 3.1.1 Introduction 24
- 3.1.2 Methods 24
- 3.1.3 Results 26
- 3.1.4 Conclusions 28

3.2 USE OF ANTIVIRAL AGENTS IN PANDEMIC PLANS 28
- 3.2.1 Introduction 28
- 3.2.2 Methods 30
- 3.2.3 Results 31
- 3.2.4 Discussion 35
- 3.2.5 Conclusions 37

4 APPENDICES 38

4.1 APPENDIX 1. SEARCH RESULTS OF ANTIVIRAL AGENTS IN SEASONAL INFLUENZA 38
- 4.1.1 Search for trials, meta-analyses and systematic reviews 38
- 4.1.2 Search for guidelines 48

4.2 APPENDIX 2. QUALITY APPRAISAL OF THE RCTS AND THE META-ANALYSES 53

4.3 APPENDIX 3. QUALITY APPRAISAL OF THE GUIDELINES 59

4.4 APPENDIX 4. EVIDENCE TABLES FOR THE RCTS 62

4.5 APPENDIX 5. USE OF ANTIVIRAL AGENTS IN SELECTED PANDEMIC PLANS 97
- 4.5.1 Australia 97
- 4.5.2 Canada 99
- 4.5.3 United Kingdom 102
- 4.5.4 United States 104
- 4.5.5 The Netherlands 107

4.5.6 Switzerland 109
4.5.7 Norway 111
4.5.8 Spain 113
4.5.9 Slovak Republic 113
4.5.10 Czech Republic 115
4.5.11 Germany 116
4.5.12 Belgium 119
4.5.13 France 119

4.6 APPENDIX 6. SUMMARY OF PRODUCT CHRACTERISTICS FOR TAMIFLU (OSELTAMIVIR) AND RELENZA (ZANAMIVIR) 121
4.6.1 TAMIFLU (oseltamivir) - Summary of Product Characteristics 121
4.6.2 RELENZA (zanamivir) - Summary of Product Characteristics 145

5 REFERENCES 153

List of Abbreviations

ARR	Absolute risk reduction
CCTR	Cochrane Central Register of Controlled Trials
CEBAM	Belgian Centre for Evidence-Based Medicine
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
E-CDC	European Centre for Disease Prevention and Control
EMS	Emergency medical service
FDA	Food and Drug Administration
GI	Gastro-intestinal
HA	Hemagglutinin
HCW	Health care worker
HTA	Health Technology Assessment
ICU	Intensive care unit
ILI	Influenza like illness
INAHTA	International Network of Agencies for Health Technology Assessment
ITT	Intent to treat
LCI	Laboratory confirmed influenza
LCI Nederland	Landelijke coordinatiestructuur infectieziektenbestrijding Nederland
LRTC	Lower respiratory tract complication
MA	Meta analysis
NA	Neuraminidase
NAI	Neuraminidase inhibitor
NDA	No data available
NHG	Nederlands Huisartsen Genootschap
NNT	Number needed to treat
NS	Not significant
OR	Odds ratio
PEP	Post-exposure prophylaxis
RCT	Randomised controlled trial
SPC	Summary of product characteristics
SR	Systematic review
TAP	Targeted prophylaxis
WHO	World Health Organisation

1 INTRODUCTION

1.1 RESEARCH TOPICS

The three project research questions were defined as follows.

1. What are the available efficacy and safety data of antiviral agents (limited to neuraminidase inhibitors) in the prevention and treatment of seasonal and pandemic influenza?

2. How can these agents best be used to prevent or treat seasonal influenza and pandemic influenza in general?

3. Are there any recommendations for specific groups or situations, eg health care workers in case of pandemic influenza?

Vaccination is generally considered as the most effective strategy to prevent serious complications of influenza in at risk groups,[1] although questioned by some.[2] In the context of this project the evidence base supporting the above statement was not reviewed and considered out of the project scope.

1.2 INFLUENZA

In non-high risk subjects, seasonal influenza is a self-limiting disease. Some people, such as older people, young children, and people with certain health conditions, are at high risk for serious flu complications. Influenza is caused by the influenza virus, a single-stranded RNA-virus characterized by three surface proteins: hemagglutinin (HA), neuraminidase (NA), and the ion channel M2.

Flu viruses spread mainly from person to person through coughing or sneezing of people with influenza. Sometimes people may become infected by touching something with flu viruses on it and then touching their mouth or nose. Most healthy adults may be able to infect others beginning 1 day before symptoms develop and up to 5 days after becoming sick.

Specific influenza viruses also infect animals eg birds and pigs. Although it is unusual for people to get influenza virus infections directly from animals, sporadic human infections and outbreaks caused by certain avian influenza A viruses and pig influenza viruses have been reported. These sporadic human infections and outbreaks, however, do not result in sustained transmission among humans.

Humans can be infected with influenza types A, B and C. Influenza A and B are the two types of influenza viruses that cause epidemic disease. Influenza A viruses are further categorized into subtypes on the basis of the hemagglutinin and neuraminidase antigens. Influenza B viruses undergo antigenic drift less rapidly than influenza A viruses.

The influenza A virus genome consists of eight single-stranded RNA segments of negative sense. The antigenicity of influenza viruses changes gradually by point mutations during viral replication (antigenic drift) or drastically by genetic re-assortment of RNA segments (antigenic shift). Immunological pressure on the hemagglutinin and neuraminidase antigens is thought to drive the antigenic drift. Immunity to the surface antigens, particularly the hemagglutinin, reduces the likelihood of infection and severity of disease if infection occurs. Frequent emergence of antigenic variants through antigenic drift is the virologic basis for recurrent epidemics of influenza and the reason for the usual incorporation of one or more new strains in each year's influenza vaccine.

The re-assortment (genetic shift) of genes between different influenza A strains infecting one host, may generate novel antigenic variants and give rise to pandemics of disease in humans. An influenza pandemic is a worldwide influenza epidemic caused by a new subtype of influenza virus, spreading easily between people and leading to high levels of morbidity and mortality.

It is being debated that the influenza pandemic of 1918 may have followed the introduction of an avian-like H1N1 virus into the human population[3, 4]. The H2N2 and H3N2 viruses responsible for the 1957 and 1968 human pandemics, respectively, were generated by re-assortment between human and avian viruses.[5] Since the last influenza pandemic of 1977, which was caused by the re-emergence of the H1N1 subtype, two subtypes of influenza A (H1N1 and H3N2) have been co-circulating in humans together with influenza B viruses. In 2001, influenza A (H1N2) viruses that probably emerged after genetic re-assortment between human A (H3N2) and A (H1N1) viruses began circulating widely.[6]

Avian influenza A viruses usually do not infect humans. Antigenic drift has also been detected among avian influenza viruses, but to a lesser extent than in human viruses, possibly because of limited immunological pressure in short-lived birds. However, more than 200 confirmed cases of human infection with avian influenza A H5N1 viruses have been reported since 1997.

Most cases of avian influenza infection in humans are thought to have resulted from direct contact with infected poultry or contaminated surfaces and occurred in Southeast Asia. Mortality among hospitalized patients has been high. To date, human infections with avian influenza A viruses have not resulted in sustained human-to-human transmission. Because influenza A viruses have the potential to change and gain the ability to spread easily between people, monitoring for human infection and person-to-person transmission as well as preparation for a possible pandemic is considered important.[7] Also drug evaluation agencies have looked into the issue as illustrated by the recent EMEA pandemic influenza crisis management plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals.[8]

1.3 TESTING FOR INFLUENZA

A variety of laboratory tests can be used to detect influenza A viruses directly in human clinical specimens. These include viral culture, polymerase chain reaction (PCR), direct fluorescent antibody testing, and enzyme immunoassays for influenza A virus antigens, along with the rapid influenza antigen detection tests. The use of such rapid antigen tests is critically reviewed in a recent 2006 FDA document entitled "Cautions in Using Rapid Tests for Detecting Influenza A Viruses" (http://www.fda.gov/cdrh/oivd/tips/rapidflu.pdf).

In addition to diagnosis of individual patients, testing is needed to maintain vigilance for newly emerging influenza A subtypes and for monitoring influenza activity. Culture and methods other than rapid antigen testing are essential for detecting influenza infection missed by rapid testing, for confirming influenza infection particularly when prevalence is low, for monitoring the circulating influenza A subtypes and strains, for annual vaccine strain selection, and for monitoring potential emergence of resistance to antiviral drugs.

At the present time, none of the FDA-cleared rapid influenza A tests can differentiate influenza A virus subtypes or discriminate between those subtypes that commonly infect humans (e.g., H3N2 and H1N1) and those that typically infect birds.

Optimum specimens for influenza virus testing are nasopharyngeal aspirates obtained within three days of onset of symptoms. Rapid influenza tests have also been evaluated with other specimen types such as nasal and throat swabs. It is well-recognized that testing done with children will appear more sensitive because children shed virus more abundantly and longer than adults.

The following table provides levels of sensitivity and specificity for rapid tests that were FDA cleared during the past few years.

Table 1. Levels of sensitivity and specificity (compared with traditional detection methods i.e., culture and/or immunofluorescent assays) for rapid tests that were FDA cleared during the past few years.

Specimen Type	Influenza Virus Type Detected	Population[a]	Sensitivity (95% CI)[c]	% Specificity (95% CI)[c]
Throat swab	Influenza A	Pediatric[b]	65 to 90	81 to 91
		Adult	24 to 91	69 to 94
Throat swab	Both Influenza A & B	Not specified	59 to 82	81 to 93
Nasopharyngeal wash/aspirate	Influenza A	Pediatric[b]	82 to 95	98 to 100
		Adult	53 to 87	90 to 100
Nasal wash	Influenza A	Pediatric[b]	36 to 88	92 to 99
		Adult	9 to 99	59 to 100
Nasal wash and aspirate	Influenza A	Not specified	65 to 84	95 to 99
Nasal swab	Both Influenza A & B	Not specified	65 to 87	87 to 97

[a] From the U.S., Australia, or New Zealand during seasons where A/H3 and A/H1 were predominant circulating influenza A viruses (derived from WHO Flunet, http://gamapserver.who.int/GlobalAtlas/home.asp) [b] Age range not specified; majority are <10 years [c] 95% Confidence Interval. Reference: http://www.fda.gov/cdrh/oivd/tips/rapidflu.pdf

Rapid influenza tests cleared for use in the U.S. generally demonstrate a sensitivity of >60% when compared to culture and/or immunofluorescent assays. False negatives are likely, and may vary by age and type of specimen. While specificity of cleared rapid tests is generally high (>90-95%), false positive test results occur and again may vary by age and specimen type. Positive and negative predictive values of these tests are highly dependent on prevalence, or current level of influenza activity. During peak influenza activity in a season, positive predictive values are higher, with false positives less likely; and negative predictive values are lower, with false negatives more likely. Conversely, during low influenza activity (e.g., off-season or beginning of a season), negative predictive values are higher and positive predictive values lower, with false positive test results more likely. In conclusion, the currently used rapid antigen detection tests are not sensitive enough, and rapid molecular diagnostic tests are not yet routinely available.

At this time, preliminary information from rapid antigen testing in Asia suggests poor sensitivity compared with culture-positive human influenza A (H5N1) cases. Furthermore, the best clinical specimen to use for detecting H5N1 infections is not known.

1.4 ANTIVIRAL AGENTS

Possible uses of antiviral agents are treatment of influenza and pre- or postexposure prophylaxis. There are two classes of drugs and in total four antiviral agents with activity against the influenza viruses.[9] Amantadine (AMANTAN, Altana) and rimantadine (FLUMADINE, registered in the US, rimantadine is not marketed in Belgium) are M2 membrane protein ion channel activity inhibitors. Oseltamivir (TAMIFLU, Roche) and zanamivir (RELENZA, GSK) are neuraminidase inhibitors. Some of their characteristics are summarized in table 2. In appendix 6 the summary of product characteristics (SPC) is given for oseltamivir and zanamivir, as provided by the marketing authorisation holder.

Neuraminidase enzymes are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is essential for the release of recently formed virus particles from infected cells and the further spread of infectious virus in the body. Compared with the two M2 inhibitors, the neuraminidase inhibitors are also effective against influenza B viruses, have fewer adverse side effects, and the virus less often develops resistance. The systemic absorption of zanamivir is limited. It is available only for oral inhalation.

Safety of oseltamivir

See also the summary of product characteristics in appendix 6. Safety and efficacy of repeated treatment of prophylaxis courses have not been studied. There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behaviour throughout the treatment period. (http://www.fda.gov/medwatch/safety/2006/Tamiflu_dhcp_letter.pdf)

In postmarketing experience, rare cases of anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme, have been reported with TAMIFLU.

In treatment studies in adult patients, the most frequently reported adverse events were nausea and vomiting. In treatment studies in patients 1 to 12 years old, the most frequently reported adverse event was vomiting (15%). In prophylaxis studies in adult patients, adverse events were similar to those seen in the treatment studies.

Safety of zanamivir

See also the summary of product characteristics in appendix 6. There have been rare reports of patients with previous history of respiratory disease (asthma, COPD) and very rare reports of patients without previous history of respiratory disease, who have experienced acute bronchospasm and/or serious decline in respiratory function after use of Relenza (see also SPC in appendix 6).

Table 2. Antiviral agents with activity against the influenza viruses, modified from Fagan et al.[10]

Agent and class	Type inhib.	Route of administration	Usual dosage for treatment (T) and prevention (P) in adults	Side effects
Amantadine (AMANTANE) M2 blocking	A	Oral (capsule 100 mg and syrup)	100 mg twice daily (6.59 euro for 60 capsules of 100mg)*	CNS and GI symptoms
Rimantadine (not marketed in Belgium) M2 blocking	A	Oral (tablet 100 mg and syrup)	100 mg twice daily ($22 for five-day course)**	CNS and GI symptoms
Oseltamivir (TAMIFLU) Neuraminidase inhibitor	A, B	Oral (capsule 75 mg and powder for oral suspension)	T: 75 mg twice daily for five days (29.49 euro) P: 75 mg once daily for 10 days	GI symptoms (and rarely CNS symptoms)
Zanamivir (RELENZA) Neuraminidase inhibitor	A, B	Oral inhalation (blisters of 5 mg powder for inhalation using the Diskhaler device)	T: Two 5 mg inhalations twice daily for five days (28.21 euro) P: Two 5 mg inhalations once daily for 10 days	Bronchospasm in patients with COPD or asthma

CNS = central nervous system; GI = gastrointestinal; COPD = chronic obstructive pulmonary disease.
*- Approved cost in Belgium; **Average wholesale cost, based on Red Book, Montvale, N.J.: Medical Economics Data, 2004.

The recent A H5N1 strains of "bird flu" are resistant to M2 inhibitors. As patterns of antiviral resistance to M2 ion-channel inhibitors and neuraminidase inhibitors tend to shift over time, systematic monitoring of the emergence of resistant viruses is essential.[11]

Resistance of influenza A viruses to oseltamivir has been observed, more frequently in children than in adults, and transmission of oseltamivir-resistant strains has been reported.[12] Strains resistant to oseltamivir may be sensitive to zanamivir. [12, 13]

2 ANTIVIRAL AGENTS IN SEASONAL INFLUENZA

2.1 METHODS AND SOURCES OF EVIDENCE

2.1.1 Literature search for seasonal influenza

Published Randomised Controlled Trials (RCTs), systematic reviews and meta-analyses concerning efficacy and safety of neuraminidase inhibitors in the prevention and treatment of seasonal influenza were first searched in Pubmed. Embase was not searched because of the time constraints for this project. Additional searches were done in the Cochrane Central Register of Controlled Trails <3rd Quarter 2006 and in the Cochrane reviews. The pharmaceutical company GlaxoSmithKline makes a database available via the Internet with the protocols of the zanamivir clinical trials (http://ctr.glaxowellcome.co.uk/Summary/zanamivir/studylist.asp). Via the KCE additional information was received from the two pharmaceutical companies GlaxoSmithKline (for zanamivir) and Roche (for oseltamivir). References of articles were read and additional studies of interest and were eventually withheld for critical appraisal. The search in the databases was performed between the 1st of September 2006 and 15th of September of 2006.

The recommendations of the neighbouring countries on the use of neuraminidase inhibitors for prevention and treatment of seasonal influenza were searched.

A first search was done in Pubmed with a limit to Practice Guidelines. Additionally the worldwide web was searched for guidelines on this topic made available by recognised guideline developers/ providers, such as Centers of Disease Control and Prevention in the USA, and WHO. Especially the guidelines on the use of antiviral drugs of the neighbouring countries were searched. Requests for guidelines were launched by KCE via the networks of the International Network of Agencies for Health Technology Assessment (INAHTA) and by the Belgian Centre for Evidence-Based Medicine (CEBAM) via the Guidelines International Network (GIN).

Safety data were searched on the website of the European and U.S. regulatory authorities: EMEA and FDA. The information was added as appropriate to the information retrieved from the original randomised controlled trials.

2.1.2 Selection of the literature

Two researchers read independently from each other the abstracts of the literature found and decided for in or exclusion according to the relevance for the research questions. When there was disagreement the full article was ordered to enable a more thorough assessment of the methodology and outcomes of the publication.

The detailed search results with the reason for in and exclusion are given in Appendix 1.

2.1.3 Quality appraisal, data extraction and grading recommendations

The literature was appraised in a standardised way, independently by at least two of the researchers.

The appropriate checklists from the Dutch Cochrane Collaboration were used for RCTs and Meta-analyses/ Systematic Reviews.

The RCTs that were already scored by Turner et al[1] or Matheson et al[14] and withheld as valid studies for their meta-analyses were not scored again by the researchers.

The guidelines were scored using the AGREE instrument. In agreement with the KCE the scoring was done for only two of the most important domains of the AGREE instrument being domain 2, subject and purpose, and domain 3, methodology.

A consensus meeting was held to compare the appraisals of the RCTs, MA/SR and guidelines. Non-valid RCTs were not included in the evidence-table.

The basis for the evidence tables was taken from the meta-analyses of Turner et al.[1] The data from the single appraised and valid RCT published after this meta-analyses was added.[15] In the evidence tables we withheld also the description of the trials that have been done but not published in peer reviewed journals.

Appendix 2 shows the list of the RCTs and meta-analyses that were read and appraised. Reason for invalidity is given.

Appendix 3 shows the quality appraisal of the guidelines.

Appendix 4 shows the evidence tables for the RCTs.

The strength of recommendations and the quality of evidence of the practice guidelines developed were graded as detailed below.

Table 3. The strength of recommendations and the quality of evidence of the practice guidelines graded according to GRADE, as reported by Guyatt et al.[16]

Grade of Recommendation/ Description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1/ strong recommendation A/ high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong Recommendation, can apply to most patients in most circumstances without reservation
1/ strong recommendation B/ moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from Observational studies	Strong ecommendation, can apply to most patients in most circumstances without reservation
1/ strong recommendation C/ low-quality or very low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2/ weak recommendation A/ high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2/ weak recommendation B/ moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2/ weak recommendation C/ low quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

2.2 DISCUSSION ON RCTS AND META-ANALYSES

Very little valid trials have been performed independently from what the pharmaceutical companies have done to obtain marketing approval for the drug. The quality of the trials was assessed by Jadad scores in Turner[1] and by the Cochrane list for evaluating RCTs. Under-powering and post-hoc subgroup analyses were the most important shortcomings. Quite some studies were never published in peer reviewed journals as seen in the evidence table of unpublished trials (Appendix 4).

The trial setup and especially the definition of the endpoints were different throughout the studies, therefore the comparison of the studies was difficult, as was the pooling in meta-analyses.[1, 17]

The intention to treat analysis is more appropriate to consider because it corresponds best with reality as inclusion starts from influenza-like illness (ILI) or clinically diagnosed influenza. Moreover, the laboratory confirmed clinical influenza (LCI) analysis is a subgroup analysis.

The most important clinical outcome measures related to treatment of influenza are the prevention of complications of influenza, hospitalisation and mortality in high risk populations. These outcomes were scarcely reported (mostly in the form of a serious adverse event). Most studies were not powered to detect any differences for these more rare outcomes between treatment groups. The trials were designed to demonstrate efficacy of the primary endpoint, being reduction in time to resolution of illness.

Few studies[18-21] have reported on the effect of NAI's on viral load as estimated by mean nasal titres of excreted viruses at 24 hours and 48 hours since randomisation. While both drugs seem to decrease nasal shedding of influenza virus at 24 and 48 hours after the start of the treatment, it does not interrupt it. As this is not an outcome of clinical relevance for physicians, it was not reported in the evidence tables.

To overcome the problem of small study-groups, pooling of trials has been done at several points in time. Monto et al.[22] and Lalezari et al.[23] have pooled data from the trials with zanamivir done by the pharmaceutical company to generate data on the incidence of complications. Kaiser et al.[24] did the same for oseltamivir. None of these publications can be considered of very high quality as they were not based on an extensive literature search and were performed without any quality appraisal of the RCTs. In Kaiser et al.[24] most of the data used for the pooling come from the unpublished trials (see evidence table of unpublished trials). Subgroup analysis is a problem in all of these studies. Instead we appraised the meta-analyses from Turner et al.[1] Jefferson et al.[17] and Matheson et al.[14] as very valid. The search strategies used by these authors included all trials, published or not, and quality appraisal of all included trials was done.

Very few studies were performed in high risk groups. No studies have been published on the effect of oseltamivir in a high risk adult population. The data available are generated from sub-group analyses. One study was done with oseltamivir in children with asthma.[25] With zanamivir one study was done and published in adult COPD patients.[26] The data on efficacy in high risk children is also generated from sub-group analyses.

2.2.1 Treatment

Treatment results are mainly based on the pooled estimates of Turner et al.[1]

In the treatment trials zanamivir was given in the inhaled form 10mg 2x/day (during 5 days) and oseltamivir in the oral form 75mg 2x/day (during 5 days).

Zanamivir and oseltamivir gave a reduction in duration of illness in a healthy population of adults and children of 1 day (ILI and LCI).

There was no significant reduction in duration of illness in a high risk population of adults (ILI and LCI). Only for zanamivir in the LCI group a significant reduction of two days could be found (based on only one trial).

No specific studies were conducted in high risk children with zanamivir. A subgroup analysis of high risk children was not able to show any effect of zanmivir on the reduction of duration of illness.[1]

One study was done with oseltamivir in children with astma, and showed no effect on the duration of illness in this group.[25]

Oseltamivir is associated with a significant reduction in the time to return to normal activities of 1.5 days in healthy adults and even of 2.5 days in high risk adults (ILI and LCI). For zanamivir this is only the case in healthy adults with lab confirmed influenza (0.5 day).

In healthy children from 5 to 12 years treated with zanamivir no significant reduction in the time to return to normal activities could be found.

In the high risk group with lab confirmed influenza a reduction of 2.5 days was found after zanamivir treatment but this is based on one trial with a subgroup analysis of 22 patients.

In children from 1 to 12 years treated with oseltamivir a reduction in the time to return to normal activities was found of more than one day (ILI and LCI).

In one study with high risk children (asthma, age 6-12 yrs) treated with oseltamivir no reduction in time to return to normal activities could be found.[25]

Table 4a. Median time to event outcomes data for both zanamivir and oseltamivir

Summary tables of the median time to event outcomes data for both zanamivir and oseltamivir [1]					
Median time symptoms alleviated, ITT, ILI population (in days)			Median time symptoms alleviated, influenza positive population, LCI (in days)		
	Difference (treatment – placebo)			Difference (treatment – placebo)	
Adults	Zanamivir Pooled estimate (95% CI)	Oseltamivir Pooled estimate (95% CI)	Adults	Zanamivir Pooled estimate (95% CI)	Oseltamivir Pooled estimate (95% CI)
'High-risk'	–0.93 (–1.90 to +0.05)	–0.35 (–1.40 to +0.71)	'High-risk'	–1.99 (–3.08 to –0.90)	–0.45 (–1.88 to +0.97)
'Healthy'	–0.78 (–1.31 to –0.26)	–0.86 (–1.41 to -0.31)	'Healthy'	–1.26 (–1.93 to –0.59)	–1.38 (–1.96 to –0.80)
Children	Zanamivir Crude estimate (95% CI)	Oseltamivir Crude estimate (95% CI)	Children	Zanamivir Crude estimate (95% CI)	Oseltamivir Crude estimate (95% CI)
'High-risk'	–2.0 (–6.9 to 2.9)	NDA	'High-risk'	–3.8 (–7.6 to 0.1)	+0,4 ; p = 0,5420
'Healthy'	–1.0 (–1.5 to –0.5)	–0.9 (–1.5 to –0.3)	'Healthy'	–1.0 (–1.6 to –0.4)	–1,5 (–2,2 to –0,8)
Median time return to normal activities, ITT, ILI population (in days)			Median time return to normal activities, influenza positive population, LCI (in days)		
	Difference (treatment – placebo)			Difference (treatment – placebo)	
Adults	Zanamivir Pooled estimate (95% CI)	Oseltamivir Pooled estimate (95% CI)	Group	Zanamivir Pooled estimate (95% CI)	Oseltamivir Pooled estimate (95% CI)
'High-risk'	–0.09 (–0.95 to +0.78)	–2.45 (–4.86 to –0.05)	'High-risk'	–0.20 (–1.19 to +0.79)	–3.00 (–5.88 to –0.13)
'Healthy'	–0.51 (–1.04 to +0.02)	–1.33 (–1.96 to –0.71)	'Healthy'	–0.46 (–0.90 to –0.02)	–1.64 (–2.58 to –0.69)
Children	Zanamivir Crude estimate (95% CI)	Oseltamivir Crude estimate (95% CI)	Children	Zanamivir Crude estimate (95% CI)	Oseltamivir Crude estimate (95% CI)
'High-risk'	–1.0 (–3.5 to 1.5)	NDA	'High-risk'	–2.5 (–4.4 to –0.6)	+0,5 ; p = 0,4555
'Healthy'	–0.5 (–1.3 to 0.3)	–1,3 (–1,8 to –0,7)	'Healthy'	–0.5 (–1.4 to 0.4)	–1.9 (–2.7 to –1,1)

ITT= intent to treat
Crude estimate: term used in case data are from a single study

Complications

Complications associated with influenza were defined as otitis media in children, sinusitis, bronchitis or pneumonia. Often the indirect outcome of an antibiotic prescription was taken to measure the incidence of complications due to influenza. Turner et al. did not pool results for these outcomes.

Zanamivir was associated with a 30% (95%CI: 4% to 48%) protection against complications requiring antibiotics (number needed to treat, NNT 22), but no significant effect against pneumonia in healthy adults (LCI).[22]

In a high risk population there was no significant reduction in complications requiring antibiotics or in pneumonia after zanamivir.[23]

In children with confirmed influenza (one trial) no significant differences where found after zanamivir for the incidence of complications requiring antibiotics.[27]

After oseltamivir in healthy adults (13-65 yrs) with lab confirmed influenza a 68% (95%CI: 48% to 84%) reduction was seen in lower respiratory tract complications requiring antibiotics (absolute risk reduction, ARR= 3.6%; NNT=28). Oseltamivir reduced the number of clinically diagnosed pneumonia in healthy adults (ARR = 1.2%; NNT = 83 LCI).[24]

In healthy children (LCI, 1-12 year) a 35% reduction in the incidence of acute otitis media was observed after oseltamivir (NNT=10).[28]

In the high risk population with lab confirmed influenza oseltamivir was associated with a 38% reduction (95%CI: 6% to 60%) in the incidence of lower respiratory tract complications requiring the use of antibiotics (NNT=16). No reduction in the incidence of pneumonia was seen.[24] There is no detailed information on the vaccination status of the patients in this high risk group.

None of the trials were designed to assess an effect of NAIs on influenza complications, including hospitalisation and mortality. According to Turner et al., hospitalisation rate and mortality were very low in all trial arms during the trial follow-up period, and no conclusions can be drawn.

Table 4b. Results of zanamivir and oseltamivir treatment trials on complications

Results of zanamivir and oseltamivir treatment trials on complications										
Zanamivir	ARR	NNT	OR (95 CI)	Efficacy (95CI)		Oseltamivir	ARR	NNT	OR (95 CI)	Efficacy (95CI)
						Lower respiratory tract complications requiring use of antibiotics [24]				
						Influenza positive, 'healthy'	3.6%	28	0.32 (0.16 to 0.59)	68% (41% - 84%)
						Influenza positive, 'high-risk'	6.2%	16	0.62 (0.40 to 0.94)	38% (6% - 60 %)
Complications requiring use of antibiotics [22, 23]						Complications requiring use of antibiotics [1]				
ITT, all	4.5%	22	0.71 (0.56 to 0.90)	29% (10% - 44%)						
ITT, 'high-risk'	9.0%		0.57 (0.31 to 1.03)							
Influenza positive, all	5.2%		0.82 (0.61 to 1.10)							
Influenza positive, 'healthy'	4.5%	22	0.70 (0.52 to 0.96)	30% (4% - 48%)		Influenza positive, 'healthy	4.40%	23	0.40 (0.16 to 0.93)	60% (7% - 84%)
						Influenza positive, children	10.00%	10	0.65 (0.43 to 0.97)	35% (3% - 57%)
Influenza positive, 'high-risk'	9.0%		0.55 (0.24 to 1.23)							
Influenza positive 'high-risk'	10.4%		0.49 (0.23 to 1.04)							
Number of individuals developing pneumonia [1]						Number of individuals developing pneumonia [24]				
ITT, all	0.70%		0.49 (0.21 to 1.06)							
ITT, 'high-risk'	0.30%		0.90 (0.21 to 3.62)							
Influenza positive, all	0.90%		0.43 (0.15 to 1.10)			Influenza positive, all	1.10%	91	0.37 (0.15 to 0.86)	63% (14% - 85%)
Influenza positive, 'high-risk'	1.20%		0.69 (0.10 to 3.64)			Influenza positive, 'high-risk'	0.60%		0.76 (0.24 to 2.23)	
						Influenza positive, 'healthy'	1.20%	83	0.15 (0.06 to 0.72)	85% (28% - 94%)
Influenza positive, children	0.50%		0.55 (0.01 to 10.72)							

2.2.2 Prevention

The evidence tables are given in appendix 4 (table A4.21 for oseltamivir and A4.22 for zanamivir).

Outcomes in prophylactic studies are only registered during the period the medication was taken.

Zanamivir could demonstrate a 81% post-exposure prophylactic effect in households (5 to 10 days medication 10 mg 1x/day - starting within 36 hours after start illness in index case)(ITT analysis: families NNT = 5 -7; persons NNT= 15).

Oseltamivir gave a 90% post-exposure prophylactic effect in households (7 days medication 75mg 1x/day - starting within 48 hours after start illness in index case), (ITT analysis: families NNT= 9; persons NNT=15).

Zanamivir showed a 69 % prophylactic effect among healthy adults during a seasonal influenza epidemic (28 days medication – 10mg 1x/day).(NNT=24)

A 74 % prophylactic effect[1] (42 days medication – 75mg 1x/day) among healthy adults (NNT=27) and a 92% prophylactic effect (80% vaccinated - 42 days medication – 75mg 1x/day) among elderly in residential homes[29] was demonstrated by oseltamivir during a seasonal influenza epidemic (NNT=25).

One zanamivir outbreak control study in a residential home could not demonstrate any significant effect.[30] No such study was done for oseltamivir.

2.3 DISCUSSION ON GUIDELINES

Of all the retrieved guidelines, 12 were withheld as relevant to the research topic, and only 11 were scored with the AGREE instrument, as the Nederlands Huisartsen Genootschap (NHG) document[31] was not a real guideline. One publication[32] was scored as a guideline but was actually a HTA and did not forward real recommendations for appropriate use of antiviral drugs. See appendix 3: quality appraisal of the guidelines.

Most guidelines had reasonable scores for domain 1, scope and purpose. All the guidelines scored less then 50% in domain 3, rigour of development. The search strategies used, the methods used to select references and the procedure to develop the recommendation were often very poorly reported. Although still a low score, the guidelines from NICE[33, 34] and Domus Medica[35] got the highest points, followed by the Swedish guideline[36] and the guideline edited by the Advisory Committee on Immunization Practices (ACIP, USA)[37]. The low score is not necessary the reflection of a poor recommendation but often caused by poor reporting of the procedures used.

Major conclusions stated in the guidelines:

- Influenza vaccination is the most effective way of preventing illness and complications from influenza and antiviral drugs for the prevention or treatment of influenza shouldn't be used instead of immunisation.
- The guidelines are only applicable in circumstances where it is known to have circulation of influenza A or B in the community.
- Guidelines recommend having a surveillance system in place that is able to detect the start of an influenza outbreak as soon as possible.
- If the use of antiviral drugs is indicated they should be started as soon as possible for treatment. This should be less then 48 hours after the onset of symptoms. Also for prophylaxis the antiviral drugs should be started within 48 hours after the contact with the index case.

Big differences exist between guidelines, from highly recommended to not recommended. Especially on the use of antiviral agents in long term care settings, the differences are great, reflecting the lack of available evidence.

2.3.1 Treatment

Treatment of healthy persons presenting within 48 hours with influenza like illness is generally not recommended by the 4 guidelines with the highest score. In contrast, the German guideline[38] recommends treatment for all persons with ILI presenting within 48 hours.

The recommendation on treatment of persons with high risk conditions presenting within 48 hours is less consistent: from highly recommended in the German guideline, to not recommended in the Dutch NHG statement[31].

NICE recommends treatment for persons with high risk conditions, whether vaccinated or not, who present with ILI to the physician.[34] Also persons with an immunodeficiency should be treated according to the NICE guideline and the German guideline, despite the lack of evidence to do so.

The Swedish[36] and the French guideline[39] take a more case by case approach where high fever and poor general condition might be an indication for treatment.

The guideline from the USA[37] and from the Landelijke Coordinatiestructuur Infectieziektenbestrijding Nederland[40] state that little evidence is available on the efficacy of antiviral agents in high risk groups and they remain somewhat vague on what to do.

For treatment, both drugs, zanamivir and oseltamivir, can be used. The Swedish guideline recommends to use zanamivir if the circulating virus seems to be influenza B, but is the only one to make this difference. Most guidelines recommend to check the product insert of each product before prescribing.

2.3.2 Prevention

2.3.2.1 Non institutionalised circumstances

In healthy adults, none of the highest scoring guidelines recommends the prophylactic use of antiviral drugs to prevent influenza after contact with an influenza case, although some mention that is can be done.[37, 41] The German guideline recommends chemoprophylaxis with antiviral drugs during an influenza epidemic as PEP (household) for unvaccinated persons after close contact to sick persons if the drug administration can be started within 2 days. The Canadian guideline[42, 43] recommends this as well but only if the index case has lab confirmed influenza. The Swedish guideline recommends PEP in a household but only if a high risk patient is member of the family. The American guideline recommends also prophylaxis for non vaccinated household members of unvaccinated or considered unvaccinated high risk patients (remark: care-takers and household members of high risk patients should be vaccinated).

In high risk persons, prophylaxis is generally recommended for those that are not vaccinated, or can be considered as not well protected by vaccination because of immunodeficiency, or because of mismatch between the vaccine strain and the circulating influenza strain. Circulation of influenza in the community is for almost all guidelines sufficient to start prophylaxis (after vaccination if still possible), i.e. no direct contact with a sick person is required (Sweden, USA, Canada, Netherlands, Germany). This is not the case for NICE, where prophylaxis is recommended for high-risk patients who are not vaccinated (or can considered as not vaccinated/ well protected by vaccination) and had contact with a person with influenza like illness. The Swedish guideline recommends for the unvaccinated and persons with immuno-deficiency to strengthen hygienic measures and avoid public gatherings during peak influenza activity in the community.

The length of the prophylaxis is variable: from 2 weeks if vaccination is still an option, during the peak influenza season up to 6 weeks if vaccination is not possible or in case of mismatch. In trials, prophylactic doses of NAIs were never administered for more than 6 weeks consecutively.

Care-takers of high risk patients (institutionalised or not) and who are not vaccinated or vaccinated but mismatch is present, should take prophylaxis during peak influenza activity for up to 6 weeks. They should take prophylaxis up to 2 weeks after vaccination. This is recommended by the American and Canadian guideline, and can also be understood as such by the Swedish guideline.

2.3.2.2 Institutionalised circumstances

Most guidelines state the importance of influenza vaccination for residents and HCWs working in institutions housing high care patients before the start of the influenza season.

Confirmation of influenza of the index case should be done. The French guideline[39] is more precise on which type of assay to be used depending on the number of suspected cases. Measures should be put in place already before the confirmation of influenza arrives, based on sensitive clinical case definition and known circulation of influenza in the community.

Most guidelines mention the lack of evidence for the use of antiviral drugs to control an outbreak in an institutionalised context. We can see different approaches in the guidelines on the use of (post-exposure) prophylaxis.

Use of antiviral agents in (post-exposure) prophylaxis

Residents

Most guidelines recommend NAIs for residents, regardless of vaccination status, who came in contact with a patient or HCW presenting with ILI.

Health Care Workers

- In the Netherlands the guideline[44] recommends to give antiviral agents to all HCW who came in contact, regardless of vaccination status.
- French guideline recommends not to give antiviral drugs to any HCW (as they should be vaccinated).
- U.S. and Canadian guidelines recommend prophylaxis for unvaccinated staff who provide care.

Prophylaxis should continue for 7-8 days after the onset of the last case of influenza has been declared in the institution.

All guidelines mention additional measures like cohort nursing, avoiding gatherings, reduce visitors, hygienic measures etc. to be put in place.

The Dutch guideline recognises the weak evidence basis of their guideline and the difference in regard to the other guidelines i.e. the broad use of PEP for patients and HCW regardless of vaccination status. Their goal for this broad use is to disrupt very quickly the circulation of the virus in the institution. They suggest therefore that the use of PEP should be undertaken as a research objective.

2.3.2.3 In hospitals

PEP for the hospitalised person is recommended.

In high risk wards, such as transplantation unit, antiviral prophylaxis should be given to all patients in the ward, regardless of vaccination status (Swedish guideline), taking into account the SPC.

2.4 PRACTICE GUIDELINES

As detailed before, the strength of recommendations and the quality of evidence of the practice guidelines were graded according to Guyatt et al.[16] Briefly, recommendations are strong (=1) or weak (=2) and the quality of the evidence is rated as high (=A), moderate (=B) or low/very low (=C).

Antiviral drugs for the prevention or treatment of influenza should not be used instead of immunisation.

The use of NAIs will only be considered in high risk groups, especially when the chance to become infected is higher than normal (eg. institutionalised). High risk groups correspond with those defined for influenza vaccination. In casu: 1) chronic respiratory tract diseases (COPD = or > stadium II, asthma); 2) cardiovascular diseases (except hypertension without complications); 3) chronic renal diseases; 4) immunodeficiency; 5) diabetes mellitus; 6) 65 years or older.

The guidelines are only applicable in circumstances where it is known to have circulation of influenza A or B in the community.

An active local surveillance system capable to detect the start of an influenza outbreak is obligatory (http://www.iph.fgov.be/flu/) and physicians should be informed instantly about the evolution of an influenza epidemic.

There is a problem of rapid confirmation of influenza in a clinical context. The currently routinely used rapid antigen detection tests are not sensitive, especially in early stages of influenza. More sensitive molecular diagnostic tests (eg PCR) are currently only available in specialized laboratories.

If the use of antiviral drugs is indicated they should be started as soon as possible. For treatment it should be less then 48 hours after the onset of symptoms. Also for prophylaxis the antiviral drugs should be started within 36-48 hours after the contact with the index case.

NAIs cannot replace hygienic measures to prevent transmission.

NAIs are prone to the occurrence of resistance. Any inappropriate prescription or use should be discouraged for this reason. This includes the preventive storage of NAIs at private homes.

The generalised use of NAIs cannot be recommended in the prophylaxis or treatment of seasonal influenza because at this moment in time there is no scientific proof available that shows a clinically relevant effect of these products on the incidence of complications and mortality in high risk persons. Despite the fact that the at risk groups usually include healthy persons of 65 and older, they are at a much lower risk for complications than the real high risk persons (with comorbidity).

Children with high risk conditions: no separate data available to support any recommendation.

Pregnant women: no recommendations possible because of lack of evidence on efficacy and safety.

2.4.1 Treatment

Routine treatment with NAIs of healthy adults or children presenting with influenza like illness is not recommended (Grade 1A).

The use of NAIs can only be considered on a case by case basis in high risk adults with comorbidity, regardless of vaccination status presenting within 48 hours after onset of influenza like illness (Grade 2C). The evidence is however lacking demonstrating a reduction in complication rate in at risk adults.

2.4.2 Prevention

2.4.2.1 Non institutionalised circumstances

The efficacy of NAIs has been demonstrated in 6 weeks of pre-exposure prophylaxis of health adults. Yet pre-exposure prophylaxis is not recommended in this group as the risk for complications is small and does not outweigh the possible side effects and the risk for development of viral resistance (Grade 1A).

In children and persons at high risk pre-exposure prophylaxis for seasonal influenza is not recommended as no studies are available.

The efficacy of NAIs has been demonstrated in the prophylaxis of healthy adults after contact with an influenza case. Yet post-exposure prophylaxis is not recommended in this group as the risk for complications is small and does not outweigh the possible side-effects and the risk for development of viral resistance (Grade 2A).

In frail high risk persons post-exposure prophylaxis can be considered for those who live in close contact with a probable influenza case AND who are not vaccinated, or can be considered as not well protected by vaccination because of immunodeficiency or in case of mismatch between the circulating and vaccine strains confirmed at national level. A catch-up vaccination, if appropriate, is recommended. Confirmation of the index case is preferable (see remarks on lab tests), but prophylaxis should be started as soon as possible (less than 36-48 hours after contact with the index case) (Grade 2C).

Pregnant women with high risk conditions: no recommendations possible because of lack of evidence on efficacy and safety.

2.4.2.2 Institutionalised circumstances

Every residence for the elderly should have a detailed intervention plan describing preventive and control measures to be put in place to reduce the impact of transmissible diseases including influenza. Together with the hygienic and other measures, the following recommendations should be incorporated in such a plan.

Vaccination of residents and HCW is the most important preventive measure to take. No prophylaxis with NAIs for the health care workers is recommended.

Long term pre-exposure prophylaxis without contact is not recommended in this context (Grade 1B).

Post-exposure prophylaxis with oseltamivir for high risk residents, regardless of vaccination status after contact with a possible influenza case can be considered (Grade 2C).

Confirmation of the index case is recommended, but prophylaxis should be started as soon as possible (less than 36-48 hours after contact with the index case). With a negative test-result (see remarks on lab tests) prophylaxis should be interrupted.

A catch-up vaccination, if appropriate, is recommended.

2.4.2.3 In hospitals

The following recommendations should be incorporated in a detailed intervention plan for dealing with transmissible diseases, including influenza, within the hospital.

Post-exposure prophylaxis for the hospitalised person at risk can be considered case by case.

Confirmation of the index case is a must, but prophylaxis should be started as soon as possible (less than 36-48 hours after contact with the index case). With a negative test-result prophylaxis should be interrupted (Grade 2C).

In high risk wards, such as transplantation units, antiviral prophylaxis can be considered to be given to all patients in the ward, regardless of vaccination status (Grade 2C).

3 ANTIVIRAL AGENTS IN PANDEMIC INFLUENZA

First we present a literature review on efficacy and safety of antiviral agents in pandemic influenza. In contrast to the situation for seasonal influenza, no controlled trials are available. Second, we present a brief review of selected national pandemic plans and try to identify the rationale used for decision making in those plans. No analysis of the currently available modelling approaches was possible in the context of this rapid assessment.

3.1 LITERATURE REVIEW

3.1.1 Introduction

This literature review on antiviral agents in pandemic influenza focuses on the effectiveness of antiviral agents to treat or prevent infections with H5N1 influenza virus. The H5N1 virus is at present of the greatest concern for human health for two main reasons. First, the H5N1 virus has caused in a high proportion of patients hospitalized very severe disease or death. Second, there is a major concern that the H5N1 virus – if given enough opportunities – will develop the characteristics it needs to start another influenza pandemic. The virus has met all prerequisites for the start of a pandemic save one: an ability to spread efficiently and in a sustainable way among humans.

However, while H5N1 is the virus of greatest concern, the possibility that other avian influenza viruses, known to infect humans, might cause a pandemic cannot be ruled out.[41]

3.1.2 Methods

The literature review is based on the following.

First, WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus.[45] This document was developed in March 2006. It is based on:

- Systematic reviews and health technology assessments according to the GRADE methodology
- Data available from pre-clinical studies of H5N1
- Expert consultation

Second, a Medline search for additional pre-clinical studies on the effectiveness of antiviral agents in treatment and prevention of H5N1 infections. The following search strategy was used.

- Influenza A virus, subtype H5N1 [MESH] AND antiviral agents [MESH] AND (models, animal [MESH] OR animal models [TEXT])
- Influenza A virus, subtype H5N1 [MESH] AND antiviral agents [MESH] AND (virus replication [MESH] OR cells, culture [MESH])

Third, a comprehensive search was conducted in Medline and Embase for recent data on effectiveness of antiviral agents in treatment and prevention of pandemic flu or avian influenza, as detailed below.

Medline/Pubmed search strategy (search date: 11-11-2006)

- (("Disease Outbreaks"[MeSH] OR "disease outbreak*"[TEXT] OR "epidemic*"[TEXT] OR "pandemic*"[TEXT]) AND "humans"[MeSH Terms]) AND (("Influenza, Human"[MeSH] OR "Influenza A Virus, H5N1 Subtype"[Mesh] OR "influenza"[TEXT] OR "H5N1"[TEXT] OR "avian flu"[TEXT] OR "avian influenza"[TEXT]) AND "humans"[MeSH Terms]) AND (("Antiviral Agents"[MeSH] OR "Amantadine"[MeSH] OR "neuraminidase inhibitor*"[TEXT] OR "Rimantadine"[MeSH] OR "peramivir"[Substance Name] OR "zanamivir"[Substance Name] OR "GS 4071"[Substance Name] OR "antiviral agent*"[TEXT] OR "tamiflu"[TEXT] OR "relenza"[TEXT] OR "oseltamivir"[TEXT] OR "zanamivir"[TEXT] OR "peramivir"[TEXT] OR "amantadine"[TEXT] OR "rimantadine"[TEXT]) AND "humans"[MeSH Terms]) AND "humans"[MeSH Terms]
- Same search with "postexposure prophylaxis"[TEXT] added.

Limits: added to Pubmed since 1-1-2006.

Finally, references of recently published reviews were checked.

A similar strategy was used for the search in Embase (search date 18-9-2006).

- (('epidemic'/exp AND [humans]/lim AND [embase]/lim) OR ('disease outbreak' AND [humans]/lim AND [embase]/lim) OR ('disease outbreaks' AND [humans]/lim AND [embase]/lim) OR (epidemic* AND [humans]/lim AND [embase]/lim) OR (pandemic* AND [humans]/lim AND [embase]/lim)) AND (('influenza'/exp AND [humans]/lim AND [embase]/lim) OR ('influenza virus a'/exp AND [humans]/lim AND [embase]/lim) OR (influenza AND [humans]/lim AND [embase]/lim) OR (h5n1 AND [humans]/lim AND [embase]/lim) OR ('avian flu' AND [humans]/lim AND [embase]/lim) OR ('avian influenza' AND [humans]/lim AND [embase]/lim)) AND (('antivirus agent'/exp AND [humans]/lim AND [embase]/lim) OR ('amantadine'/exp AND [humans]/lim AND [embase]/lim) OR ('neuraminidase inhibitor'/exp AND [humans]/lim AND [embase]/lim) OR ('rimantadine'/exp AND [humans]/lim AND [embase]/lim) OR ('peramivir'/exp AND [humans]/lim AND [embase]/lim) OR ('zanamivir'/exp AND [humans]/lim AND [embase]/lim) OR ('4 acetamido 5 amino 3 (1 ethylpropoxy) 1 cyclohexene 1 carboxylic acid'/exp AND [humans]/lim AND [embase]/lim) OR ('oseltamivir'/exp AND [humans]/lim AND [embase]/lim) OR ('antiviral agent' AND [humans]/lim AND [embase]/lim) OR ('neuraminidase inhibitor' AND [humans]/lim AND [embase]/lim) OR ('neuraminidase inhibitors' AND [humans]/lim AND [embase]/lim) OR ('antiviral agent' AND [humans]/lim AND [embase]/lim) OR ('antiviral agents' AND [humans]/lim AND [embase]/lim) OR (tamiflu AND [humans]/lim AND [embase]/lim) OR (relenza AND [humans]/lim AND [embase]/lim) OR (oseltamivir AND [humans]/lim AND [embase]/lim) OR (zanamivir AND [humans]/lim AND [embase]/lim) OR (peramivir AND [humans]/lim AND [embase]/lim) OR (amantadine AND [humans]/lim AND

[embase]/lim) OR (rimantidine AND [humans]/lim AND [embase]/lim))

Papers published in 2006 were checked.

3.1.3 Results

3.1.3.1 Effectiveness of antiviral agents in H5N1

Randomised controlled trials.

At the moment no controlled clinical trials are available for H5N1 patients. Existing evidence on the effectiveness of antiviral agents in influenza is entirely obtained from patients with seasonal influenza which is caused by other influenza virus strains. For the results of these clinical trials we refer to the section on seasonal influenza.

Patient series

Ten patients in Vietnam.[46]

Five patients were treated with oseltamivir for 5 days. The antiviral treatment was started between day 5 and 12 after onset of illness. Two patients recovered, three died. In the surviving patients, therapy was started on day 5 and day 12 respectively. The other patients started therapy on day 5 or 6. The other five patients not treated with oseltamivir died.

Twelve confirmed cases in Thailand.[47]

Seven patients were treated with oseltamivir. Two out of seven survived. Treatment tended to have been started earlier in those who survived (a median of 4.5 days from onset compared with 9 days for those who died), and both survivors received the complete 5-day course of drug, whereas only two of the five patients who died received the complete course. One out of five patients not treated with oseltamivir survived.

Eight patients in Vietnam.[12]

All were treated with oseltamivir on the day of admission (2 to 8 days after onset of illness). Four patients died, four survived. In two patients resistance of the H1N5 virus to oseltamivir was shown (cfr infra).

Ten patients in Eastern Turkey.[48]

Seven patients were treated with oseltamivir. Three patients not treated, and one patient treated with oseltamivir died. All patients were children. The surviving children were between 3 – 9 years old, while the four fatalities were between 12-15 years old.

Pre-clinical studies of effectiveness of antiviral agents in H5N1 infection

Studies in animal models

Oseltamivir prophylaxis is efficacious against lethal challenge with H5N1 virus in mice.[49]

Viral virulence may affect the antiviral treatment schedule (higher doses and a longer treatment course may be necessary).[49]

Survival of animals increases when treatment is started earlier: when treatment was delayed until 48 h after virus exposure all of the mice died, but survival was longer. Oseltamivir was not effective in preventing death and extending the length of survival when treatment began 60 h or more after virus inoculation.[50]

In a model of lethal challenge in mice, zanamivir reduces lung titers of the virus and decreases morbidity and mortality.[51]

Zanamivir protected mice from infection with H9N2 viruses (closely related to H5N1) and increased the mean survival day and the number of survivors infected with H6N1 and H5N1 viruses.[52]

In vitro studies (WHO, 2006,[45], unless stated otherwise)

Oseltamivir:

- inhibits both replication and NA of H5N1
- H5N1 strains with high-resistance to oseltamivir were isolated from two patients

Zanamivir:

- inhibits both replication and NA of H5N1
- no viruses with reduces sensitivity to zanamivir identified until now

Amantadine, rimantadine

- Z H5N1 viruses isolated in Vietnam and Thailand are resistant to amantadine[53]
- 31% of H5 avian strains from southeast Asia carried mutations making it insensitive to amantadine
- 61% of 22 influenza virus strains (not H5N1) isolated since 2003 in Asia resistant to amantadine and rimantadine

Other:

- Ribavirine, viramidine: both compounds were inhibitory to all the influenza viruses evaluated (including H5N1)
- H5N1 escaped antiviral activity of interferons and TNF-alpha.
- Combinations: zanamivir, oseltamivir + amantadine: not tested in H5N1. In other influenza virus strains: marked reduction of extra-cellular virus yield. Synergism and additive effects seen at various concentrations.

3.1.3.2 Development of resistance

Two reports[12, 54] of resistance to oseltamivir of H5N1 influenza virus have been published.

- A partially resistant virus strain in a 14 year old girl receiving a prophylactic dose of oseltamivir (75 mg/d). After starting a therapeutic dose the patient recovered. The virus strain stayed susceptible to zanamivir.
- A high level resistant strain in a mother and 13 year old daughter receiving a therapeutic dose of oseltamivir (2 x 75 mg). Both patients died.

3.1.4 Conclusions

The direct data on the effectiveness of antiviral agents in patients with H5N1 infection are sparse. In vitro and animal models show activity against the virus. Treatment experiences with antiviral agents in H5N1 infected patients are inconclusive. There are no controlled clinical trials. Evidence is predominantly derived from studies of infection with human influenza viruses during seasonal epidemics, and is thus indirect. Generalisation of results from these studies to H5N1 patients may not be appropriate since the majority of these studies focus on early treatment of uncomplicated human influenza in otherwise healthy adults in which infection has been acquired following human-to-human transmission. So far, most patients with H5N1 infection have presented late in the course of illness and were hospitalized after the onset of severe disease. Many of those infected with H5N1 virus have been children.[45]

Finally there are reports that high-level resistance of H5N1 virus against oseltamivir can develop and cause treatment failure which should at least warn us not to put all eggs in one basket.

3.2 USE OF ANTIVIRAL AGENTS IN PANDEMIC PLANS

3.2.1 Introduction

The World Health Organization (WHO) has developed a global influenza preparedness plan,[55] which defines the stages of a pandemic as follows.follows.(http://www.cdc.gov/flu/pandemic/phases.htm)

Interpandemic period

- Phase 1: No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is considered to be low.
- Phase 2: No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.

Pandemic alert period

- Phase 3: Human infection(s) with a new subtype but no human-to-human spread, or at most rare instances of spread to a close contact.
- Phase 4: Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans.
- Phase 5: Larger cluster(s) but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans but may not yet be fully transmissible (substantial pandemic risk).

Pandemic period

- Phase 6: Pandemic: increased and sustained transmission in general population.

Influenza experts agree that another pandemic is likely to happen but are unable to say when. The specific characteristics of a future pandemic virus cannot be predicted. Nobody knows how pathogenic a new virus would be, which age groups it would affect, and although the effectiveness of neuraminidase inhibitors (NAI) in seasonal influenza is relatively well studied, there are doubts as to the generalisability of the evidence from seasonal influenza to avian influenza.[17]

In a context of such uncertainty, decisions concerning indications for antiviral drugs during a flu pandemic, and therefore the quantities to be stockpiled can only be based on assumptions as regards the forthcoming pandemic: (1) epidemiological assumptions, about the overall attack rate, and age-specific attack rates, and (2) assumptions about the effectiveness of antivirals (NAIs) to reduce influenza-related morbidity and mortality, and the effectiveness of different strategies (prophylaxis, treatment) to decrease transmission, and therefore decrease the attack rate. These assumptions vary from country to country, taking into account the epidemiology of past pandemics, what is known of the few human cases of H5N1 flu (the best candidate for the next pandemic), and the effectiveness of NAIs in seasonal flu.

An additional factor is the limited NAI production capacity at global level. Production capacity has increased recently as Roche – the manufacturer of oseltamivir - announced deals with other companies to boost production. Some generic drug makers have also started producing their own version of oseltamivir, some with a sub-license from Roche, some without[56]. The limited production capacity combined with budgetary constraints, makes it a necessity at country level to establish priorities for the use of antiviral agents given a limited stockpile.

Priorities can be defined in terms of strategy (pre-exposure prophylaxis, post-exposure prophylaxis, and treatment), on clinical grounds (severity of the disease, and persons to be targeted, for instance based on their presumed risk for severe complications), or value judgements on their societal importance in a pandemic context (for instance, health care workers). Note that pre-exposure prophylaxis (unlike post-exposure prophylaxis) is a very resource-consuming strategy, as antiviral drugs need to be taken for a long time (the duration of the pandemic in a particular setting) and a large number of persons could potentially be eligible, thus rapidly depleting the stockpile.

Basically all pandemic plans acknowledge that they are only 'educated guess' and include a disclaimer such as '…recommendations will need to be reconsidered at the time of a pandemic when information on the available drug supply, epidemiology of disease, and impacts on society are known'[57].

Clinical recommendations and clinical guidelines as regards the use of antiviral drugs during an influenza pandemic therefore depend to a large extent on non-clinical criteria and priorities chosen by decision makers - for instance, the choice for a certain strategy, such as post-exposure prophylaxis to reduce transmission, or priorities set for treatment, given a limited stockpile. In this review of national pandemic plans, we focus on the most useful information for decision makers in Belgium, like the rationale underlying priority choices made in other countries. We also collected information on planned research activities (beyond surveillance and monitoring of resistance of the pandemic strain to antiviral drugs) and on evaluation of the effectiveness of antiviral treatment.

3.2.2 Methods

We intended to review pandemic plans from the main Western countries. Pandemic plans were retrieved using web addresses listed on the European Centre for Disease Prevention and Control (E-CDC) website[58], or (for non-European countries) through a Google search using the words "pandemic plan influenza + country name". The research team identified the key data to be extracted, then developed a data extraction sheet and a framework for analysis. For each country data were extracted by 2 different researchers, discrepancies in findings (if any) were resolved through discussion. Population data (to allow computing the proportion of the population covered by the stockpile, when possible) were found on the CIA World Fact Book[59].

We concentrated on oseltamir as the main drug stockpiled. One treatment course consists of 10 doses of 75 mg (2 doses*5 days), similar to one post-exposure prophylaxis course (1 dose *10 days). The duration of a pre-exposure prophylaxis course will vary according to the duration of the epidemic, but for planning purposes is usually calculated as one dose per day for 6 or 8 weeks. For the sake of clarity, drug needs and stockpile are always expressed as 'number of treatment courses' (10 doses of oseltamivir) regardless of their intended use (treatment or prophylaxis).

Post-exposure prophylaxis (PEP) refers to prophylaxis among persons likely to have been exposed to the virus; the term 'targeted prophylaxis' (TAP) is also sometimes used in that sense. To avoid confusion when addressing the issue of prophylaxis, we will explicitly refer to *pre*-exposure prophylaxis, or *post*-exposure prophylaxis.

We present here only a short summary of the most significant findings, making a (to some extent arbitrary) selection of countries best illustrating the variety of possible choices in pandemic plans. A more detailed overview by country for the 13 countries selected can be found in Appendix 5.

3.2.3 Results

3.2.3.1 Stockpile of neuraminidase inhibitors and coverage

Table 5. Intended stockpile and coverage

Country	Population 2006 (millions)	N treatment courses (millions)	N treatment courses/ population
Belgium	10.4	3.0	30%
Australia	20.3	8.75	43%
FR	60.9	14.0	23%
NL	16.5	5.0	30%
Norway	4.6	1.4	30%
SZ	7.3	3.3	46%
UK	60.6	14.6	24%
US	299.9	40	14%

* Figures are rounded . FR: France, NL: the Netherlands, SZ: Switzerland, UK: United Kingdom, US: United States

3.2.3.2 Choice of strategies

Pandemic alert period (WHO phase 3 to 5)

Most plans more or less explicitly make provision for the treatment of cases, and for the post-exposure prophylaxis of contacts in the 'alert period' with an objective of early containment of the epidemic in the country.

In Australia needs are explicitly computed for this alert period.[60] Each case is expected to lead to post-exposure prophylaxis in 20 contacts and to justify pre-exposure prophylaxis for 50 health care workers (HCWs) conducting 'seek and contain activities'. Containment needs during this phase are estimated to 10 % of the total oseltamivir drug stockpile.

In Switzerland[61] 0.3% of total stockpile (10.000 / 3.3 millions treatment courses) is expected to be used during the pandemic alert phase.

Pandemic period (WHO phase 6)

Strategies chosen for the established pandemic (phase 6) show wide variation between countries (table 2). Australia explicitly allocates the majority of its stockpile to pre-exposure prophylaxis interventions, at the expenses of treatment, on the grounds that 'the most recent epidemiological modeling shows that combined interventions, including use of antiviral drugs, could delay the onset of a pandemic in Australia for many months.[60]

At the other extreme the UK (like Belgium) plans to treat all influenza cases (that is, all cases meeting the given clinical case definition for influenza, and meeting requirement for early initiation of treatment); it does not consider any prophylaxis strategy. In the UK, the rationale for treating all cases (including uncomplicated ones) is that this would 'lessen the severity and duration of illness, reduce the need for antibiotics, and lower demand for hospital care'.[62]

Table 6. Strategies for antiviral use during an established influenza pandemic and percent of intended stockpile allocated to the strategy.* Selected countries.

Country	Pre-exposure prophylaxis (%)		Post-exposure prophylaxis (%)		Treatment (%)	
Belgium	No	-	No	-	Yes	100%
France	No	-	No	-	Yes	100%
The Netherlands	No	-	Yes - Control outbreak (institutions)	-	Yes	
Norway	Exposed HCWs,	?	No	?	Yes	
UK	No	-	No	-	Yes	100%
Switzerland	Exposed HCWs	31%	No		Yes	59%
Australia	Health / safety work, high risk of exposure (e.g. core of HCWs)	65%	Yes (persons with lower risk of exposure)	10%	Yes	10%
US	HCWs Emergency dept, ICU	12%	Yes - Control outbreak (institutions)	5%	Yes	83%
Canada	HCWs	?	Yes - Control outbreak (institutions)	?	Yes	?

HCWs: health care workers. ICU: intensive care unit. * Percentages: it was not always possible to separate the amount of stockpile used during the alert phase; data are not directly comparable across countries and are only indicative.

The rationale used for prioritizing health care workers are

- they are at increased risk of acquiring infection and/or passing it to vulnerable patients (UK, Australia, US),
- they perform essential services (UK, Australia, US), and
- their availability reduces morbidity and mortality (Australia, Canada) [63].

3.2.3.3 Treatment with antiviral drugs: eligibility criteria and priority setting

In some countries, priority lists for treatment are established.

Table 7. Patients with influenza*: criteria to be eligible for antiviral treatment. Selected countries.

Country	Clinical criteria: patients		Societal utility		Other/ Comment
	Hospitalised	At high risk	HCWs	Others	
Belgium	Treatment of all cases intended				
Australia	Limited number of cases (10% of stockpile = 0.87 millions treatment= treatment for 4% of population), within a trial; no more defined				
US	Yes	Yes	Yes	Pandemic health responders, public safety, decision makers	No treatment of ambulatory cases (if not in a listed category) -
Canada	Yes	Yes	Yes	Essential service workers	
UK	Treatment of all cases intended, but priority to HCWs if stockpile not sufficient				
SW	Treatment of all cases intended				
NL	Treatment of all cases intended, priority to patients at high risk, HCWs, hospitalized patients if stockpile not sufficient				

NL: the Netherlands. SZ: Switzerland. US: United States. UK: United Kingdom
* patients meeting given case-definition for influenza. HCWs: health care workers.

The Canadian pandemic plan provides clear and detailed clinical guidelines for patient assessment and eligibility for antiviral treatment.[64]

3.2.3.4 Research

The necessity for monitoring the development of resistance to antiviral drugs is widely acknowledged in all plans.

All plans also underscore the need for an evaluation of the strategies chosen (for instance, effectiveness of treatment in reducing morbidity and mortality), and some announce their intention to develop study protocols in that respect. In Australia, a limited number of influenza cases will be treated, all within a trial, and the choice of who will be treated will be based on how best treated patients can be enrolled in the research protocol and contribute to increasing knowledge, rather than on clinical criteria.

Some countries (like the US) also include basic research (like testing new treatment protocols, or developing new drugs) in their research plans.

3.2.3.5 An example: priority setting in the US.

The US pandemic plan[57] is an example of clarity and transparency in its priority setting exercise (table 8). Total antiviral needs have been computed to 133 millions courses but the recommended stockpile is only 40 millions courses, enough to cover priority groups 1-7, and therefore explicitly excludes treatment for outpatients who do not fall in a particularly category listed elsewhere (36% of all needs) , and prophylaxis for health care workers, even those directly in patient contact (24% of all needs).

Table 8. Antiviral Drug Priority Group Recommendations in the United States [57].

	Group	Strategy	Needs (million courses)	%	Rationale	
1	Patients admitted to hospital***	T	7.50	6%	Medical practice and ethics: treat those with serious illness and who are most likely to die.	STOCKPILE
2	Health care workers (HCWs) with direct patient contact, emergency medical service (EMS) providers	T	2.40	2%	HCWs needed for quality medical care.	
3	Highest risk outpatients (immunocompromised persons and pregnant women)	T	0.70	1%	Groups at greatest risk of hospitalization and death	
4	Pandemic health responders (public health, vaccinators, vaccine and antiviral manufacturers), public safety (police, fire, corrections), government decision-makers	T	0.90	1%	Groups are critical for an effective public health response to a pandemic.	
5	Increased risk outpatients— children 12-23 months old, persons >65 yrs old, and persons with underlying medical conditions	T	22.40	17%	Groups are at high risk for hospitalization and death.	
6	Outbreak response in nursing homes and other residential settings	PEP (+T)	2.00	2%	Strategy is effective in stopping outbreaks; vaccination priorities do not include nursing home residents.	
7	HCWs in emergency departments, intensive care units, dialysis centers, and EMS providers	P	4.80	4%	Groups most critical to effective healthcare response. Prevention of absenteeism.	
8	Pandemic societal responders (e.g., critical infrastructure groups as defined in the vaccine priorities) and HCW without direct patient contact	T	2.70	2%	These groups have impact on maintaining health, implementing a pandemic response, and maintaining societal functions	
9	Other outpatients	T	47.30	36%	Includes others who develop influenza and do not fall within the above groups	
10	Highest risk outpatients	P	10.00	8%	Prevents illness in the highest risk groups for hospitalization and death	
11	Other HCWs with direct patient contact	P	32.00	24%	Prevention would best reduce absenteeism and preserve optimal function	
	Total needs		133	100%		

*Strategy: Treatment (T) requires a total of 10 capsules and is defined as 1 course. Post-exposure prophylaxis (PEP) also requires a single course. Pre-exposure prophylaxis (P) is assumed to require 40 capsules (4 courses) though more may be needed if community outbreaks last for a longer period. ***There are no data on the effectiveness of treatment at hospitalization. If stockpiled antiviral drug supplies are very limited, the priority of this group could be reconsidered based on the epidemiology of the pandemic and any additional data on effectiveness in this population.

3.2.3.6 Situation in Belgium

Stockpile

In Belgium, stockpiling of NAIs sufficient for 30% of the population was started based on a recommendation by the High Council of Health for Belgium. The model published by Longini[65] was used in the decision making. Whereas post-exposure prophylaxis was considered at early stages of the pandemic, the stockpiled NAIs were aimed for therapeutic use only during the phase 6 of the pandemic. The reasons for this choice were economic, the uncertainty about possible side-effects of continued use of NAI during more than 6 weeks, as well as ethical dilemma's (which subgroup of the population has the right to use NA prophylactically, and which not?). The planned stockpile consists of 2.7 million treatment courses of oseltamivir and 0.3 million treatment courses of zanamivir. This amount of NAIs should be sufficient to treat all ill people in the country. Treatment with zanamivir may be appropriate, eg in case an influenza strain resistant to oseltamivir is being spread during the pandemic.

Mathematical model

In the preparation phase and during the course of a pandemic, it is important to be able to estimate a projection of the number of people that will fall ill because of influenza, the number of consultations of primary care physicians, the number of hospital admissions, the number of fatalities, etc.). Using different preventive and therapeutic interventions, the authorities can try to have a positive impact on a pandemic. A mathematical model has to take a number of variables into account. The current INFLUBEL 2.0 simulation model (M. Van Ranst, University of Leuven), makes age- and risk group-specific assumptions about the attack rate, basic reproduction number, and virulence parameters of a novel pandemic strain, and allows to simulate a pandemic in a definable population with a definable social interaction matrix. It allows for simulation of intervention with vaccines and antiviral agents.

3.2.4 Discussion

3.2.4.1 Comparison of strategic choices between countries, and their impact on the estimation of antiviral needs.

The two most striking findings of this review of national pandemic plans are

- the wide variation in choices made for the allocation of antiviral drugs during an influenza pandemic beyond the containment phase, and
- the wide variation in degree of transparency in this resource allocation exercise.

Some countries give priority to treatment of all patients and have planned their stockpile almost exclusively on this basis (Belgium, France, UK, the Netherlands, for instance); no prophylaxis strategies (pre or post) are included in their planning beyond the alert phase. This option has the merit of being simple and clear, but not necessarily the most effective, or cost-effective. Clinical guidelines can be very simple (treat all those meeting the clinical case-definition for influenza). Needs are easy to compute, and the stockpile (number of treatments as a proportion of the population) approximately corresponds to the expected attack rate (25-30%).

Other countries - like the US and Canada – explicitly intend to limit treatment to pre-specified categories of patients based on severity criteria, value judgments on their societal utility (for instance, hospitalized patients, or patients with pre-existing risk of complicated influenza, health care workers). In addition some groups can be eligible for post-exposure prophylaxis (residents in institutions), with an epidemiological rationale – outbreak prevention - or pre-exposure prophylaxis with a societal utility rationale (HCWs in intensive care units). This strategy is less costly. Of all the countries reviewed, the US has the lowest stockpile relative to its population (14%). Guidelines become more sophisticated as they must include algorithms and a precise identification of those eligible for treatment (see Canadian clinical guidelines). Detailed priority setting is required.

By contrast, Australia is the only country (reviewed here) which has chosen to allocate the largest proportion of its antiviral resources to pre-exposure prophylaxis strategies, with a rationale of containment and delaying the spread of the disease. Only a minority of the influenza patients will be treated, and the rationale for treatment will be contribution to research, rather than a clinical one. Switzerland combines both objectives of containment and treatment of all cases. Australia and Switzerland have the largest stockpile of all countries reviewed (43% and 46% of their population, respectively).

3.2.4.2 Ethical and socio-cultural considerations in priority setting for pandemic influenza

There are ethical, political, and public health implications in deciding who receives potentially life-saving interventions.[63] A recent study analyzed in details the processes of priority setting for vaccine and antiviral drugs and carried out an exhaustive and extensive review of national preparedness plans for influenza.[63] It found that only 2 out of 25 English-language plans that prioritize at least one pharmaceutical intervention, referred to consultations with ethicists. The wide variation in allocation decisions that was observed (priority lists for vaccines or antiviral drugs) was attributed not only to differences in the interpretation of evidence, but also to socio-cultural factors (for instance, the decision to prioritize children for vaccine, against WHO recommendations).

A recent WHO document discusses several ethical points of relevance for the pandemic situation (http://www.who.int/ethics/influenza_project/en/index.html).

3.2.4.3 The impact of different strategies for mitigating an influenza pandemic: result from modeling studies

National influenza pandemic preparedness plans currently focus on reducing the impact associated with a constant attack rate, rather than on reducing transmission.[66] However recent studies based on mathematical and epidemiological modeling have tried to measure the effectiveness of several strategies (and combination of strategies) to mitigate the impact of a pandemic influenza.[66-68] These models take into account a wide range of epidemiological, operational, and clinical parameters. For instance, the treatment of a symptomatic individual is assumed to reduce infectiousness by 60% from the point in time drug is first taken.[67]

The supplemental information of the publication by Ferguson et al.[67] provides details of such a simulation. It shows results for particular combinations of strategies. For example, the (early) treatment of 90% of the cases, and post-exposure prophylaxis of 90% of household contacts, combined with household quarantine of cases and contacts (70% complying) and reactive workplace

closure (10% closed) could reduce the attack rate by 50% (from 34% to 17%) for an antiviral stockpile of 42% of the population. The results are sensitive to R_0 (the basic reproductive number, or the average number of secondary cases generated by an index case) and to the timing of treatment.

3.2.5 Conclusions

An analysis of national pandemic plans for influenza has shown a large variation in the strategic decisions made for the use of antiviral drugs during a flu pandemic, ranging from treatment-for-all cases only, to most of the resources being allocated within a containment objective. These choices have consequences in terms of the quantities of drugs needed, and for clinical guidelines.

In the case of pandemic flu, it is not the (meager) clinical evidence that will drive clinical guidelines. Rather clinical guidelines derive from strategic choices made by decision makers trying to make the best use of available resources. The variability of choices made in different countries can be explained by the basic uncertainty surrounding the forthcoming influenza pandemic, socio-cultural factors, and resources available.

Current scientific thinking now revolves about the results of complex mathematical modeling exercises and the possibility to reduce transmission and decrease the attack rate with different combination of strategies including early treatment of cases and post-exposure prophylaxis of household members. The application of such models to the Belgian situation and the possible impact on recommendations on the use of antiviral agents remains to be investigated.

Strategic choices for the allocation of antiviral drugs, whatever they are (choice of a strategy: treatment, and/or pre or post exposure prophylaxis, priorities for allocation) need to be explicit, and their rationale provided. Given the ethical, political, and public health implications in deciding who receives potentially life-saving interventions,[63] ethical advise should support decision making.

4 APPENDICES

4.1 APPENDIX 1. SEARCH RESULTS OF ANTIVIRAL AGENTS IN SEASONAL INFLUENZA

Between September 1st and 15th 2006 the mentioned databases and website were searched for the available literature. The search was focused on the literature with the highest level of evidence being meta-analyses, systematic reviews and randomised controlled trials.

The guidelines searched via the world wide web were consulted in that same period.

4.1.1 Search for trials, meta-analyses and systematic reviews

Publications from Medline, Cochrane Central Register of Controlled Trials (CCTR), GlaxoSmithKline clinical trial register were searched.

The first step in the literature search is the listing of the most appropriate search terms for this topic. The research team came to the following terms

Table A1.1. Search terms

Seasonal influenza and antiviral drugs
Zanamivir
Oseltamivir
Neuraminidase inhibitors
Influenza

Depending on the databases searched those terms were translated into the appropriate MeSH terms and/ or keywords.

A table with all the references of this search is available in table A1.2

4.1.1.1 Search in Pubmed

MEDLINE/PUBMED	neuraminidase inhibitors in seasonal influenza
Search terms	"Neuraminidase/antagonists and inhibitors"[MAJR] OR ("zanamivir"[Substance Name] OR zanamivir[Text Word]) OR ("GS 4071"[Substance Name] OR oseltamivir[Text Word]) AND (Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp])
TOTAL	66 articles

4.1.1.2 Cochrane Central Register of Controlled Trials <3rd Quarter 2006>)

The results of the search in the Cochrane Central Register of Controlled Trials were compared with the results from the Pubmed search. Only additional articles not found in the Pubmed search were withheld.

Cochrane Central Register of Controlled Trials <3rd Quarter 2006>)	
Search terms	oseltamivir.mp.
TOTAL	41
Not found in Pubmed	10
Search terms	zanamivir.mp.
TOTAL	45
Not found in Pubmed	9

4.1.1.3 Cochrane reviews

The Cochrane collaboration makes via its website www.cochrane.org systematic reviews available on several topics. By searching on topic "Acute Respiratory Infections Review Group" and selecting Influenza Prevention and Treatment – neuraminidase inhibitors, 2 systematic reviews were retrieved.[14,69]

4.1.1.4 GlaxoSmithKline clinical trial register

Available at http://ctr.glaxowellcome.co.uk/Summary/zanamivir/studylist.asp

In September 2006, 21 clinical trials were made available for consultation on the website. Of these 15 were phase III clinical trails. Not all of the studies have been published in peer reviewed journals. In this register we found 2 published trials[15, 30] not retrieved in the previous search of Pubmed and Cochrane Central Register of Controlled.

Table A1.2: References of the literature search in Pubmed, CCTR, GSK trial register with reason for exclusion

Title	Exclusion	Reason for exclusion
Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Lancet. 1998 Dec 12;352(9144):1877-81.		
Aoki FY, Fleming DM, Griffin AD, Lacey LA, Edmundson S. Impact of zanamivir treatment on productivity, health status and healthcare resource use in patients with influenza. Zanamivir Study Group. Pharmacoeconomics. 2000 Feb;17(2):187-95.		
Boivin G, Goyette N, Hardy I, Aoki F, Wagner A, Trottier S. Rapid antiviral effect of inhaled zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults. J Infect Dis. 2000 Apr;181(4):1471-4.		
Hayden FG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. N Engl J Med. 1999 Oct 28;341(18):1336-43.		
Hayden FG, Belshe R, Villanueva C, Lanno R, Hughes C, Small I, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J Infect Dis. 2004 Feb 1;189(3):440-9.		
Hayden FG, Osterhaus AD, Treanor JJ, Fleming DM, Aoki FY, Nicholson KG, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. GG167 Influenza Study Group. N Engl J Med. 1997 Sep 25;337(13):874-8		
Kaiser L, Henry D, Flack NP, Keene O, Hayden FG. Short-term treatment with zanamivir to prevent influenza: results of a placebo-controlled study. Clin Infect Dis. 2000 Mar;30(3):587-9.		
Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med. 2003 Jul 28;163(14):1667-72.		
Kashiwagi S, Kudoh S, Watanabe A, Yoshimura I. [Efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir for prophylaxis against influenza--placebo-controlled double-blind multicenter phase III trial]. Kansenshogaku Zasshi. 2000 Dec;74(12):1062-76.		
Li L, Cai B, Wang M, Zhu Y. [A multicenter study of efficacy and safety of oseltamivir in treatment of naturally acquired influenza]. Zhonghua Nei Ke Za Zhi. 2001 Dec;40(12):838-42.		

Title	Exclusion	Reason for exclusion
Li L, Cai B, Wang M, Zhu Y. A double-blind, randomized, placebo-controlled multicenter study of oseltamivir phosphate for treatment of influenza infection in China. Chin Med J (Engl). 2003 Jan;116(1):44-8.		
Makela MJ, Pauksens K, Rostila T, Fleming DM, Man CY, Keene ON, et al. Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomized, double-blind, placebo-controlled European study. J Infect. 2000 Jan;40(1):42-8.		
Matsumoto K, Ogawa N, Nerome K, Numazaki Y, Kawakami Y, Shirato K, et al. Safety and efficacy of the neuraminidase inhibitor zanamivir in treating influenza virus infection in adults: results from Japan. GG167 Group. Antivir Ther. 1999;4(2):61-8.		
Monto AS, Fleming DM, Henry D, de Groot R, Makela M, Klein T, et al. Efficacy and safety of the neuraminidase inhibitor zanamivirin the treatment of influenza A and B virus infections. J Infect Dis. 1999 Aug;180(2):254-61.		
Monto AS, Robinson DP, Herlocher ML, Hinson JM, Jr., Elliott MJ, Crisp A. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. Jama. 1999 Jul 7;282(1):31-5.		
Nicholson KG, Aoki FY, Osterhaus AD, Trottier S, Carewicz O, Mercier CH, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. Lancet. 2000 May 27;355(9218):1845-50.		
Puhakka T, Lehti H, Vainionpaa R, Jormanainen V, Pulkkinen M, Sharp S, et al. Zanamivir: a significant reduction in viral load during treatment in military conscripts with influenza. Scand J Infect Dis. 2003;35(1):52-8.		
Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. Jama. 2000 Feb 23; 283(8):1016-24.		
Welliver R, Monto AS, Carewicz O, Schatteman E, Hassman M, Hedrick J, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. Jama. 2001 Feb 14;285(6):748-54.		
Barroso L, Treanor J, Gubareva L, Hayden FG. Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomized, controlled trials for prophylaxis and treatment. Antivir Ther. 2005;10(8):901-10.	exclusion	Experimental
Boivin G, Osterhaus AD, Gaudreau A, Jackson HC, Groen J, Ward P. Role of picornaviruses in flu-like	exclusion	No efficacy study

Title	Exclusion	Reason for exclusion
illnesses of adults enrolled in an oseltamivir treatment study who had no evidence of influenza virus infection. J Clin Microbiol. 2002 Feb;40(2):330-4.		
Calfee DP, Peng AW, Hussey EK, Lobo M, Hayden FG. Safety and efficacy of once daily intranasal zanamivir in preventing experimental human influenza A infection. Antivir Ther. 1999;4(3):143-9.	exclusion	Experimental
Cass LM, Brown J, Pickford M, Fayinka S, Newman SP, Johansson CJ, et al. Pharmacoscintigraphic evaluation of lung deposition of inhaled zanamivir in healthy volunteers. Clin Pharmacokinet. 1999;36 Suppl 1:21-31.	exclusion	Volunteers
Cass LM, Efthymiopoulos C, Bye A. Pharmacokinetics of zanamivir after intravenous, oral, inhaled or intranasal administration to healthy volunteers. Clin Pharmacokinet. 1999;36 Suppl 1:1-11.	exclusion	Pharmacokinetics
Cass LM, Efthymiopoulos C, Marsh J, Bye A. Effect of renal impairment on the pharmacokinetics of intravenous zanamivir. Clin Pharmacokinet. 1999;36 Suppl 1:13-9.	exclusion	Pharmacokinetics
Cass LM, Gunawardena KA, Macmahon MM, Bye A. Pulmonary function and airway responsiveness in mild to moderate asthmatics given repeated inhaled doses of zanamivir. Respir Med. 2000 Feb;94(2):166-73.	exclusion	No clinical outcomes
Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner D, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. Bmj. 2003 Jun 7;326(7401):1235.		
Cox RJ, Mykkeltvedt E, Sjursen H, Haaheim LR. The effect of zanamivir treatment on the early immune response to influenza vaccination. Vaccine. 2001 Sep 14;19(32):4743-9.		
Deng WW, Li QY, Zhong NS. [A multicenter study of efficacy and safety of oseltamivir in the treatment of suspected influenza patients]. Zhonghua Yi Xue Za Zhi. 2004 Dec 17;84(24):2132-6.	exclusion	Article in Chinese
Diggory P, Fernandez C, Humphrey A, Jones V, Murphy M. Comparison of elderly people's technique in using two dry powder inhalers to deliver zanamivir: randomised controlled trial. Bmj. 2001 Mar 10;322(7286):577-9.	exclusion	No clinical outcome
Fritz RS, Hayden FG, Calfee DP, Cass LM, Peng AW, Alvord WG, et al. Nasal cytokine and chemokine responses in experimental influenza A virus infection: results of a placebo-controlled trial of intravenous zanamivir treatment. J Infect Dis. 1999 Sep;180(3):586-93	exclusion	No clinical outcome, experimental
Gubareva LV, Kaiser L, Matrosovich MN, Soo-Hoo Y, Hayden FG. Selection of influenza virus mutants in experimentally infected volunteers treated with oseltamivir. J Infect Dis. 2001 Feb 15;183(4):523-31.	exclusion	Experimental

Title	Exclusion	Reason for exclusion
Hayden FG, Gubareva LV, Monto AS, Klein TC, Elliot MJ, Hammond JM, et al. Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. N Engl J Med. 2000 Nov 2;343(18):1282-9.		
Hayden FG, Jennings L, Robson R, Schiff G, Jackson H, Rana B, et al. Oral oseltamivir in human experimental influenza B infection. Antivir Ther. 2000 Sep;5(3):205-13.	exclusion	Experimental influenza
Hayden FG, Treanor JJ, Betts RF, Lobo M, Esinhart JD, Hussey EK. Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. Jama. 1996 Jan 24-31;275(4):295-9.	exclusion	Experimental
Hayden FG, Treanor JJ, Fritz RS, Lobo M, Betts RF, Miller M, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. Jama. 1999 Oct 6;282(13):1240-6.	exclusion	Experimental
Hedrick JA, Barzilai A, Behre U, Henderson FW, Hammond J, Reilly L, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. Pediatr Infect Dis J. 2000 May;19(5):410-7.		
Hill G, Cihlar T, Oo C, Ho ES, Prior K, Wiltshire H, et al. The anti-influenza drug oseltamivir exhibits low potential to induce pharmacokinetic drug interactions via renal secretion-correlation of in vivo and in vitro studies. Drug Metab Dispos. 2002 Jan;30(1):13-9.	exclusion	Pharmacokinetics
Hu SL, Lin JT, Yu XZ, Wang AX, Zhu JH, Cui DJ, et al. [Cost effectiveness analysis of oseltamivir phosphorus in the treatment of influenza]. Zhonghua Yi Xue Za Zhi. 2004 Oct 2;84(19):1664-7.	exclusion	Article in Chinese, not applicable in Belgian context
Ison MG, Gnann JW, Jr., Nagy-Agren S, Treannor J, Paya C, Steigbigel R, et al. Safety and efficacy of nebulized zanamivir in hospitalized patients with serious influenza. Antivir Ther. 2003 Jun;8(3):183-90.		
Johnston SL, Ferrero F, Garcia ML, Dutkowski R. Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. Pediatr Infect Dis J. 2005 Mar;24(3):225-32.		
Kaiser L, Fritz RS, Straus SE, Gubareva L, Hayden FG. Symptom pathogenesis during acute influenza: interleukin-6 and other cytokine responses. J Med Virol. 2001 Jul;64(3):262-8.	exclusion	Immune response, no clinical outcomes
Kaiser L, Keene ON, Hammond JM, Elliott M, Hayden FG. Impact of zanamivir on antibiotic use for respiratory events following acute influenza in adolescents and adults. Arch Intern Med. 2000 Nov 27;160(21):3234-40.		
Lalezari J, Campion K, Keene O, Silagy C. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. Arch Intern Med. 2001 Jan		

Title	Exclusion	Reason for exclusion
22;161(2):212-7.		
Lin JT, Yu XZ, Cui DJ, Chen XY, Zhu JH, Wang YZ, et al. A multicentre, randomized, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population. Curr Med Res Opin. 2006 Jan;22(1):75-82.		
Massarella JW, He GZ, Dorr A, Nieforth K, Ward P, Brown A. The pharmacokinetics and tolerability of the oral neuraminidase inhibitor oseltamivir (Ro 64-0796/GS4104) in healthy adult and elderly volunteers. J Clin Pharmacol. 2000 Aug;40(8):836-43.	exclusion	Pharmacokinetics
Mauskopf JA, Cates SC, Griffin AD, Neighbors DM, Lamb SC, Rutherford C. Cost effectiveness of zanamivir for the treatment of influenza in a high risk population in Australia. Pharmacoeconomics. 2000 Jun;17(6):611-20.	exclusion	Cost-effectiveness in other countries difficult to extrapolate
Monto AS, Pichichero ME, Blanckenberg SJ, Ruuskanen O, Cooper C, Fleming DM, et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. J Infect Dis. 2002 Dec 1;186(11):1582-8.		
Monto AS, Webster A, Keene O. Randomized, placebo-controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. J Antimicrob Chemother. 1999 Nov;44 Suppl B:23-9.		
Oo C, Barrett J, Hill G, Mann J, Dorr A, Dutkowski R, et al. Pharmacokinetics and dosage recommendations for an oseltamivir oral suspension for the treatment of influenza in children. Paediatr Drugs. 2001;3(3):229-36.	exclusion	Pharmacokinetics
Oo C, Snell P, Barrett J, Dorr A, Liu B, Wilding I. Pharmacokinetics and delivery of the anti-influenza prodrug oseltamivir to the small intestine and colon using site-specific delivery capsules. Int J Pharm. 2003 May 12;257(1-2):297-9.	exclusion	Pharmacokinetics
Peng AW, Hussey EK, Moore KH. A population pharmacokinetic analysis of zanamivir in subjects with experimental and naturally occurring influenza: effects of formulation and route of administration. J Clin Pharmacol. 2000 Mar;40(3):242-9.	exclusion	Pharmacokinetics
Peng AW, Milleri S, Stein DS. Direct measurement of the anti-influenza agent zanamivir in the respiratory tract following inhalation. Antimicrob Agents Chemother. 2000 Jul;44(7):1974-6.	exclusion	No clinical outcome
Peters PH, Jr., Gravenstein S, Norwood P, De Bock V, Van Couter A, Gibbens M, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. J Am Geriatr Soc. 2001 Aug;49(8):1025-31.		

Title	Exclusion	Reason for exclusion
Sato M, Hosoya M, Kato K, Suzuki H. Viral shedding in children with influenza virus infections treated with neuraminidase inhibitors. Pediatr Infect Dis J. 2005 Oct;24(10):931-2.		
Schilling M, Povinelli L, Krause P, Gravenstein M, Ambrozaitis A, Jones HH, et al. Efficacy of zanamivir for chemoprophylaxis of nursing home influenza outbreaks. Vaccine. 1998 Nov;16(18):1771-4.		
Snell P, Oo C, Dorr A, Barrett J. Lack of pharmacokinetic interaction between the oral anti-influenza neuraminidase inhibitor prodrug oseltamivir and antacids. Br J Clin Pharmacol. 2002 Oct;54(4):372-7.	exclusion	Pharmacokinetics
Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. Health Technol Assess. 2003;7(35):iii-iv, xi-xiii, 1-170.		
Vallee JP. [Flu and antiviral agents....]. Presse Med. 2000 Jan 22;29(2):84-5.		
Walker JB, Hussey EK, Treanor JJ, Montalvo A, Jr., Hayden FG. Effects of the neuraminidase inhibitor zanamavir on otologic manifestations of experimental human influenza. J Infect Dis. 1997 Dec;176(6):1417-22.	exclusion	Experimental influenza
Webster A, Boyce M, Edmundson S, Miller I. Coadministration of orally inhaled zanamivir with inactivated trivalent influenza vaccine does not adversely affect the production of antihaemagglutinin antibodies in the serum of healthy volunteers. Clin Pharmacokinetic.1999;36 Suppl 1:51-8.		
Whitley RJ, Hayden FG, Reisinger KS, Young N, Dutkowski R, Ipe D, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J. 2001 Feb;20(2):127-33.		
Zambon M, Hays J, Webster A, Newman R, Keene O. Diagnosis of influenza in the community: relationship of clinical diagnosis to confirmed virological, serologic, or molecular detection of influenza. Arch Intern Med. 2001 Sep 24;161(17):2116-22.	exclusion	Not on antiviral drugs
Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet. 2006 Jan 28;367(9507):303-13.		
Lin JT, Yu XZ, Cui DJ, Chen XY, Zhu JH, Wang YZ, et al. [A multicenter randomized controlled study of the efficacy and safety of oseltamivir in the treatment of influenza in a high risk population]. Zhonghua Jie He He Hu Xi Za Zhi. 2004 Jul;27(7):455-9.	exclusion	In Chinese; published in English in Curr Med Res Opin. 2006 Jan;22(1):75-82.
Calfee DP, Peng AW, Hussey EK, Lobo M, Hayden FG. Safety and efficacy of once daily intranasal zanamivir in preventing experimental human influenza A infection Antimicrob Agents Chemother. 1999 Jul;43(7):1616-20	exclusion	Experimental, also published in Antivir Ther. 1999;4(3):143-9.

Title	Exclusion	Reason for exclusion
Bardsley-Elliot A NS. Oseltamivir. Drugs. 1999. 58(5):851-60.	exclusion	No original study
Hayden F, Reisinger K, Withley R. The impact of oseltamivir treatment on upper and lower respiratory tract complications of acute influenza in chilrdren. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2000;16(Suppl 31).	exclusion	Same study as [28]
Kashiwagi S, Kudoh S, Watanabe A. [Clinical efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir in treating acute influenza--placebo-controlled double-blind multicenter phase III trial]. [Japanese]. Kansenshogaku Zasshi Journal of the Japanese Association for Infectious Diseases. 1044;74(12):1044-61.	exclusion	Is second part of the trail already reported on in[70]
Lin J et al. A multicenter study of efficacy and safety of oseltamivir in the treatment of influenza in the high risk population [Abstract]. Respirology. 2004;9(Suppl).	exclusion	Only abstract. Published as [71]
Martin C, Mahoney P. Oral oseltamivir reduces illness and is safe in patients with chronic cardiac and /or respiratory disease. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2000; 16(Suppl 31).	exclusion	Abstract only
Oo C, Barret J. Lack of pharmacokinetic interaction between the oral anti-influenza prodrug oseltamivir and aspirin. Antimicrobial Agents & Chemotherapy. 1993; 46(6):1993-5.	exclusion	Experimental – volunteers
Pappas D, Owen Hendley J. Otitis media. A scholarly review of the evidence. Minerva pediatrica. 2003; 55(5):407-14.	exclusion	Not on antiviral drugs
Singh S, Barghoorn J. Bagdonas A. Clinical benfits with oseltamivir in treating influenza in adult populations: results of a pooled and subgroup analysis. Clinical Drug Investigation. 2003; 23(9):561-9.		
Tan W. A Randomized, Double-blinded and Controlled Clinical Evaluation of Oseltamivir in the Treatment of Influenza. Clinical Medical Journal of China. 2002; 9(5):528-31.	exclusion	No abstract – in chinese
Whitley Rj, Reisinger K. S. Hayden F. G. Oral oseltamivir is effective and safe in the treatment of influenza virus infections in children. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2000. 16(Suppl 31).	exclusion	Is published in [28]
Yanagawa Y, Ogura M. Fujimoto E. Effects and cost of glycyrrhizin in the treatment of upper respiratory tract infections in members of the Japanese maritime self-defense force: preliminary report of a prospective, randomized, double-blind, controlled, parallel-group, alternate-day treatment assignment clinical trial. Current Therapeutic Research, Clinical & Experimental. 2004; 65(1):26-33.	exclusion	Not on study subject
Anonymous. Zanamivir: a second look. Still no tangible impact on influenza. Prescrire international. 2001.10(56):175-7.		

Title	Exclusion	Reason for exclusion
Berger W. Effect of inhaled zanamivir on pulmonary function and illness duration in asthma and/or chronic obstructive pulmonary disease copd patients with influenza. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology Vol. 2001 86		
Calfee D. Protective efficacy of reduced frequency dosing of intranasal Zanamivir in experimental human influenza. 38th Interscience Conference of Antimicrobial Agents and Chemotherapy. 1998.	exclusion	Experimental
Calfee D. Safety and efficacy of intravenous zanamivir in preventing experimental human influenza A virus infection. Antimicrobial agents and chemotherapy. 1616 43(7):1616-20.	exclusion	Pharmacokinetics
Campion. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. Lancet. 352(9144):1877-81.	exclusion	Double; same study as [72]
Fleming D, et al. 'High Risk" and Otherwise Healthy Patients Demonstrate Alleviation of Influenza Symptoms 2.5 Days Earlier Following Inhaled Zanamivir Treatment (abstract). Infectious Diseases Society of America. 1998.		
Hirji Z. Utility of zanamivir for chemoprophylaxis of concomitant influenza A and B in a complex continuing-care population. Canada communicable disease report = Releve des maladies transmissibles au Canada. 2001. 27(3):21-4.	exclusion	No RCT study design
Murphy Kr Efficacy and safety of inhaled zanamivir for the treatment of influenza in patients with asthma or chronic obstructive pulmonary disease: A double-blind, randomised, placebo-controlled, multicentre study. Clinical Drug Investigation. 2000;20(5):337-49.		
Silagy C, et al. Impact of Zanamivir on Health Status, Productivity and Health Care Resource Use in Patients with Influenza (abstract). Infectious Diseases Society of America. 1998.	exclusion	Same as [72]
Matheson, NJ. Symmonds-Abrahams, M. Sheikh, A. Shepperd, S. Harnden, A. Neuraminidase inhibitors for preventing and treating influenza in children. [Systematic Review] Cochrane Acute Respiratory Infections Group Cochrane Database of Systematic Reviews. 2006 Issue 4		
Ambrozaitis A VEG, Rubinstein E. Inhaled zanamivir versus placebo for the prevention of influenza outbreaks in an unvaccinated long-term care population. J AM GERIATR SOC 2001;49(4):S130-S1.		
Ambrozaitis A, Gravenstein S, van Essen GA, et al. Inhaled Zanamivir Versus Placebo for the Prevention of Influenza Outbreaks in an Unvaccinated Long-term Care Population. Journal of the American Medical Directors Association. 2005 Nov-Dec;6(6):367-74.		

4.1.2 Search for guidelines

4.1.2.1 Search in Pubmed

MEDLINE/PUBMED	neuraminidase inhibitors in seasonal influenza
Search terms	"GS 4071"[Substance Name] OR oseltamivir[Text Word]) OR ("zanamivir"[Substance Name] OR zanamivir[Text Word]) AND Practice Guideline[ptyp]
TOTAL	6 references

Table A1.3: Results of search in Pubmed for practice guidelines on use of NAIs in seasonal influenza with reason for exclusion

Practice guidelines in Pubmed	Exclusion	Reason for exclusion
Statement on influenza vaccination for the 2005-2006 season. An advisory committee statement. Can Commun Dis Rep. 2005 Jun 1531(ACS-6):1-30.	no	
Barnett D. Clinical effectiveness and cost effectiveness of zanamivir (Relenza): translating the evidence into clinical practice, a National Institute for Clinical Excellence view. Philos Trans R Soc Lond B Biol Sci. 2001 Dec 29;356(1416):1899-903.	yes	Double with NICE guidelines on the topic
Bridges CB, Fukuda K, Uyeki TM, Cox NJ, Singleton JA. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2002 Apr 12;51(RR-3):1-31.	yes	Too old/ newer version to search for
Preboth M. ACIP releases guidelines on the prevention and control of influenza. Advisory Committee on Immunization Practices. Am Fam Physician. 2001 Oct 1; 64(7):1270, 2-5.	yes	Too old, based on ACIP recommendation
Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R. Guidelines for preventing health-care--associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep. 2004 Mar 26;53(RR-3):1-36.	yes	Not on research topic
Wutzler P, Kossow KD, Lode H, Ruf BR, Scholz H, Vogel GE. Antiviral treatment and prophylaxis of influenza in primary care: German recommendations. J Clin Virol. 2004 Oct 31(2):84-91.	no	

4.1.2.2 Guidelines search from our neighbouring countries and international guideline developers

Via the world wide web guidelines were searched on the topic. Not all of our neighbouring countries have guidance on the appropriate use of antiviral drugs in seasonal influenza. Hereunder a list of the guidelines with comments on relevance to the research question.

Belgium

Preventie van Influenza. Aanbeveling voor geode medische praktijkvoering. Domus Medica 2005 (www.domusmedica.be)

The Netherlands

GR: pandemie plan: Antivirale middelen bij een grieppandemie: no information on seasonal influenza

http://www.gr.nl/adviezen.php?ID=909

LCI: Landelijke Coordinatiestructuur Infectieziektenbestrijding

Protocol infectieziekten: Influenza

http://www.infectieziekten.info/index.php3

Nederlands Huisartsengenootschap (NHG)

- NHG-standpunt 'Voorschrijven van virusremmers bij (vogel)griep' – oktober 2005 http://nhg.artsennet.nl/content/resources/AMGATE_6059_104_TICH_L710416610/AMGATE_6059_104_TICH_R161011550547557
- NHG-standpunt 'Wat te doen bij influenza door het Fujian-virus? – December 2003' http://nhg.artsennet.nl/content/resources//AMGATE_6059_104_TICH_R127659868430694
- Standaard Influenza 'Influenza en Influenzavaccinatie' – December 1996: no information on use of NAIs http://nhg.artsennet.nl/upload/104/standaarden/M35/start.htm

Germany

Wutzler P, Kossow KD, Lode H, Ruf BR, Scholz H, Vogel GE. Antiviral treatment and prophylaxis of influenza in primary care: German recommendations. J Clin Virol. 2004 Oct 31(2):84-91.

Luxemburg

http://www.ms.etat.lu/MIN_SANT/Publication/Grippe/recommandations.htm: no information on the use of antivirals

France

- Institut de veille sanitaire http://www.invs.sante.fr/surveillance/grippe_dossier/default.htm
- Guidance on procedures to be followed in a long term care facility are made available by the High Commissioner of Public Hygiene of the French Republic http://www.sante.gouv.fr/htm/dossiers/grippe_collectivite/protocole.htm
- Haute Autorité de Santé : no information on the use of antivirals http://www.anaes.fr/anaes/anaesparametrage.nsf/Page?ReadForm&Section=/anaes/anaesparametrage.nsf/accueilpresentation?readform&Defaut=y&

UK

- NICE: Flu prevention - amantadine and oseltamivir: http://www.nice.org.uk/page.aspx?o=TA67; Flu treatment - zanamivir (review), amantadine and oseltamivir: http://www.nice.org.uk/guidance/TA58
- SIGN: no information: http://www.sign.ac.uk/

New Zealand

New Zealand Guidelines Group: no information http://www.nzgg.org.nz/index.cfm?screensize=other&ScreenResSet=yes&CFTOKEN

CDC

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm

WHO

http://www.who.int/mediacentre/factsheets/fs211/en/

4.1.2.3 Additional references obtained using INAHTA/GIN network (request for information by KCE).

Canadian Agency for Drugs and Technologies in Health (CADTH)

- Oseltamivir and Zanamivir for the Prevention of Influenza – August 31, 2006
- Neuraminidase inhibitors and M2 channel blockers for the prophylaxis and treatment of influenza – April 27, 2006: not a recommendation

Uhnoo I, Linde A, Pauksens K, Lindberg A, Eriksson M, Norrby R; Swedish Consensus Group. Treatment and prevention of influenza: Swedish recommendations.Scand J Infect Dis. 2003;35(1):3-11.

Table A1.4: Results of the guideline search without excluded guidelines

Guidelines on use of neuraminidase inhibitors in seasonal influenza
Statement on influenza vaccination for the 2005-2006 season. An advisory committee statement. Can Commun Dis Rep. 2005 Jun 15 31(ACS-6):1-30
LCI: Landelijke Coordinatiestructuur Infectieziektenbestrijding, Nederland - Protocol infectieziekten: Influenza
http://www.infectieziekten.info/index.php3
Nederlands Huisartsen Genootschap: NHG-standpunt 'Voorschrijven van virusremmers bij (vogel)griep' – oktober 2005 http://nhg.artsennet.nl/content/resources/AMGATE_6059_104_TICH_L710416610/AMGATE_6059_104_TICH_R161011550547557
Nederlands Huisartsen Genootschap: NHG-standpunt 'Wat te doen bij influenza door het Fujian-virus? – December 2003 http://nhg.artsennet.nl/content/resources//AMGATE_6059_104_TICH_R127659868430694
France - Grippe saisonnière
http://www.invs.sante.fr/surveillance/grippe_dossier/default.htm
UK - NICE
Flu prevention -Amantadine and oseltamivir 2003 http://www.nice.org.uk/page.aspx?o=TA67
Flu treatment - zanamivir - amantadine - oseltamivir update 2005 http://www.nice.org.uk/guidance/TA58
CDC
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm
WHO
http://www.who.int/mediacentre/factsheets/fs211/en/
Canadian Agency for Drugs and Technologies in Health (CADTH) Oseltamivir and Zanamivir for the Prevention of Influenza – August 31, 2006
Germany Wutzler P, Kossow KD, Lode H, Ruf BR, Scholz H, Vogel GE. Antiviral treatment and prophylaxis of influenza in primary care: German recommendations. J Clin Virol. 2004 Oct. 31(2):84-91.
Uhnoo I, Linde A, Pauksens K, Lindberg A, Eriksson M, Norrby R; Swedish Consensus Group. Treatment and prevention of influenza: Swedish recommendations. Scand J Infect Dis. 2003;35(1):3-11.
Govaerts F, Van de Vyver N, Pilaet A. Preventie van Influenza. Aanbeveling voor goede medische praktijkvoering. Domus Medica. 2005.

4.2 APPENDIX 2. QUALITY APPRAISAL OF THE RCTS AND THE META-ANALYSES

Table A2.1. Results of the search for RCTs and MA with quality appraisal information (RCTs appraised by Turner and Matheson were not re-appraised by the research team)

Reference	Quality appraisal in Jefferson or Matheson (between brackets if after appraisal status changed)	Quality appraisal by research group and reason for not valid
Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Lancet. 1998 Dec 12;352(9144):1877-81.	Yes	
Aoki FY, Fleming DM, Griffin AD. Impact of zanamivir treatment on productivity, health status and healthcare resource use in patients with influenza. Zanamivir Study Group. Pharmacoeconomics. 2000 Feb;17(2):187-95.	Yes	
Boivin G, Goyette N, Hardy I. Rapid antiviral effect of inhaled zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults. J Infect Dis. 2000 Apr;181(4):1471-4.	Yes	
Hayden FG, Atmar RL, Schilling M. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. N Engl J Med. 1999 Oct 28;341(18):1336-43.	Yes	
Hayden FG, Belshe R, Villanueva C. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J Infect Dis. 2004 Feb 1;189(3):440-9.	Yes	
Hayden FG, Osterhaus AD, Treanor JJ. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. GG167 Influenza Study Group. N Engl J Med. 1997 Sep 25;337(13):874-8	Yes	
Kaiser L, Henry D, Flack NP. Short-term treatment with zanamivir to prevent influenza: results of a placebo-controlled study. Clin Infect Dis. 2000 Mar;30(3):587-9.	Yes	
Kaiser L, Wat C, Mills T. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med. 2003 Jul	Yes	

Reference	Quality appraisal in Jefferson or Matheson (between brackets if after appraisal status changed)	Quality appraisal by research group and reason for not valid
28;163(14):1667-72.		
Kashiwagi S, Kudoh S, Watanabe A. [Efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir for prophylaxis against influenza--placebo-controlled double-blind multicenter phase III trial]. Kansenshogaku Zasshi. 2000 Dec;74 (12):1062-76.	Yes	
Li L, Cai B, Wang M, Zhu Y. [A multicenter study of efficacy and safety of oseltamivir in treatment of naturally acquired influenza]. Zhonghua Nei Ke Za Zhi. 2001 Dec;40(12):838-42.	Yes	
Makela MJ, Pauksens K, Rostila T. Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomized, double-blind, placebo-controlled European study. J Infect. 2000 Jan;40(1):42-8.	Yes	
Matsumoto K, Ogawa N, Nerome K. Safety and efficacy of the neuraminidase inhibitor zanamivir in treating influenza virus infection in adults: results from Japan. GG167 Group. Antivir Ther. 1999;4(2):61-8.	Yes	
Monto AS, Fleming DM, Henry D. Efficacy and safety of the neuraminidase inhibitor zanamivirin the treatment of influenza A and B virus infections. J Infect Dis. 1999 Aug;180(2):254-61.	Yes	
Monto AS, Robinson DP, Herlocher ML. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. Jama. 1999 Jul 7;282(1):31-5.	Yes	
Nicholson KG, Aoki FY, Osterhaus AD. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. Lancet. 2000 May 27;355(9218):1845-50.	Yes	
Puhakka T, Lehti H, Vainionpaa R. Zanamivir: a significant reduction in viral load during treatment in military conscripts with influenza. Scand J Infect Dis. 2003;35(1):52-8.	Yes	
Treanor JJ, Hayden FG, Vrooman PS. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. JAMA. 2000 Feb 23;283(8):1016-24.	Yes	

Reference	Quality appraisal in Jefferson or Matheson (between brackets if after appraisal status changed)	Quality appraisal by research group and reason for not valid
Welliver R, Monto AS, Carewicz O. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. Jama. 2001 Feb 14;285(6):748-54.	Yes	
Cooper NJ, Sutton AJ, Abrams KR. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. BMJ. 2003 Jun 7;326(7401):1235	No	valid
Cox RJ, Mykkeltvedt E, Sjursen H, Haaheim LR. The effect of zanamivir treatment on the early immune response to influenza vaccination. Vaccine. 2001 Sep 14;19(32):4743-9.	No	background information
Deng WW, Li QY, Zhong NS. [A multicenter study of efficacy and safety of oseltamivir in the treatment of suspected influenza patients]. Zhonghua Yi Xue Za Zhi. 2004 Dec 17;84(24):2132-6.	No	Not valid
Hayden FG, Gubareva LV, Monto AS. Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. N Engl J Med. 2000 Nov 2;343(18):1282-9.	No (yes)	Valid, based on study NAI 30010
Hedrick JA, Barzilai A, Behre U. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. Pediatr Infect Dis J. 2000 May;19(5):410-7.	No (yes, is study NAI 30028 in Turner)	Valid
Ison MG, Gnann JW, Jr., Nagy-Agren S. Safety and efficacy of nebulized zanamivir in hospitalized patients with serious influenza. Antivir Ther. 2003 Jun;8(3):183-90.	No	Not valid; intervention drug not commercialised
Johnston SL, Ferrero F, Garcia ML. Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. Pediatr Infect Dis J. 2005 Mar;24(3):225-32.	No (yes, in Matheson)	Valid study but underpowered to show significant results on primary outcomes
Kaiser L, Keene ON, Hammond JM. Impact of zanamivir on antibiotic use for respiratory events following acute influenza in adolescents and adults. Arch Intern Med. 2000 Nov 27;160(21):3234-40.	No	not valid; no systematic literature search, no quality appraisal of included studies,
Lalezari J, Campion K, Keene O. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. Arch	No	not valid; no systematic literature search; no quality

Reference	Quality appraisal in Jefferson or Matheson (between brackets if after appraisal status changed)	Quality appraisal by research group and reason for not valid
Intern Med. 2001 Jan 22;161(2):212-7.		appraisal of included studies
Lin JT, Yu XZ, Cui DJ, Chen XY. A multicentre, randomized, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population. Curr Med Res Opin. 2006 Jan;22(1):75-82.	No	Not valid, open label
Monto AS, Pichichero ME, Blanckenberg SJ. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. J Infect Dis. 2002 Dec 1;186(11):1582-8.	No (yes, publication based on study n° 30031 in Turner)	Valid
Monto AS, Webster A, Keene O. Randomized, placebo-controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. J Antimicrob Chemother. 1999 Nov;44 Suppl B:23-9.	No	Not valid, no randomisation of the patients pooled
Peters PH, Jr., Gravenstein S, Norwood P, De Bock V. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. J Am Geriatr Soc. 2001 Aug;49(8):1025-31.	No (yes, in Turner study WV 15825)	valid
Sato M, Hosoya M, Kato K, Suzuki H. Viral shedding in children with influenza virus infections treated with neuraminidase inhibitors. Pediatr Infect Dis J. 2005 Oct;24(10):931-2.	No	Background information; no data-extraction possible
Schilling M, Povinelli L, Krause P. Efficacy of zanamivir for chemoprophylaxis of nursing home influenza outbreaks. Vaccine. 1998 Nov;16(18):1771-4.	No	Not valid, no RCT
Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. Health Technol Assess. 2003;7(35):iii-iv, xi-xiii, 1-170.	No	Valid, same as study [73]
Vallee JP. [Flu and antiviral agents....]. Presse Med. 2000 Jan 22;29(2):84-5.	No	Not valid, no RCT
Webster A, Boyce M, Edmundson S, Miller I. Coadministration of orally inhaled zanamivir with inactivated trivalent influenza vaccine does not adversely affect the production of antihaemagglutinin antibodies in the serum of healthy volunteers. Clin Pharmacokinet. 1999;36 Suppl 1:51-8.	No	Not valid, no design for efficacy outcome (Phase I study)
Whitley RJ, Hayden FG, Reisinger KS. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J. 2001 Feb;20(2):127-33.	Yes	

Reference	Quality appraisal in Jefferson or Matheson (between brackets if after appraisal status changed)	Quality appraisal by research group and reason for not valid
Matheson, NJ. Symmonds-Abrahams. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database of Syst Rev. 2003(3):CD002744	No	valid
Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet. 2006 Jan 28;367(9507):303-13.	No	Valid
Anonymous. Zanamivir: a second look. Still no tangible impact on influenza. Prescrire international. 2001;10(56):175-7.	No	Not valid, no RCT
Berger W. Effect of inhaled zanamivir on pulmonary function and illness duration in asthma and/or chronic obstructive pulmonary disease copd patients with influenza. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology Vol. 2001 86	No	Not valid, insufficient information for data-extraction
Fleming D, et al. 'High Risk" and Otherwise Healthy Patients Demonstrate Alleviation of Influenza Symptoms 2.5 Days Earlier Following Inhaled Zanamivir Treatment (abstract). Infectious Diseases Society of America. 1998.	No	Double publication is same as [74]
Ambrozaitis A, Van Essen G, Rubinstein E. Inhaled zanamivir versus placebo for the prevention of influenza outbreaks in an unvaccinated long-term care population. J Am Geriatr Soc 2001;49(4):S130-S1.	No	Valid but doubtful clinical relevance as on not vaccinated population
Silagy C. Impact of Zanamivir on Health Status, Productivity and Health Care Resource Use in Patients with Influenza (abstract). Infectious Diseases Society of America. 1998.	No	Double publication, same study as [72]
Murphy K. Efficacy and safety of inhaled zanamivir for the treatment of influenza in patients with asthma or chronic obstructive pulmonary disease: A double-blind, randomised, placebo-controlled, multicentre study. Clinical Drug Investigation. 2000;20(5):337-49.	No (yes, in Turner study NAI 30008)	Valid
Singh S, Barghoorn J. Bagdonas A. Clinical benfits with oseltamivir in treating influenza in adult populations: results of a pooled and subgroup analysis. Clinical Drug Investigation. 2003; 23(9):561-9.	No	more recent MA analyses available
Ambrozaitis A, Gravenstein S, van Essen GA. Inhaled Zanamivir Versus Placebo for	No	Not found before deadline

Reference	Quality appraisal in Jefferson or Matheson (between brackets if after appraisal status changed)	Quality appraisal by research group and reason for not valid
the Prevention of Influenza Outbreaks in an Unvaccinated Long-term Care Population. Journal of the American Medical Directors Association. 2005 Nov-Dec;6(6):367-74.		(made available by the company after the deadline)

4.3 APPENDIX 3. QUALITY APPRAISAL OF THE GUIDELINES

#	GUIDELINE NAME	PUBLISHER	DATE	AGREE INSTRUMENT: standardized domain SCORES						RECOMMENDATION
				Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	
				Scope and purpose	Stakeholder involvement	Rigour of development	Clarity and presentation	Applicability	Editorial independence	
1	Statement on influenza Vaccination for the 2006 - 2007 season	CCDR - Public Health Agency Canada	2006	61%		7%				Unsure
2	Treatment and Prevention of Influenza: Swedish Recommendations	Uhnoo I, Linde A, Pauksens K, Lindberg A, Eriksson M, Norrby R. Swedish Recommendations. Scan J Infect Dis 35:3-11, 2003	2003	89%		24%				to be recommended
3	Flu Treatment - Zanamivir (review), amantadine and oseltamivir	NHS - NICE. Issue Date February 2003 - Review Date 2006	Reviewed in 2006	56%		38%				unsure recommendation
4	Flu Prevention- Amantadine and oseltamivir	NHS - NICE. Issue Date September 2003 - Review Date August 2006	Reviewed in 2006	56%		24%				unsure recommendation
5	Oseltamivir and Zanamivir for the prevention of Influenza	Canadian Agency for Drugs and Technologies in Health - Health Technology Inquiry Service. August 31e 2006	August 31st 2006	100%		76%				recommended
6	Prevention and Control of Influenza. Recommendations of the Advisory Committee on	Department of Health and Human Services CDC Atlanta. MMWR	July 28, 2006	72%		21%				unsure recommendation

#	GUIDELINE NAME	PUBLISHER	DATE	AGREE INSTRUMENT: standardized domain SCORES						RECOMMENDATION
				Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	
				Scope and purpose	Stakeholder involvement	Rigour of development	Clarity and presentation	Applicability	Editorial independence	
	Immunization Practices.									
7	Influenza	World Health Organisation Factsheet N°211	Revised March 2003	0%		0%				not recommended
8	Protocol infectieziekten: Influenza	Landelijke Coordinatiestructuur infectieziektenbestrijding	February 2003 AnnexIV February 2004	39%		14%				unsure recommendation
9	Grippe saisonnière	Institut de veille sanitaire - Ministère de la Santé et des Solidarités - France	Updated: 15 September 2006	17%		0%				not recommended
	Protocole de mise en place de la chimio-prophylaxie dans une collectivité de personnes à risque lors d'une épidémie de grippe, en période de circulation du virus grippal		Complement to circular N° 444 of 17 Septembre, 17th 2004							
10	Antiviral treatment and prophylaxis of influenza in primary care: German recommendations	Wutzler P et al. Journal of Clinical Virology 31 (2004) 84-91	May 2004	44%		12%				not recommended

#	GUIDELINE NAME	PUBLISHER	DATE	AGREE INSTRUMENT: standardized domain SCORES						RECOMMENDATION
				Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	
				Scope and purpose	Stakeholder involvement	Rigour of development	Clarity and presentation	Applicability	Editorial independence	
11	NHG-Standpunt 'Voorschrijven van virusremmers bij (vogel)griep	Nederlands Huisartsen Genootschap	October 2005	no scoring done		no scoring done				
12	Preventie van influenza	Domus Medica	2005	96%		87%				

4.4 APPENDIX 4. EVIDENCE TABLES FOR THE RCTS

Table A4.1. Characteristics and results of zanamivir treatment trials

Trial	Data source + extra information	Jadad score	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (days)	Follow-up (days)
NAIA2005 NAIB2005	Considered as one trial.[75]	4	Previously healthy adults of at least 13 years of age. Present within 48 hours after onset of symptoms. Influenza was confirmed to be circulating before recruitment started in each centre. There were no 'high-risk' individuals. vaccinated individuals were excluded from the study	144 placebo (inhaled + intranasal) 132 10 mg inhaled + placebo intranasal twice daily 141 10 mg inhaled + 6.4 mg intranasal twice daily	5	28
NAIB2007	[Ref.: GlaxoSmithKline database]	2	At least 13, 16 or 18 years old (depending on centre). Present within 48 hours after onset of symptoms. Note that ~13% of participants considered 'high risk'	183 placebo 188 10 mg inhaled twice daily 183 10 mg inhaled + 6.4 mg intranasal twice daily	5	5
NAIA2008 NAIB2008	Considered as one trial. Placebo group is 2 combined arms of placebo twice and placebo four times daily. [22]	4	Previously healthy persons at least 13 or 18 years old (depending on centre). Present within 48 hours after onset of symptoms. Note that 13% of participants considered 'high risk'. 0.8% of the study population were vaccinated	422 Placebo 419 10 mg inhaled + 6.4 mg intranasal twice daily 415 10 mg inhaled + 6.4 mg intranasal four times daily	5	21

Table A4.1. Characteristics and results of zanamivir treatment trials						
Trial	**Data source + extra information**	**Jadad score**	**Patient characteristics**	**Trial design arms (no. of patients in each arm)**	**Treatment duration (days)**	**Follow-up (days)**
NAIB3001	MIST-group[72]	5	Previously healthy persons at least 12 years old. Present within 36 hours after onset of symptoms. Influenza activity in area confirmed. Recruitment started when influenza activity was seen to be increasing. Note that 17% of participants considered 'high risk'. 6% of the study population were vaccinated	228 placebo 227 10 mg inhaled twice daily	5	28
NAIA3002	[Ref.: GlaxoSmithKline database]	2	Previously healthy persons at least 12 years old. Present within 48 hours after onset of symptoms. Note that 14% of participants considered 'high risk'.	365 placebo 412 10 mg inhaled twice daily	5	28
NAIB3002	Makela et al., [74]	5	At least 12 years old. Present within 48 hours after onset of symptoms. Recruitment started when influenza was known to be circulating locally. Note that 9% of participants considered 'high risk'. 4% of the study population were vaccinated	182 placebo 174 10 mg inhaled twice daily	5	28
NAI30008	Murphy et al., [26]	5	Persons with asthma or COPD, at least 12 years old. Recruitment started when	263 placebo 262 10 mg inhaled twice daily	5	28

Table A4.1. Characteristics and results of zanamivir treatment trials						
Trial	**Data source + extra information**	**Jadad score**	**Patient characteristics**	**Trial design arms (no. of patients in each arm)**	**Treatment duration (days)**	**Follow-up (days)**
			influenza was known to be circulating in the community. Present within 36 hours after onset of symptoms. 23% of the study population were vaccinated			
NAI30009	Hedrick et al., [27]	3	Previously healthy children 5–12 years old. Present within 36 hours after onset of symptoms. Recruitment started when influenza was known to be circulating in the community. Influenza was confirmed to be circulating before recruitment started in each centre. Note that 8% of participants considered 'high risk'. 2% of study population were vaccinated	247 placebo 224 10 mg inhaled twice daily	5	28
NAI30010	Analysis of index cases from a study set up to examine the prevention of transmission of influenza A and B within families Hayden et al., [76]	3	Eligible families were those with two to five members, including at least one adult and at least one child between 5 and 17 years old. Once laboratory confirmed influenza activity had been documented in the community, families in which one member contracted an ILI (the 'index case') began to take the study drug. The treatment trial consisted of the 'index cases' only. Present within 36 hours after onset of symptoms. Note that 7% of participants considered 'high risk'. 10% of the study population were vaccinated	158 placebo 163 10 mg inhaled twice daily	5	28

Table A4.2. Characteristics and results of zanamivir treatment trials										
Trial	**Median number of days to the alleviation of symptoms for 'healthy' individuals (ITT group)**					**Median number of days to the alleviation of symptoms for 'healthy' individuals in the zanamivir treatment trials (influenza positive group)**				
		Placebo Median (SE)	Inhaled 10 mg b.d. Median (SE)	Inhaled 10 mg b.d. and intranasal Median (SE)	Inhaled 10 mg b.d. vs placebo Median difference (95% CI)		Placebo Median (SE)	Inhaled 10 mg b.d. Median (SE)	Inhaled 10 mg b.d. and intranasal Median (SE)	Inhaled 10 mg b.d. vs placebo Median difference (95% CI)
NAIA2005 NAIB2005		[N = 144; R = 134]	[N = 132; R = 123]	[N = 141; R = NDA]			[N = 89; R = 83]	[N = 85; R = 80]	[N = NDA; R = NDA]	
	Published	5.0 (NDA)	5.0 (NDA)	4.0 (NDA)	NDA	Published	NDA	NDA	NDA	NDA
	Published re-analysis	4.5 (0.3)	3.5 (0.3)	NDA	–1.0 (–1.8 to –0.2)	Published re-analysis	4.5 (0.5)	3.5 (0.3)	NDA	–1.0 (–2.6 to 0.6)
NAIB2007		[N = 159; R = 35]	[N = 165; R = 57]	[N = NDA; R = NDA]			[N = 101; R = 22]	[N = 96; R = 33]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	NDA	NDA	NDA	NDA
	Published re-analysis	>3.5 (NDA)	>3.5 (NDA)	NDA	NDA	Published re-analysis	>3.5 (NDA)	>3.5 (NDA)	NDA	NDA
NAIA2008 NAIB2008	a	[N = NDA; R = NDA]		[N = NDA; R = NDA]		a	[N = NDA; R = NDA]		[N = NDA; R = NDA]	
	Published	NDA		NDA		Published	NDA		NDA	
	Published re-analysis	NDA		NDA		Published re-analysis	NDA		NDA	
NAIB3001	NAIB3001	[N = 189; R = 146]	[N = 190; R = 156]				[N = 132; R = 104]	[N = 137; R = 117]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	6.0 (0.3)	5.0 (0.4)		–1.0 (–1.9 to –0.1)	Published re-analysis	6.0 (0.4)	4.5 (0.2)		–1.5 (–2.7 to –0.3)
NAIA3002	NAIA3002	[N = 305; R = 266]	[N = 363; R = 323]				[N = 214; R = 190]	[N = 276; R = 245]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	5.0 (0.3)	5.0 (0.2)		0.0 (–0.7 to 0.7)	Published re-analysis	6.0 (0.3)	5.0 (0.2)		–1.0 (–5.3 to 3.3)
NAIB3002	NAIB3002	[N = 163; R = 133]	[N = 161; R = 142]				[N = 123; R = 101]	[N = 124; R = 111]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	6.5 (0.6)	5.0 (0.4)		–1.5 (–2.9 to –0.1)	Published re-analysis	6.5 (0.7)	5.0 (0.4)		–1.5 (–3.0 to 0.0)

Table A4.2. Characteristics and results of zanamivir treatment trials										
Trial	**Median number of days to the alleviation of symptoms for 'healthy' individuals (ITT group)**					**Median number of days to the alleviation of symptoms for 'healthy' individuals in the zanamivir treatment trials (influenza positive group)**				
NAI30008										
NAI30009										
NAI30010	NAI30010	[N = 149; R = 136]	[N = 151; R = 139]				[N = 75; R = 71]	[N = 72; R = 68]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	5.5 (0.4)	4.5 (0.2)		–1.0 (–1.9 to –0.1)	Published re-analysis	5.5 (0.3)	4.5 (0.2)		–1.0 (–2.3 to 0.3)
	NDA, no data available; b.d., twice daily (bis die); N, no. of individuals; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).					NDA = no data available; N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).				
	a Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.					a Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.				

Table A4.3. Characteristics and results of zanamivir treatment trials										
Trial	**Median number of days to the alleviation of symptoms for 'high-risk' individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to the alleviation of symptoms for 'high-risk' individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
NAIA2005 NAIB2005										
NAIB2007		[N = 24; R = 8]	[N = 23; R = 13]	[N = NDA; R = NDA]			[N = 17; R = 5]	[N = 17; R = 9]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	NDA	NDA	NDA	NDA
	Published re-analysis	>3.5 (NDA)	3.5 (0.4)	NDA	NDA	Published re-analysis	>3.5 (NDA)	3.5 (0.5)	NDA	NDA
NAIA2008 NAIB2008	a	[N = 68; R = NDA]		[N = 48; R = NDA]		a	[N = NDA; R = NDA]		[N = NDA; R = NDA]	
	Published	7.8 (NDA)		6.3 (NDA)		Published	NDA		NDA	
	Published re-analysis	NDA		NDA		Published re-analysis	NDA		NDA	
NAIB3001		[N = 39; R = 24]	[N = 37; R = 32]		–2.5 (–8.0 to 1.0);		[N = 28; R = 17]	[N = 24; R = 21]		–3.3 (–8.5 to 1.8);
	Published	8.0 (NDA)	5.5 (NDA)		p = 0.048	Published	8.3 (NDA)	5.0 (NDA)		p = 0.161
	Published re-analysis	7.0 (1.4)	5.0 (0.5)		–2.0 (–5.0 to 1.0)	Published re-analysis	8.0 (2.8)	5.0 (0.6)		–3.0 (–8.5 to 2.5)
NAIA3002		[N = 60; R = 53]	[N = 49; R = 42]				[N = 43; R = 38]	[N = 36; R = 32]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	6.0 (0.9)	7.5 (1.5)		1.5 (–1.9 to 4.9)	Published re-analysis	6.0 (1.1)	5.5 (1.8)		–0.5 (–4.7 to 3.7)
NAIB3002		[N = 19; R = 15]	[N = 13; R = 12]				[N = 18; R = 14]	[N = 12; R = 11]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	11.5 (1.4)	9.0 (3.0)		–2.5 (–9.0 to 4.0)	Published re-analysis	11.5 (1.6)	9.0 (2.2)		–2.5 (–7.8 to 2.8)

Table A4.3. Characteristics and results of zanamivir treatment trials										
Trial	**Median number of days to the alleviation of symptoms for 'high-risk' individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to the alleviation of symptoms for 'high-risk' individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
NAI30008		[N = 263; R = 222]	[N = 262; R = 226]				[N = 153; R = 134]	[N = 160; R = 142]		
	Published	7.0 (NDA)	6.0 (NDA)		NDA	Published	7.0 (NDA)	5.5 (NDA)		–1.5 (–3.3 to 0.5)
	Published re-analysis	6.5 (0.5)	5.5 (0.3)		–1.0 (–2.1 to 0.1)	Published re-analysis	7.0 (0.5)	5.0 (0.3)		–2.0 (–3.2 to –0.8)
NAI30009										
NAI30010		[N = 11; R = 11]	[N = 10; R = 9]				[N = 6; R = 6]	[N = 4; R = 4]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	6.5 (2.5)	5.8 (1.2)		–0.8 (–6.0 to 4.5)	Published re-analysis	10.5 (6.4)	4.3 (0.7)		–6.3 (–18.8 to 6.3)
	NDA. no data available; N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).					NDA, no data available; N = Number of individuals; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).				
	a Also compared with 40 mg inhaled + 25.6 mg intranasal (N = 42): median 5.0 [difference: –2.8 (–3.5 to –0.3)].					a Also compared with 40 mg inhaled + 25.6 mg intranasal (N = NDA): median NDA [difference: –3.0, p = 0.009].				

Table A4.4. Characteristics and results of zanamivir treatment trials										
Trial	**Median number of days to the alleviation of symptoms for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to the alleviation of symptoms for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
NAIA2005 NAIB2005		[N = 144; R = 134]	[N = 132; R = 123]	[N = 141; R = NDA]			[N = 89; R = 83]	[N = 85; R = 80]	[N = 88; R = NDA]	
	Published	5.0 (NDA)	5.0 (NDA)	4.0 (NDA)	0.0 (NDA)	Published	5.0 (NDA)	4.0 (NDA)	4.0 (NDA)	–1.0 (NDA);p = 0.05
	Published re-analysis	4.5 (0.3)	3.5 (0.3)	NDA	–1.0 (–1.8 to –0.2)	Published re-analysis	4.5 (0.5)	3.5 (0.3)	NDA	–1.0 (–2.1 to 0.1)
NAIB2007		[N = 183; R = 43]	[N = 188; R = 70]	[N = 183; R = NDA]			[N = 118; R = 27]	[N = 113; R = 42]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	NDA	NDA	NDA	NDA
	Published re-analysis	>3.5 (NDA)	>3.5 (NDA)	NDA	NDA	Published re-analysis	>3.5 (NDA)	>3.5 (NDA)	NDA	NDA
NAIA2008 NAIB2008	a	[N = 422; R = NDA]		[N = 419; R = NDA]		a	[N = 240; R = NDA]		[N = 241; R = NDA]	
	Published	7.0 (NDA)		6.0 (NDA)		Published	7.0 (NDA)		5.5 (NDA)	
	Published re-analysis	NDA		NDA		Published re-analysis	NDA		NDA	
NAIB3001		[N = 228; R = 170]	[N = 227; R = 188]				[N = 160; R = 121]	[N = 161; R = 138]		
	Published	6.5 (NDA)	5.0 (NDA)		–1.5 (–2.3 to –0.5); p = 0.011	Published	6.0 (NDA)	4.5 (NDA)		–1.5 (–2.3 to –0.5);p = 0.004
	Published re-analysis	6.0 (0.3)	5.0 (0.3)		–1.0 (–1.9 to –0.1)	Published re-analysis	6.0 (0.4)	4.5 (0.2)		–1.5 (–2.3 to –0.7)
NAIA3002		[N = 365; R = 319]	[N = 412; R = 365]				[N = 257; R = 228]	[N = 312; R = 277]		
	Published	NDA	NDA	NDA		Published	NDA	NDA		NDA
	Published re-analysis	5.5 (0.3)	5.0 (0.2)	–0.5 (–1.1 to 0.1)		Published re-analysis	6.0 (0.3)	5.0 (0.2)		–1.0 (–1.7 to –0.3)
NAIB3002		[N = 182; R = 148]	[N = 174; R = 154]				[N = 141; R = 115]	[N = 136; R = 122]		

Table A4.4. Characteristics and results of zanamivir treatment trials										
Trial	**Median number of days to the alleviation of symptoms for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to the alleviation of symptoms for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
	Published	7.5 (NDA)	5.0 (NDA)		–2.5 (–3.5 to –0.8); p < 0.001	Published	7.5 (NDA)	5.0 (NDA)		–2.5 (–4.0 to –1.0);p < 0.001
	Published re-analysis	7.0 (0.6)	5.0 (0.3)		–2.0 (–3.3 to –0.7)	Published re-analysis	7.5 (0.6)	5.0 (0.4)		–2.5 (–3.8 to –1.2)
NAI30008		[N = 263; R = 222]	[N = 262; R = 226]				[N = 153; R = 134]	[N = 160; R = 142]		
	Published	7.0 (NDA)	6.0 (NDA)		–1.0 (NDA); p = 0.123	Published	7.0 (NDA)	5.5 (NDA)		–1.5 (–3.3 to –0.5);p = 0.009
	Published re-analysis	6.5 (0.5)	5.5 (0.3)		–1.0 (–2.0 to 0.1)	Published re-analysis	7.0 (0.5)	5.0 (0.3)		–2.0 (–3.2 to –0.8)
NAI30009		[N = 247; R = 217]	[N = 224; R = 213]				[N = 182; R = 161]	[N = 164; R = 158]		
	Published	5.0 (NDA)	4.5 (NDA)		–0.5 (–1.5 to 0.0);p = 0.011	Published	5.3 (NDA)	4.0 (NDA)		–1.3 (–2.0 to –0.5);p < 0.001
	Published re-analysis	5.0 (0.2)	4.0 (0.2)		–1.0 (–1.5 to –0.5)	Published re-analysis	5.0 (0.2)	4.0 (0.2)		–1.0 (–1.6 to –0.4)
NAI30010		[N = 158; R = 145]	[N = 163; R = 150]				[N = 81; R = 77]	[N = 76; R = 72]		
	Published	NDA	NDA		NDA	Published	7.5 (NDA)	5.0 (NDA)		P = 0.01
	Published re-analysis	5.5 (0.4)	4.5 (0.3)		–1.0 (–2.0 to 0.0)	Published re-analysis	5.5 (0.4)	4.5 (0.2)		–1.0 (–1.9 to –0.1)
	NDA, no data available; N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).					NDA, no data available; N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).				
	a Also compared with 40 mg inhaled + 25.6 mg intranasal (N = 415): median 6.0 [difference: –1.0 (–2.0 to 0.0)].					a Also compared with 40 mg inhaled + 25.6 mg intranasal (N = 241): median 5.5 [difference: –1.5 (–2.0 to 0.0)].				

Table A4.5.										
Trial	**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
NAIA2005 NAIB2005		[N = 144; R = 129]	[N = 132; R = 121]	[N = NDA; R = NDA]			[N = 89; R = 78]	[N = 85; R = 76]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	4.0 (NDA)	4.0 (NDA)	NDA	0.0 (NDA)
	Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)	Published re-analysis	3.5 (0.3)	3.5 (0.4)	NDA	0.0 (–0.9 to 0.9)
NAIB2007		[N = 159; R = 88]	[N = 165; R = 94]	[N = NDA; R = NDA]			[N = 101; R = 53]	[N = 96; R = 52]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	NDA	NDA	NDA	NDA
	Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)	Published adjusted	3.5 (0.3)	3.5 (0.3)	NDA	0.0 (–0.8 to 0.8)
NAIA2008 NAIB2008		[N = NDA; R = NDA]		[N = 239; R = NDA]		a	[N = NDA; R = NDA]		[N = NDA; R = NDA]	
	Published	NDA		NDA		Published	NDA		NDA	
	Published re-analysis	NDA		NDA		Published re-analysis	NDA		NDA	
NAIB3001		[N = 189; R = 128]	[N = 190; R = 150]				[N = 132; R = 93]	[N = 137; R = 112]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	8.0 (0.4)	7.0 (0.3)		–1.0 (–2.0 to 0.0)	Published re-analysis	8.0 (0.5)	7.0 (0.3)		–1.0 (–2.2 to 0.2)
NAIA3002		[N = 305; R = 233]	[N = 363; R = 292]				[N = 214; R = 165]	[N = 276; R = 222]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	6.5 (0.3)	6.5 (0.3)		0.0 (–0.8 to 0.8)	Published re-analysis	7.0 (0.3)	6.5 (0.3)		–0.5 (–1.4 to 0.4)
NAIB3002		[N = 163; R = 113]	[N = 161; R = 123]				[N = 123; R = 87]	[N = 124; R = 96]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-	8.0 (0.6)	6.0 (0.4)		–2.0 (–3.4 to –0.6)	Published re-	8.5 (0.7)	6.5 (0.5)		–2.0 (–3.6 to –0.4)

Table A4.5.										
Trial	**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
	analysis					analysis				
NAI30008										
NAI30009										
NAI30010	NAI30010	[N = 149; R = 145]	[N = 151; R = 146]				[N = 75; R = 74]	[N = 72; R = 71]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	4.5 (0.3)	3.5 (0.3)		–1.0 (–1.8 to –0.2)	Published re-analysis	5.0 (0.3)	4.5 (0.3)		–0.5 (–1.3 to 0.3)
	NDA, no data available; N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).					NDA, no data available; N, no. of individuals; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).				
	a Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.					a Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.				

Table A4.6. Characteristics and results of zanamivir treatment trials										
Trial	**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	Placebo Median (SE)	Inhaled 10 mg b.d. Median (SE)	Inhaled 10 mg b.d. and intranasal Median (SE)	Inhaled 10 mg b.d. vs placebo Median difference (95% CI)	Trial	Placebo Median (SE)	Inhaled 10 mg b.d. Median (SE)	Inhaled 10 mg b.d. and intranasal Median (SE)	Inhaled 10 mg b.d. vs placebo Median difference (95% CI)
NAIA2005 NAIB2005		[N = 144; R = 129]	[N = 132; R = 121]	[N = NDA; R = NDA]			[N = 89; R = 78]	[N = 85; R = 76]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	4.0 (NDA)	4.0 (NDA)	NDA	0.0 (NDA)
	Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)	Published re-analysis	3.5 (0.3)	3.5 (0.4)	NDA	0.0 (–0.9 to 0.9)
NAIB2007		[N = 159; R = 88]	[N = 165; R = 94]	[N = NDA; R = NDA]			[N = 101; R = 53]	[N = 96; R = 52]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	NDA	NDA	NDA	NDA
	Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)	Published adjusted	3.5 (0.3)	3.5 (0.3)	NDA	0.0 (–0.8 to 0.8)
NAIA2008 NAIB2008		[N = NDA; R = NDA]		[N = 239; R = NDA]		a	[N = NDA; R = NDA]		[N = NDA; R = NDA]	
	Published	NDA		NDA		Published	NDA		NDA	
	Published re-analysis	NDA		NDA		Published re-analysis	NDA		NDA	
NAIB3001		[N = 189; R = 128]	[N = 190; R = 150]				[N = 132; R = 93]	[N = 137; R = 112]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	8.0 (0.4)	7.0 (0.3)		–1.0 (–2.0 to 0.0)	Published re-analysis	8.0 (0.5)	7.0 (0.3)		–1.0 (–2.2 to 0.2)
NAIA3002		[N = 305; R = 233]	[N = 363; R = 292]				[N = 214; R = 165]	[N = 276; R = 222]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	6.5 (0.3)	6.5 (0.3)		0.0 (–0.8 to 0.8)	Published re-analysis	7.0 (0.3)	6.5 (0.3)		–0.5 (–1.4 to 0.4)
NAIB3002		[N = 163; R = 113]	[N = 161; R = 123]				[N = 123; R = 87]	[N = 124; R = 96]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	8.0 (0.6)	6.0 (0.4)		–2.0 (–3.4 to –0.6)	Published re-analysis	8.5 (0.7)	6.5 (0.5)		–2.0 (–3.6 to –0.4)
NAI30008										
NAI30009										

Table A4.6. Characteristics and results of zanamivir treatment trials										
Trial	**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (influenza positive group)**				
NAI30010	NAI30010	[N = 149; R = 145]	[N = 151; R = 146]				[N = 75; R = 74]	[N = 72; R = 71]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	4.5 (0.3)	3.5 (0.3)		–1.0 (–1.8 to –0.2)	Published re-analysis	5.0 (0.3)	4.5 (0.3)		–0.5 (–1.3 to 0.3)
	NDA, no data available; N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).					NDA, no data available; N, no. of individuals; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).				
	a Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.					a Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.				

Table A4.7										
Trial	**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
NAIA2005 NAIB2005		[N = 144; R = 129]	[N = 132; R = 121]	[N = NDA; R = NDA]			[N = 89; R = 78]	[N = 85; R = 76]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	4.0 (NDA)	4.0 (NDA)	NDA	0.0 (NDA)
	Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)	Published re-analysis	3.5 (0.3)	3.5 (0.4)	NDA	0.0 (–0.9 to 0.9)
NAIB2007		[N = 159; R = 88]	[N = 165; R = 94]	[N = NDA; R = NDA]			[N = 101; R = 53]	[N = 96; R = 52]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	NDA	NDA	NDA	NDA
	Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)	Published adjusted	3.5 (0.3)	3.5 (0.3)	NDA	0.0 (–0.8 to 0.8)
NAIA2008 NAIB2008		[N = NDA; R = NDA]		[N = 239; R = NDA]		a	[N = NDA; R = NDA]		[N = NDA; R = NDA]	
	Published	NDA		NDA		Published	NDA		NDA	
	Published re-analysis	NDA		NDA		Published re-analysis	NDA		NDA	
NAIB3001		[N = 189; R = 128]	[N = 190; R = 150]				[N = 132; R = 93]	[N = 137; R = 112]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	8.0 (0.4)	7.0 (0.3)		–1.0 (–2.0 to 0.0)	Published re-analysis	8.0 (0.5)	7.0 (0.3)		–1.0 (–2.2 to 0.2)
NAIA3002		[N = 305; R = 233]	[N = 363; R = 292]				[N = 214; R = 165]	[N = 276; R = 222]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	6.5 (0.3)	6.5 (0.3)		0.0 (–0.8 to 0.8)	Published re-analysis	7.0 (0.3)	6.5 (0.3)		–0.5 (–1.4 to 0.4)
NAIB3002		[N = 163; R = 113]	[N = 161; R = 123]				[N = 123; R = 87]	[N = 124; R = 96]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA

Table A4.7										
Trial	**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
	Published re-analysis	8.0 (0.6)	6.0 (0.4)		–2.0 (–3.4 to –0.6)	Published re-analysis	8.5 (0.7)	6.5 (0.5)		–2.0 (–3.6 to –0.4)
NAI30008										
NAI30009										
NAI30010	NAI30010	[N = 149; R = 145]	[N = 151; R = 146]				[N = 75; R = 74]	[N = 72; R = 71]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	4.5 (0.3)	3.5 (0.3)		–1.0 (–1.8 to –0.2)	Published re-analysis	5.0 (0.3)	4.5 (0.3)		–0.5 (–1.3 to 0.3)
	NDA, no data available; N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).					NDA, no data available; N, no. of individuals; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).				
	a Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.					a Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.				

Table A4.8.										
Trial	**Median number of days to return to normal activities for 'high-risk' individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to return to normal activities for 'high-risk' individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
NAIA2005 NAIB2005										
NAIB2007		[N = 24; R = 11]	[N = 23; R = 19]	[N = NDA; R = NDA]			[N = 17; R = 8]	[N = 17; R = 13]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	NDA	NDA	NDA	NDA
	Published re-analysis	3.5 (0.5)	3.5 (0.2)	NDA	0.0 (–1.1 to 1.1)	Published re-analysis	3.5 (0.5)	3.5 (0.2)	NDA	0.0 (–1.0 to 1.0)
NAIA2008 NAIB2008	a	[N = NDA; R = NDA]		[N = NDA; R = NDA]		a	[N = NDA; R = NDA]		[N = NDA; R = NDA]	
	Published	NDA		NDA		Published	NDA		NDA	
	Published re-analysis	NDA		NDA		Published re-analysis	NDA		NDA	
NAIB3001		[N = 39; R = 16]		[N = 37; R = 25]			[N = 28; R = 11]	[N = 24; R = 18]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	>12.5 (NDA)	7.0 (1.2)		NDA	Published re-analysis	>12.5 (NDA)	7.0 (1.2)		NDA
NAIA3002		[N = 60; R = 39]	[N = 49; R = 30]				[N = 43; R = 28]	[N = 36; R = 22]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-	9.5 (1.1)	11.0 (3.3)		1.5 (–5.3 to 8.3)	Published	9.5 (1.6)	11.0 (3.3)		1.5 (–5.7 to 8.7)

Table A4.8.										
Trial	**Median number of days to return to normal activities for 'high-risk' individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to return to normal activities for 'high-risk' individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
	analysis					re-analysis				
NAIB3002		[N = 19; R = 11]	[N = 13; R = 11]				[N = 18; R = 11]	[N = 12; R = 10]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	14.5 (5.9)	9.0 (0.9)		–5.5 (–17.1 to 6.1)	Published re-analysis	14.5 (6.1)	8.5 (1.1)		–6.0 (–18.1 to 6.1)
NAI30008		[N = 263; R = 201]	[N = 262; R = 200]				[N = 153; R = 120]	[N = 160; R = 125]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	9.0 (0.6)	8.5 (0.5)		–0.5 (–2.0 to 1.0)	Published re-analysis	9.0 (0.8)	8.5 (0.6)		–0.5 (–2.5 to 1.5)
NAI30009										
NAI30010		[N = 11; R = 10]	[N = 10; R = 8]				[N = 6; R = 5]	[N = 4; R = 3]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	4.0 (1.7)	5.5 (0.9)		1.5 (–2.2 to 5.2)	Published re-analysis	16.5 (6.1)	6.0 (0.4)		–10.5 (–22.5 to 1.5)
	NDA, no data available; N, no. of individuals; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).					NDA, no data available; N, no. of individuals; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).				
	a Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.					a Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.				

Table A4.9.										
Trial	**Median number of days to return to normal activities for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to return to normal activities for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
NAIA2005 NAIB2005		[N = 144; R = 129]	[N = 132; R = 121]	[N = NDA; R = NDA]			[N = 89; R = 78]	[N = 85; R = 76]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	4.0 (NDA)	4.0 (NDA)	NDA	0.0 (NDA)
	Published re-analysis	3.5 (0.2)	3.5 (0.2) NDA	0.0 (–0.6 to 0.6)		Published re-analysis	3.5 (0.3)	3.5 (0.4)	NDA	0.0 (–0.9 to 0.9)
NAIB2007		[N = 183; R = 99]	[N = 188; R = 113]	[N = NDA; R = NDA]			[N = 118; R = 61]	[N = 113; R = 65]	[N = NDA; R = NDA]	
	Published	NDA	NDA	NDA	NDA	Published	NDA	NDA	NDA	NDA
	Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)	Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)
NAIA2008 NAIB2008	a	[N = 422; R = NDA]		[N = 415; R = NDA]		a	[N = 240; R = NDA]		[N = NDA; R = NDA]	
	Published	6.0 (NDA)		5.0 (NDA)		Published	NDA		NDA	
	Published re-analysis	NDA		NDA		Published re-analysis	NDA		NDA	
NAIB3001		[N = 228; R = 144]	[N = 227; R = 175]				[N = 160; R = 104]	[N = 161; R = 130]		
	Published	9.0 (NDA)	7.0 (NDA)		–2.0 (–4.0 to 0.0);p < 0.001	Published	9.0 (NDA)	<7.0 (NDA)		–2.0 (–4.0 to –0.3);p < 0.001
	Published re-analysis	8.0 (0.5)	7.0 (0.3)		–1.0 (–2.1 to 0.1)	Published re-analysis	8.0 (0.8)	7.0 (0.3)		–1.0 (–2.6 to 0.6)
NAIA3002		[N = 365; R = 272]	[N = 412; R = 322]				[N = 257; R = 193]	[N = 312; R = 244]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	7.0 (0.3)	7.0 (0.3)		0.0 (–0.8 to 0.8)	Published re-analysis	7.0 (0.4)	7.0 (0.3)		0.0 (–0.9 to 0.9)
NAIB3002		[N = 182; R = 124]	[N = 174; R = 134]				[N = 141; R = 98]	[N = 136; R = 106]		
	Published	8.5 (NDA)	7.0 (NDA)		–1.5 (–4.0 to	Published	NDA	NDA		NDA

Table A4.9.										
Trial	**Median number of days to return to normal activities for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (ITT group)**					**Median number of days to return to normal activities for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. and intranasal Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
					0.0);p = 0.025					
	Published re-analysis	8.5 (0.6)	6.5 (0.4)		–2.0 (3.4 to –0.6)	Published re-analysis	8.5 (0.6)	7.0 (0.5)		–1.5 (–3.0 to 0.0)
NAI30008		[N = 263; R = 201]	[N = 262; R = 200]				[N = 153; R = 120]	[N = 160; R = 125]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	9.0 (0.6)	8.5 (0.5)		–0.5 (–2.0 to 1.0)	Published re-analysis	9.0 (0.8)	8.5 (0.6)		–0.5 (–2.5 to 1.5)
NAI30009		[N = 247; R = 211]	[N = 224; R = 205]				[N = 182; R = 155]	[N = 164; R = 151]		
	Published	NDA	NDA		–1.0 (NDA);p = 0.019	Published	NDA	NDA		–1.0 (NDA);p = 0.022
	Published re-analysis	6.0 (0.3)	5.5 (0.3)		–0.5 (–1.2 to 0.2)	Published re-analysis	6.0 (0.3)	5.5 (0.3)		–0.5 (–1.3 to 0.3)
NAI30010		[N = 158; R = 153]	[N = 163; R = 156]				[N = 81; R = 79]	[N = 76; R = 74]		
	Published	NDA	NDA		NDA	Published	NDA	NDA		NDA
	Published re-analysis	4.5 (0.3)	4.0 (0.3)		–0.5 (–1.3 to 0.3)	Published re-analysis	5.5 (0.3)	4.5 (0.4)		–1.0 (–1.9 to –0.1)
	NDA, no data available; N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).					NDA, no data available; N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).				
	a Also compared with 40 mg inhaled + 25.6 mg intranasal (N = 415): median 4.5 [difference = –1.5; p < 0.001).					a Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.				

Table A4.10. Characteristics and results of zanamivir treatment trials in children						
Trial	**Data source + extra information**	**Jadad score**	**Patient characteristics**	**Trial design arms (no. of patients in each arm)**	**Treatment duration (days)**	**Follow-up (days)**
NAI30009	[Ref.: Hedrick et al,[27]]	3	Previously healthy children 5–12 years old. Present within 36 hours after onset of symptoms. Recruitment started when influenza was known to be circulating in the community. Influenza was confirmed to be circulating before recruitment started in each centre. Note that 8% of participants considered 'high risk'. 2% of study population were vaccinated	247 placebo 224 10 mg inhaled twice daily	5	28
NAI30010	Analysis of index cases from a study set up to examine the prevention of transmission of influenza A and B within families [Ref.: Hayden et al.,[76]]	3	Eligible families were those with two to five members, including at least one adult and at least one child between 5 and 17 years old. Once laboratory confirmed influenza activity had been documented in the community, families in which one member contracted an ILI (the 'index case') began to take the study drug. The treatment trial consisted of the 'index cases' only. Present within 36 hours after onset of symptoms. Note that 7% of participants considered 'high risk'. 10% of the study population were vaccinated	158 placebo 163 10 mg inhaled twice daily	5	28

Table A4.11. Characteristics and results of zanamivir treatment trials in children								
Trial	**Median number of days to the alleviation of symptoms for children in the zanamivir treatment trials (ITT group)**				**Median number of days to the alleviation of symptoms for children in the zanamivir treatment trials (influenza positive group)**			
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI)**
NAI30009	'Healthy'	[N = 233; R = 205]	[N = 202; R = 193]		'Healthy'	[N = 172; R = 152]	[N = 152; R = 146]	
	Published	NDA	NDA	NDA	Published	NDA	NDA	NDA
	Published re-analysis	5.0 (0.2)	4.0 (0.2)	–1.0 (–1.5 to –0.5)	Published re-analysis	5.0 (0.2)	4.0 (0.2)	–1.0 (–1.6 to –0.4)
NAI30010	'High-risk'	[N = 14; R = 12]	[N = 22; R = 20]		'High-risk'	[N = 10; R = 9]	[N = 12; R = 12]	
	Published	NDA	NDA	NDA	Published	NDA	NDA	NDA
	Published re-analysis	5.8 (2.3)	3.8 (1.0)	–2.0 (–6.9 to 2.9)	Published re-analysis	5.8 (1.9)	2.0 (0.3)	–3.8 (–7.6 to 0.1)
	NDA, no data available; N = no. of individuals, R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).							

Table A4.12. Characteristics and results of zanamivir treatment trials in children								
Trial	**Median number of days to return to normal activities for children in the zanamivir treatment trials. (ITT group)**				**Median number of days to return to normal activities for children in the zanamivir treatment trials (influenza positive group)**			
	Trial	Placebo Median (SE)	Inhaled 10 mg b.d. Median (SE)	Inhaled 10 mg b.d. vs placebo Median difference (95% CI)	Trial	Placebo Median (SE)	Inhaled 10 mg b.d. Median (SE)	Inhaled 10 mg b.d. vs placebo Median difference (95% CI)
NAI30009	'Healthy'	[N = 233; R = 200]	[N = 202; R = 184]		'Healthy'	[N = 172; R = 147]	[N = 154; R = 139]	
	Published	NDA	NDA	NDA	Published	NDA	NDA	NDA
	Published re-analysis	6.0 (0.3)	5.5 (0.3)	–0.5 (–1.3 to 0.3)	Published re-analysis	6.0 (0.3)	5.5 (0.3)	–0.5 (–1.4 to 0.4)
NAI30010	'High-risk'	[N = 14; R = 11]	[N = 22; R = 21]		'High-risk'	[N = 10; R = 8]	[N = 12; R = 12]	
	Published	NDA	NDA	NDA	Published	NDA	NDA	NDA
	Published re-analysis	7.0 (0.5)	6.0 (1.2)	–1.0 (–3.5 to 1.5)	Published re-analysis	7.0 (0.4)	4.5 (0.9)	–2.5 (–4.4 to –0.6)

NDA, no data available; N = no. of individuals, R, no. of events
(i.e. no. of individuals whose symptoms are alleviated by the end of the study).

Table A4.13. Characteristics of not published zanamivir treatment trials											
Trial	**Data source + extra information**	**Patient characteristics**	**Trial design arms (no. of patients in each arm)**	**Treatment duration (days)**	**Follow-up (days)**	**Median number of days to the alleviation of symptoms for not published zanamivir treatment trials (ITT group)**		**Median number of days to the alleviation of symptoms for not published zanamivir treatment trials (influenza positive group)**			
						Trial	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI); p-value**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI); p-value**
NAI30011	[Ref.: GlaxoSmithKline 2002 submission to NICE)	≥ 18 years of age. Present within 48 hours after onset of symptoms. Some participants 'high-risk' (10% cardiovascular N = 47; 7% respiratory, N = 33) and 5 participants (1 treatment and 4 placebo) ≥ 65 years. 9% of individuals (21 in each arm) vaccinated for the present influenza season. US-based multicentre trial	237 placebo 229 10 mg inhaled twice daily	5	21	'High-risk + healthy'	–0.50 (NDA) p = 0.692	High-risk + healthy'	[N = 107; R = NDA] 5.00 (NDA)	[N = 104; R = NDA] 4.50 (NDA)	–0.50 (NDA) p = 0.851
NAI30012	[Ref.: GlaxoSmithKline 2002 submission to NICE)	All subjects aged ≥ 65 years with or without underlying medical conditions. 20-country multicentre trial. Present within 48 hours after onset of symptoms. 44% and 47% vaccinated for the present influenza season in the placebo and treatment groups, respectively	167 placebo 191 10 mg inhaled twice daily	5	29	'High-risk'	–1.00 (–3.00 to 1.00) p = 0.159	'High-risk'	[N = 114; R = NDA] 7.5 (NDA)	[N = 120; R = NDA] 7.25 (NDA)	–0.25 (–3.25 to 2.00) p = 0.609

Table A4.14. Characteristics of not published zanamivir treatment trials								
Trial	**Median number of days to return to normal activities for not published zanamivir treatment trials (ITT group)**				**Median number of days to return to normal activities for not published zanamivir treatment trials (influenza positive group)**			
	Trial	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI); p-value**	**Trial**	**Placebo Median (SE)**	**Inhaled 10 mg b.d. Median (SE)**	**Inhaled 10 mg b.d. vs placebo Median difference (95% CI); p-value**
NAI30011	'High-risk + healthy'	NDA	NDA	NDA	'High-risk + healthy'	NDA	NDA	NDA
NAI30012	'High-risk'	[N = 167; R = NDA] >26.5 (NDA)	[N = 191; R = NDA] >26.5 (NDA)	p = 0.892	'High-risk'	[N = 114; R = NDA]>26.5 (NDA)	[N = 120; R = NDA]>26.5 (NDA)	p = 0.897

Table A4.15.

Characteristics and results of oseltamivir treatment trials in healthy children						
Trial	**Data source + extra information**	**Jadad score**	**Patient characteristics**	**Trial design arms (no. of patients in each arm)**	**Treatment duration (days)**	**Follow-up (days)**
WV15758	[Ref.: Whitley et al [28]]	4	Previously healthy children aged 1–12 years. Present <48 hours after onset of symptoms. Influenza immunisation was not an exclusion criterion. There were no 'high-risk' individuals	351 placebo 344 2 mg/kg/dose twice daily (to a max. of 100 mg/dose)	5	28

Characteristics and results of oseltamivir treatment in the influenza - infected children with asthma						
Trial	**Data source + extra information**	**Jadad score**	**Patient characteristics**	**Trial design arms (no. of patients in each arm)**	**Treatment duration (days)**	**Follow-up (days)**
WV15759 WV15871	This study is published after the systematic review of Turner et al.,(2003) and is also included as 'eligible RCT for this review' Two WV numbers were assigned as the study rolled over two seasons 25		treatment of naturally acquired, symptomatic influenza infection in 334 children with asthma aged 6 to 12 years	164 placebo 170 oseltamivir (2 mg/kg) twice daily	5	28

Table A4.16. Characteristics and results of oseltamivir treatment trials in healthy adults						
Trial	**Data source + extra information**	**Jadad score**	**Patient characteristics**	**Trial design arms (no. of patients in each arm)**	**Treatment duration (days)**	**Follow-up (days)**
WV15670	[Ref.: Nicholson et al., 2000]	5	Previously healthy, aged 18–65 years. Present within 36 hours after onset of symptoms. Persons vaccinated in the previous 12 months were excluded. There were no 'high-risk' individuals.	238 placebo 243 75 mg/dose twice daily 245 150 mg/dose twice daily	5	21
WV15671	[Ref.: Treanor et al., 2000]	5	Previously healthy, aged 18–65 years. Present within 36 hours after onset of symptoms. Persons vaccinated in the previous 12 months were excluded. There were no 'high-risk' individuals.	209 placebo a 210 75 mg/dose twice daily 208 150 mg/dose twice daily	5	21
WV15730	[Ref.:http://www.fda.gov/cder/approval/index.htm]	5	Previously healthy, aged 18–65 years. Present within 36 hours after onset of symptoms. Persons vaccinated in the previous 12 months were excluded. There were no 'high-risk' individuals.	27 placebo 31 75 mg/dose twice daily	5	21
				a Two persons in this study were excluded before treatment given and analysis is reported excluding these persons.		

Table A4.17. Characteristics and results of oseltamivir treatment trials in healthy adults outcome alleviation of symptoms									
Median number of hours to the alleviation of symptoms for 'healthy' individuals in the oseltamivir treatment trials (ITT group)					Median number of hours to the alleviation of symptoms for 'healthy' individuals in the oseltamivir treatment trials (influenza positive group)				
Trial	**Placebo Median (SE)**	**75 mg b.d. Median (SE)**	**150 mg b.d. Median (SE)**	**75 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**75 mg b.d. Median (SE)**	**150 mg b.d. Median (SE)**	**75 mg b.d. vs placebo Median difference (95% CI)**
WV15670	[N = 235; R = 191] 116.1 (7.6)	[N = 240; R = 211] 97.6 (9.9)	[N = 241; R = 213] 89.4 (6.0)	–18.5 (–43.0 to 6.0)	WV15670	[N = 161; R = 133] 116.5 (8.5)	[N = 157; R = 140] 87.4 (7.8)	[N = 155; R = 143] 81.8 (6.8)	–29.1 (–51.7 to –6.5)
WV15671	[N = 200; R = 178] 97.0 (5.3)	[N = 204;R = 182] 76.3 (6.4)	[N = 202; R = 179] 74.3 (4.0)	–20.7 (–37.0 to –4.4)	WV15671	[N = 128; R = 113] 103.3 (7.9)	[N = 121; R = 112] 71.5 (5.6)	[N = 119; R = 107] 69.9 (6.2)	–31.8 (–50.7 to –12.8)
WV15730 **a**	[N = 27; R = 21] 109.8 (31.2)	[N = 31; R = 27] 74.5 (7.2)		–35.3 (–98.5 to 27.8)	WV15730 a	[N = 19; R = 15] 143.9 (24.8)	[N = 19; R = 17] 78.2 (10.6)		–65.8 (–118.7 to –12.8)
Above 3 studies combined	[N = 462; R = 390] 105.3 (5.0)	[N = 475; R = 420] 83.2 (4.3)	[N = 443;R = 392] 81.0 (4.5)		Above 3 studies combined	[N = 308; R = 261] 112.5 (4.9)	[N = 297; R = 269] 78.2 (3.9)	[N = 274; R = 250] 78.5 (5.3)	
N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study). a Unpublished study.									

Table A4.18. Characteristics and results of oseltamivir treatment trials healthy adults outcome return to normal activities										
Trial	**Median number of hours to return to normal activities for 'healthy' individuals in the oseltamivir treatment trials (ITT group)**					**Median number of hours to return to normal activities for 'healthy' individuals in the oseltamivir treatment trials (influenza positive group)**				
	Trial	**Placebo Median (SE)**	**75 mg b.d. Median (SE)**	**150 mg b.d. Median (SE)**	**75 mg b.d. vs placebo Median difference (95% CI)**	**Trial**	**Placebo Median (SE)**	**75 mg b.d. Median (SE)**	**150 mg b.d. Median (SE)**	**75 mg b.d. vs placebo Median difference (95% CI)**
WV15670	WV15670	[N = 234; R = 153] 173.0 (8.2)	[N = 240; R = 171] 132.4 (8.2)	[N = 241; R = 172] 150.0 (7.1)	–40.6 (–63.3 to –17.8)	WV15670	[N = 161; R = 103] 174.2 (9.0)	[N = 157; R = 119] 127.1 (9.1)	[N = 155; R = 112] 133.5 (8.2)	–47.2 (–72.2 to –22.2)
WV15671	WV15671	[N = 201; R = 135] 133.0 (7.8)	[N = 204; R = 164] 108.7 (7.0)	[N = 203; R = 148] 130.2 (7.7)	–24.3 (–44.8 to –3.7)	WV15671	[N = 128; R = 90] 134.2 (8.8)	[N = 121; R = 106] 107.8 (1.5)	[N = 120; R = 89] 127.2 (10.0)	–26.3 (–43.9 to –8.8)
WV15730	WV15730a	[N = 27; R = 14] 196.2 (36.3)	[N = 31; R = 18] 152.6 (24.8)	–43.6 (–129.8 to 42.6)		WV15730a	[N = 19; R = 9] 218.7 (36.1)	[N = 19; R = 13] 130.7 (17.4)		–88.0 (–166.5 to –9.5)
	Above 3 studies combined	[N = 462; R = 302] 156.3 (5.4)	[N = 475; R = 353] 127.6 (5.1)	[N = 444; R = 320] 134.0 (5.2)		Above 3 studies combined	[N = 308; R = 202] 156.3 (6.6)	[N = 297; R = 238] 125.7 (5.4)	[N = 275; R = 201] 131.3 (3.3)	
	N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study). a Unpublished study.									

Table A4.19. Characteristics and results of oseltamivir treatment trials in healthy children								
Trial	**Median number of hours to the alleviation of symptoms for children in the oseltamivir treatment trials**				**Median number of hours to return to normal health and activities for children in the oseltamivir treatment trials**			
WV15758	Trial	Placebo Median (SE)	75 mg b.d. Median (SE)	75 mg b.d. vs placebo Median difference (95% CI)	Trial	Placebo Median (SE)	75 mg b.d. Median (SE)	75 mg b.d. vs placebo Median difference (95% CI)
	ITT	[N = 338; R = 319] 125.7 (5.1)	[N = 331; R = 310] 104.8 (5.6)	–20.9 (–35.7 to –6.1)	ITT	[N = 338; R = 325]100.1 (5.3)	[N = 331; R = 319] 70.0 (4.3)	–30.1 (–43.3 to –16.8)
	Influenza positive	[N = 225; R = 210] 137.0 (5.4)	[N = 209; R = 196]101.3 (7.1)	–35.8 (–53.3 to –18.2)	Influenza positive	[N = 225; R = 204] 111.7 (7.5)	[N = 209; R = 204] 67.1 (6.3)	–44.6 (–63.7 to –25.4)
	N, no. of individuals in the study; R, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).							
Characteristics and results of oseltamivir treatment in influenza - infected children with asthma								
Trial	Median number of hours to the alleviation of symptoms for children in oseltamivir treatment				Median number of hours to return to normal activities for children in the oseltamivir treatment			
		Placebo Median	Oseltamivir group	Placebo vs Oseltamivir; p - value		Placebo Median	Oseltamivir group	Placebo vs Oseltamivir; p - value
WV15759 WV15871	ITTI a	123.9	134.3	10.4 ; p = 0.5420	ITTI a	114	101.4	12.6 ; p = 0.4555
	Per protocol population	NDA	NDA	24.3 ; p = 0.1607	Per protocol population	116.8	100	16.8 ; p = 0.1177
	a ITTI is intention - to - treat infected population No data available							

Table A4.20. Characteristics of not published oseltamivir treatment trials – high risk persons						
Trial	**Data source + extra information**	**Jadad score**	**Patient characteristics**	**Trial design arms (no. of patients in each arm)**	**Treatment duration (days)**	**Follow-up (days)**
WV15812	[Ref.:http://www.fda.gov/cder/approval/index.htm]	4	Persons with chronic and/or respiratory disease b, aged ≥ 13 years. Present within 36 hours after onset of symptoms. Approx. 30% of the study population were vaccinated.	149 placebo 152 75 mg/dose twice daily	5	21
WV15872	[Ref.: not published]	2	Persons with chronic and/or respiratory disease aged ≥ 13 years	53 placebo 47 75 mg/dose twice daily	Not available	Not available
WV15819	[Ref.:http://www.fda.gov/cder/approval/index.htm]	4	Previously healthy, aged ≥ 65 years. Present within 36 hours after onset of symptoms. Approx. 46% of the study population were vaccinated	93 placebo 76 75 mg/dose twice daily	5	21
WV15876	[Ref.: not published]	2	Previously healthy, ≥ 65 years	44 placebo 54 75 mg/dose twice daily	5	21
WV15978	[Ref.: not published]	2	Previously healthy, aged ≥ 65 years	238 placebo 228 75 mg/dose twice daily	Not available	Not available
b Patients with chronic cardiac (excluding chronic idiopathic hypertension) or pulmonary disorders (including bronchopulmonary dysplasia and asthma but excluding cystic fibrosis) severe enough to require regular medical follow-up or hospital care. In study WV15872 the following clarification was also given: pulmonary disorders were defined as COAD (chronic obstructive airway disease), which permanently reduces the FEV1. Asymptomatic patients with a previous valve replacement or bypass surgery were also eligible.						

Table A4.21. Characteristics of oseltamivir prophylaxis trials

Trial	Data source + extra information	Jadad score	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (weeks)	Seasonal prophylaxis in a mostly vaccinated elderly population in a residential home setting (aged 64–96 years, 80% vaccinated):						
						Outcome: laboratory-confirmed clinical influenza	Total no. in placebo group	No. in placebo group with an event (%)	Total no. in oseltamivir group	No. in oseltamivir group with an event (%)	OR (95% CI)	p-Value for intervention effect
WV15825	Peters et al., [29]	4	Randomised double-blind, placebo-controlled multicentre trial comparing the efficacy of oseltamivir prophylaxis in frail elderly subjects living in 31 residential homes across the USA and Europe. 548 persons who had a mean age of 81 years (range from 64 to 96 years) took part in the study, of whom 80% had been vaccinated against influenza	276 75 mg once daily 272 placebo	6	All participants	272	12 (4.4)	276	1 (0.4)	0.08 (0.01 to 0.61)	0.002
						Vaccinated participants only	218	11 (5.0)	222	1 (0.5)	0.09 (0.001 to 0.67)	0.003
						Previous exposure prophylaxis in the general population (aged 12–85 years, 13% vaccinated)						
WV15799	Welliver et al., [77]	4	Cluster-randomised, double-blind, placebo-controlled study conducted at 76 centres in N. America and Europe to investigate the efficacy of oseltamivir in preventing the spread of influenza to household contacts of influenza-infected index cases. Household contacts were randomly assigned by household cluster within 48 hours of symptom onset in the index case (the index case did not receive antiviral treatment). Acknowledgement was made of the need to take the cluster aspect of the design into account at the analysis stage. The age of contacts ranged from 12 to 85 years. 13% of contacts in each group had received influenza vaccination. About 40% of contacts had pre-existing diseases – the most common were asthma 3.0%, hypertension 5.7%, hypersensitivity 3.9% and depression 2.9%	493 75 mg once daily 462 placebo	1	ITT analysis	462	34 (7.4)	493	4 (0.8)	0.10 (0.04 to 0.29)	<0.001
						Influenza-positive index case	206	26 (12.6)	209	3 (1.4)	0.10 (0.03 to 0.34)	<0.001

Trial	Data source + extra information	Jadad score	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (weeks)	Seasonal prophylaxis in a healthy population (aged 18–65 years, none vaccinated)								
						Outcome	Total no. in placebo group	No. in placebo group with an event (%)	Total no. in oseltamivir 75 mg/day group	No. in oseltamivir 75 mg/day group with an event (%)	Total no. in oseltamivir 150 mg/day group	No. in oseltamivir 150 mg/day group with an event(%)[a]	OR (95% CI)	p-Value for intervention effect
WV15673	Hayden et al., [78]	5	Double-blind, randomised and placebo-controlled study conducted at 3 sites in Virginia, USA. Eligible subjects were healthy adults aged 18–65 years, and had not received influenza vaccine	268 75 mg once daily 267 75 mg twice daily 268 placebo	6	Laboratory-confirmed clinical influenza	268	19 (7.1)	268	3 (1.1)	267	4 (1.5)	0.15 (0.04 to 0.51)	<0.001
WV15697	Hayden et al., [78]	5	Same design as above. Double-blind, randomised and placebo-controlled study conducted at 2 sites in Texas, USA and 1 site in Kansas City. Eligible subjects were healthy adults aged 18–65 years, and had not received influenza vaccine	252 75 mg once daily 253 75 mg twice daily 251 placebo	6		251	6 (2.4)	252	3 (1.2)	253	3 (1.2)	0.49 (0.12 to 1.99)	0.34
						a 150 mg/day arm included here for completeness.								

Table A4.22. Characteristics of zanamivir prophylaxis trials

Trial	Data source + extra information	Jadad score	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (days)	Outbreak prophylaxis in the elderly in a residential home setting:				
						No. in rimantadine group with an event (%)	Total no. in zanamivir group	No. in zanamivir group with an event (%)	OR (95% CI)	p-Value for intervention effect
NAIA 2010	In the analysis no allowance was made for the clustering and hence there is a danger the results of the study are over precise [79]	3	Randomised unblinded study of chemoprophylaxis with zanamivir versus standard care in a 735-bed nursing home. Randomisation was at a ward (of which there were 14) and not an individual level. Once existence of an outbreak was established (treatment was given only in the ward where the outbreak had occurred). Persons who refused to take part in the study were given rimantadine automatically when influenza A was confirmed in their ward. Age group of participants and percentage vaccinated not reported	Influenza A 65 10 mg inhaled + 4.4 mg twice daily 23 100 mg rimantadine once daily Influenza B 35 10 mg inhaled + 4.4 mg intranasal twice daily 17 no drug	14	1 (4.3)	65	0 (0.0)	0.11 (0.005 to 2.91)	0.25 (exact)
						1 (4.3)	65	1 (1.5)	0.34 (0.02 to 5.73)	0.46 (exact)
						1 (5.9)	35	0 (0.0)	0.15 (0.006 to 4.01)	0.33 (exact)
						1 (5.9)	35	0 (0.0)	0.15 (0.006 to 4.01)	0.33 (exact)
						None of the estimates take into account intra-cluster correlation clustering; however, it is so rare that is probably does not matter.				
						Seasonal prophylaxis in a healthy population (aged 18–64 years, 15% vaccinated):				
						No. in placebo group with an event (%)	Total no. in zanamivir group	No. in anamivir group with an event (%)	OR (95% CI)	p-Value for intervention effect
NAIA 3005	Monto et al [80]	4	Randomised double-blind, placebo-controlled trial of zanamivir for the prevention of influenza in healthy adults (two midwestern USA university communities). Persons aged 18–64 years (mean age 29 years) were eligible for participation as long as they did not have a chronic condition for which influenza vaccination was recommended (although other vaccinated persons were eligible for inclusion). 15% of participants vaccinated	553 10 mg inhaled once daily 554 placebo	28	34 (6.1)	553	11 (2.0)	0.31 (0.14 to 0.64)	<0.001

Trial	Data source + extra information	Jadad score	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (days)
NAI30010	In the analysis no allowance was made for the clustering and hence there is a danger the results of the study are over precise [76]	4	Randomised double-blind, placebo-controlled study of the treatment and prevention of influenza in families. Families (2–5 members with one child 5 years of age or older) in which one member developed ILI were randomised. Note: the index case was randomised to inhaled zanamivir 10 mg twice daily for 5 days or placebo. The mean age of household contacts was 26 years (SD = 16). 16% of participants had been vaccinated	Contact cases: 414 10 mg inhaled once a day 423 placebo	5
NAIA2009 NAIB2009	Kaiser et al.[81]	3	Randomised double-blind, placebo-controlled multicentre trial (Europe and North America) investigating the prophylactic effect of zanamivir after close contact with a person with ILI of no longer than 4 days' duration. Asymptomatic persons aged 13–65 years who had been exposed were eligible. None of the participants were vaccinated against influenza	(2 × 2 factorial study design)146 inhaled (5 mg) twice daily + intranasal sprays (16 mg/ml) per nostril (0.1 ml per spray)141 placebo inhaled + active spray 144 inhaled + placebo spray 144 placebo spray and inhalation	10

Trial	Previous exposure prophylaxis in the general population (ITT group)					Previous exposure prophylaxis in the general population (influenza positive index cases)						
	No. in placebo group with an event (%)	Total no. in zanamivir group	No. in zanamivir group with an event (%)	OR (95% CI)	p-Value for intervention effect	Outcome	Total no. in placebo group	No. in placebo group with an event (%)	Total no. in zanamivir group	No. in zanamivir group with an event (%)	OR (95% CI)	p-Value for intervention effect
NAI30010a	40 (9.5)	414	7(1.7)	0.16 (0.07 to 0.37)	<0.001	Laboratory-confirmed influenza in contact	215	33 (15.3)	195	6 (3.1)	0.18 (0.07 to 0.43)	<0.001
NAIA2009 NAIB2009	9 (6.3)	144	3 (2.1)	0.27 (0.07 to 1.05)b	0.077 b							
	a None of the above estimates take into account ICC clustering – however, it is so rare that is probably does not matter. b OR estimates is stratified by centre but the given p - value is not											

Trial	Data source + extra information	Jadad score	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (days)	Outbreak prophylaxis in a nursing home:				
						No. in placebo group with an event (%)	Total no. in zanamivir group	No. in zanamivir group with an event (%)	OR (95% CI)	p-Value for intervention effect
NAIA3004	Underpowered study, all influenza cases occurred in Lithuania, impact of difference in vaccination ratio or hygienic measures not assessed This study is published after the systematic review of Turner et al.,(2003) and is also included as 'eligible RCT for this review'	valid	A double-blind, randomized, placebo-controlled, parallel-group, multi-center study (12 centers in Netherlands, Israel, Lithuania). Study Population: subjects had to be residents of a nursing home, and able to satisfactorily use the Diskhaler. An influenza outbreak was required to have been declared locally. Vaccination was not obligatory, only 9% was vaccinated.	240 5 mg zanamivir 2 inhalations once daily total daily dose 10 mg 249 placebo	14	23 (9)	240	15 (6)	0.71 [0.38, 1.31]	p=0.355

4.5 APPENDIX 5. USE OF ANTIVIRAL AGENTS IN SELECTED PANDEMIC PLANS

4.5.1 Australia

4.5.1.1 NEEDS ASSESMENT AND STOCKPILING

Basic assumptions

Attack rate (+ duration)	AR? (Duration 12 weeks)
Case-fatality rate	Not found
Specific mortality rate	64-217/100.000 pop (13.000-44.000 deaths expected)
Groups most at risk	Not found
Other assumptions	
Hospitalisations	0.3 – 0.7 % population (58.000-148.000 expected)
Outpatients visits	5-37% population (1-7.5 millions expected)

The most important assumption driving the recommendations for the use of antiviral drugs relates to the effectiveness of containment strategies. 'The most recent epidemiological results suggest that combined interventions [i.e. *use of antivirals*] could delay the onset of a pandemic in Australia for many months [60]'

Explicit targets for use

Pandemic alert period (objective: containment)	
Treatment	Cases
PEP	Contacts (20 contacts per case expected)
Prophylaxis	Health care workers conducting 'seek and contain' activities (50 HCW per case expected)
Established pandemic	
Treatment	Within a trial only*
PEP	'Lower level risk'= medium risk of close contact exposure
Prophylaxis	'Higher risk of exposure to the virus' = continuous risk of exposure = A core of HCW

* Allocation for the trial will be based not on the state population, but on the research protocol that ensures the gathering of the best information

The use of any component within the stockpile will be guided by Australia's strategy of delaying the impact of the pandemic, to buy time to develop and distribute a vaccine[60].

Planned stockpile

Planned stockpile: 8,75 millions (treatment) courses

Population (2006) 20,264,082.

N courses/N population= 43% .

Criteria for national allocation from the stockpile

	Group	Strategy	%**
Containment phase			
	Containment needs	T+PEP+P	8-10%
Established pandemic			
	Core of professionals working in health care	P	65%
	Cases (limited number, within a trial)	T	10%
	Lower risk of exposure	PEP	10%
	Contingency reserve	-	5-7%
Total			100%

T=treatment PEP=Post-exposure prophylaxis P= prophylaxis .
One treatment course: 10 doses = one PEP course (10 days protection).
P=continuous prophylaxis: 1 dose/day * 6 weeks = 42 doses
** Proportion of stockpile

4.5.1.2 Clinical guidelines: indications for treatment with antiviral drugs during a flu pandemic

We could not find any detailed information.

Current recommendations for general practitioners and health workers (in the alert phase) [62]:

Clinical assessment of a patient with fever > 38° + respiratory symptoms + 'plausible history of exposure' (= travelers, contact with infected animals, with a case with severe respiratory illness, laboratory worker…): contact local public health unit and discuss diagnosis, investigations, treatment, hospitalization…

'More detailed patient management guidance will be provided to medical practitionners as specific information on the illness becomes available'[62]:

4.5.1.3 Surveillance, monitoring, research implying antivirals drugs[82]

Effectiveness of antivirals during a pandemic

Research project funded in Feb 2006: Do stockpiled antivirals work safely against pandemic influenza? Professor David Cooper, University of New South Wales

This project will develop a number of clinical trials that could be implemented rapidly should pandemic influenza ever be announced by health authorities in Australia/Singapore or Hong Kong. Patients with suspected influenza infection will be asked to provide informed consent prior to commencing NAI therapy. Clinical information will then be collected for a period of approximately one month along with some blood samples and swabs from the throat and nasal passages. Data will be analysed as quickly as possible to help inform the continued use of NAI therapy as a cornerstone of the public health agency response to pandemic influenza. In addition, the study team will prepare clinical trials to be conducted in essential workers who are likely to receive long-term NAI preventive treatment as well as the immediate contacts of people with presumed influenza infection who are likely to receive short-term prophylaxis with NAIs.

New drugs/ new diagnosis tests

Resistance to NAIs in A (H5N1) influenza virus: assessment, molecular basis; efficacy and resistance profile of long acting NA inhibitors against several influenza strains; PCR test for the detection of resistance.

4.5.1.4 Sources[60, 83]

- Australian government - Department of Health and Aging. The Australian Health Management Plan for Pandemic Influenza. 2006Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/ohp-pandemic-ahmppi.htm
- Australian government - Department of Health and Aging. The Australian Health Management Plan for Pandemic Influenza. Appendix 1: access to the Australian national medical stockpile during an influenza pandemic. 2006Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/ohp-pandemic-ahmppi.htm

4.5.2 Canada

Use of antiviral drugs in a pandemic context is in line with the main goals of this pandemic plan: first, to minimize serious illness and overall deaths, and second to minimize societal disruption among Canadians as a result of an influenza pandemic

4.5.2.1 NEEDS ASSESMENT AND STOCKPILING

Basic assumptions

Attack rate (+ duration)	15% to 35% will become clinically ill (unable to attend work for at least half a day) over 8 weeks
Case-fatality rate	-
Groups most at risk	Young children, elderly adults, pregnant women, and individuals with chronic diseases at greatest risk of complicated influenza[64]
Other assumptions	Based on a US model[84] - Detailed assumptions on attack rates, hospitalisations, deaths, per age and risk group.
Specific mortality rate	54-125 / 100.000 population (18.000-25.000 deaths expected)
Hospitalisations	0.14%-0.32% (47.000-109.000 expected)
Outpatient care	6-14% population (2-5 millions visits expected)

Explicit targets for use

Pandemic alert period	
Treatment	-
PEP	-
Prophylaxis	-
Established pandemic	
Treatment	Patients hospitalized with influenza-like symptoms, health-care and emergency service workers, high-risk persons in the community
PEP	Control outbreaks in residents of institutions
Prophylaxis	Essential services workers, high-risk persons hospitalized for an illness other than influenza, high-risk persons in the community

Planned stockpile

Not found

Population: 33 millions (2006)

4.5.2.2 Explicit prioritization during pandemic if stockpile not sufficient[64]

Priority	**Group**	**Strategy**
1	Patients hospitalized for influenza within 48h of onset	T
2	Ill health care and emergency services workers (within 48h of onset)	T
3	Ill high-risk persons in the community* (within 48h of onset)	T
4	Prophylaxis of health care workers	P
5	Control outbreaks in high-risk residents of institutions (nursing homes and other chronic care facilities)	PEP
6	Prophylaxis of essential service workers	P
7	Prophylaxis of high-risk persons* hospitalized for illnesses other than influenza	P
8	Prophylaxis of high-risk persons* in the community	P

T=treatment PEP=Post-exposure prophylaxis P= prophylaxis
* During a pandemic the definition of high-risk persons may change based on epidemiologic evidence.

4.5.2.3 Clinical guidelines: Indications for treatment with antiviral drugs during a flu pandemic[64]

The Canadian pandemic plan includes a large clinical section with detailed decision algorithms for outpatient settings (adults, children) / long-care facilities setting / acute care setting.

Case Definitions:

Clinical case definition: when influenza is circulating in the community, the presence of fever and cough of acute onset are good predictors of influenza. The positive predictive value increases when fever is higher than 38° and when the onset of the clinical illness is acute (less than 48 hours after the prodromes).

Confirmed cases of influenza: cases with laboratory confirmation (i.e., virus isolation from respiratory tract secretions, identification of viral antigens or nucleic acid in the respiratory tract, or a significant rise in serum antibodies) OR clinical cases with an epidemiological link to a laboratory confirmed case.

Patient management and indications for treatment

Algorithms (one for children, another for adults) for the management of patients with influenza-like illness (ILI) are provided for a 2-step assessment (triage).

1) Initial ILI assessment: patients not meeting specific severity criteria will be sent home with self-care instructions. Others are eligible for secondary assessment.

2) Secundary influenza illness assessment:

Patients could be eligible for microbiologic diagnostic tests (bacteriologic and/or virologic), depending on the clinical presentation and availability of resources. Once the pandemic strain is confirmed in a community, virologic tests will be needed only to confirm diagnosis in atypical cases (and for surveillance purposes).

According to the outcomes of secondary assessment patients will be:

- sent home with self-care instructions. Only those with co-morbidities or risk factors (belonging to a pre-established list) could be eligible for antiviral therapy provided they are assessed within 48 hours of onset. The treatment decision will be contingent on pandemic priorities.
- or admitted to hospital (priority for antiviral treatment).

4.5.2.4 Surveillance, monitoring, research implying antivirals drugs

Apart from surveillance and resistance monitoring, research issues include:

- The outcomes of specific interventions and the value of antiviral prophylaxis versus treatment.
- The benefit of antivirals in reducing complications of influenza and death, especially in high-risk persons and in those with severe influenza illness (e.g., severe viral pneumonitis).
- The efficacy and safety of antivirals for the treatment and prophylaxis of children and select high-risk groups such as infants, pregnant women, immunocompromised persons, elderly with underlying disease.
- The minimum effective dose and duration for prophylaxis or treatment of complicated and uncomplicated influenza.
- The use of combination therapy in different populations.
- The mechanism for resistance to both classes of antivirals and assessment of the biological consequences (infectiousness, virulence) of resistance.
- The use of laboratory testing including rapid diagnostics to assist in decision making for use of antivirals.

- The effect of antiviral administration on the response to live attenuated influenza vaccines.
- The shelf life of antivirals and raw materials, beyond those estimated by manufacturer.

4.5.2.5 Sources[64]

Public Health Agency of Canada. Canadian Pandemic Influenza Plan. 2004 Available from: http://www.phac-aspc.gc.ca/cpip-pclcpi/

4.5.3 United Kingdom

4.5.3.1 NEEDS ASSESMENT AND STOCKPILING[85, 86]

Basic assumptions

Attack rate (+ duration)	Cumulative clinical attack rate: 25% over one or more waves of +/-15 weeks each
Case-fatality rate	0.37% (minimum that might be expected even with treatment)
Groups most at risk	Attack rate higher in children and otherwise fit adults but mortality higher in the elderly (but uniform attack rate used across all age groups for planning purposes)
Other assumptions	Complication rate : 10% of those with symptoms; half expected to attend hospital emergency department

Explicit targets for use

Pandemic alert period	(WHO, phase 5: localised clusters of human cases) – treatment of cases and prophylaxis of contacts
Established pandemic	
Treatment	All cases meeting indications for treatment (see clinical guidelines)
PEP	No
Prophylaxis	No

Planned stockpile

14.6 millions treatment courses, Oseltamivir (including powder for children) for 61 millions population (2006) = 24%

Explicit prioritisation if stockpile not sufficient

Priority explicitly given to health care workers with influenza-like symptoms and un-immunised people in high-risk groups (no more defined)

4.5.3.2 Clinical guidelines : Indications for treatment with antiviral drugs during a flu pandemic[87]

Diagnostic and treatment decision

Clinical definition of acute influenza-like illness (ILI): presence of fever and new (or, in those with chronic lung disease, worsening) cough of acute onset in the context of influenza circulating in the community.

Laboratory confirmation not required to initiate treatment.

Primary care

Treat adults and children > 1y.o IF

- acute ILI AND
- fever (>38C), AND
- symptoms for two days or less.

Exceptions: patients unable to mount an adequate febrile response, e.g. the immunocompromised or very elderly, may still be eligible for antiviral treatment despite the lack of documented fever. Immunosuppressed patients, including those on long-term corticosteroid therapy, may suffer more prolonged viraemia, and could possibly benefit from antiviral therapy commenced later than 48 hours after the onset of ILI. Patients who are severely ill, but who have not been hospitalised due to non-clinical reasons, may benefit from antiviral therapy commenced later than 48 hours after the onset of ILI.

There is no strong evidence to support antiviral use in these exceptional situations.

Patients admitted to hospital

Treat adults and children > 1y.o IF

- acute ILI AND
- fever (>38C), AND
- symptoms for two days or less.

Patients unable to mount an adequate febrile response, e.g. the immunocompromised or very elderly, may still be eligible for antiviral treatment despite lack of documented fever. Hospitalised patients who are severely ill, particularly if also immunocompromised, may benefit from antiviral treatment started more than 48 hours from disease onset, although there is no evidence to demonstrate benefit, or lack of, in such circumstances.

In children who are severely ill in hospital oseltamivir may be used if the child has been symptomatic for <6 days (but there is no evidence to demonstrate benefit or lack of it in such circumstances)

4.5.3.3 Surveillance, monitoring, research[85, 87]

Develop and maintain capacity for antivirals susceptibility testing

Plan monitoring of effectiveness and possible adverse reactions of antivirals

4.5.3.4 Sources[85, 86]

- UK Health Departments; 2005 [updated 2005; cited September 21]. Influenza pandemic contingency plan (October 2005 edition). Available from: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4121735&chk=Z6kjQY
- Department of Health U. UK operational framework for stockpiling, distributing and using antiviral medicines in the event of pandemic influenza. 2005 September 2005.Available from: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/Publi

cationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4119491&chk=T/laww

4.5.4 United States

4.5.4.1 NEEDS ASSESMENT AND STOCKPILING

Basic assumptions

Attack rate (+ duration)	25-30% over 8 weeks
Case-fatality rate	NA
Groups most at risk	The greatest risk of hospitalization and death—as during the 1957 and 1968 pandemics and annual influenza—will be in infants, the elderly, and those with underlying health conditions.
Other assumptions	Treatment with NA inhibitor (oseltamivir or zanamivir) will decrease hospitalisation by half 35% in priority groups will have influenza-like illness , 75% will present in the first 48 hours and eligible for treatment For persons admitted to hospitals, 80% would be treated as the 48h-limit may sometimes be relaxed in more ill patients Pre-exposure prophylaxis (PEP)(oseltamivir) to be taken for 20 days (40 doses) = the equivalent of 4 treatment courses

Explicit targets for use

Pandemic alert period	
Treatment	All symptomatic cases suspected of novel influenza (ideally within 48 hours after onset of symptoms)
PEP	Contacts
Prophylaxis	Targeted chemoprophylaxis to contain small clusters, to be decided on a case-by-case basis
Established pandemic	
Treatment	All symptomatic cases
PEP	Outbreak response in nursing homes and other residential settings
Prophylaxis	Highest risk outpatients, HCWs with direct patient contact

Planned stockpile

Planned needs (treatment + PEP + pre-exposure prophylaxis): 132,7 millions courses (one course= the equivalent of one treatment course or 10 doses)

Recommended stockpile : +/- 40 millions courses, to allow coverage of 7 top priority groups (see below). 40 millions courses / 299 million persons (2006) = 14%

- 85% dedicated to treatment
- 12% dedicated to profylaxis
- 5% dedicated to post exposure profylaxis

Expected production capacity 1.25 million course/month.

Explicit prioritization during pandemic if stockpile not sufficient

Priority	Group	Strategy	%**
1	Patients admitted to hospital	T*	6%
2	Health care workers (HCW) with direct patient contact and emergency medical service (EMS) providers	T	2%
3	Highest risk outpatients—immunocompromised persons and pregnant women	T	1%
4	Pandemic health responders (public health, vaccinators, vaccine and antiviral manufacturers), public safety (police, fire, corrections), and government decision-makers	T	1%
5	Increased risk outpatients—young children 12-23 months old, persons >65 yrs old, and persons with underlying medical conditions	T	17%
6	Outbreak response in nursing homes and other residential settings	PEP*	2%
7	HCWs in emergency departments, intensive care units, dialysis centers, and EMS providers	P	4%
8	Pandemic societal responders (e.g., critical infrastructure groups as defined in the vaccine priorities) and HCW without direct patient contact	T	2%
9	Other outpatients	T	36%
10	Highest risk outpatients	P*	8%
11	Other HCWs with direct patient contact	P	24%

* T=treatment PEP=Post-exposure prophylaxis P= pre-exposure prophylaxis (4 treatment courses).
** Percentage of total needs for treatment courses, computed from data presented.

It is notable here that the treatment for outpatients (if not at particular risk) has very low priority (and is not even accounted for in the stockpile). This table also makes it clear that prophylaxis is a very resource-consuming strategy.

4.5.4.2 Clinical guidelines: Indications for treatment with antiviral drugs during a flu pandemic [88]

Diagnostic and treatment decision

Clinical definition of influenza-like illness (ILI): temperature of >38°C plus one of the following: sore throat, cough, or dyspnea (might need updating when pandemic occurs).

Earliest stage of pandemic: treatment decisions should be based on laboratory-confirmed subtype identification of the pandemic strain (positive rapid antigen test for influenza A for initiating treatment; confirmatory, definitive laboratory test required for continuation of treatment, negative results of influenza testing permitting termination of treatment).

When there is increasing disease activity in the United States, treatment decision can be based only on epidemiologic and clinical characteristics. Initiation of antiviral treatment is permitted before results from viral isolation, IFA, RT-PCR assays, or rapid antigen tests become available, since early treatment is more likely to be effective. Once infection becomes more common, negative rapid antigen test results are more likely to represent false negatives; therefore, treatment should continue while awaiting results from confirmatory testing.

Widespread pandemic: treatment decisions should be based only on (updated) clinical features and epidemiologic risk factors.

4.5.4.3 Surveillance, monitoring, research implying antivirals drugs[88]

Human surveillance and epidemiology

*Future priorities: d*etermine the impact of antiviral drugs, including the evolution of resistance.

Antiviral drug development

Ongoing activities of Health and Human Services: development/ testing of new drugs, new treatment schemes (ex : monotherapy vs combination therapy) ; supporting a clinical trial infrastructure to evaluate new influenza antiviral drugs.

Future priorities:

Studies to improve programmatic feasibility of stockpiling antiviral drugs.

Conduct clinical trials of potentially resource-sparing approaches such as dose reduction and shortened treatment courses

Study antiviral drug efficacy in severely ill hospitalized patients (including treatment started late in disease course)

Evaluate safety and dosing in infants with influenza, and alternative dosing regimens/formulations for infants and young children.

Research priorities during a pandemic

Evaluate change in natural history of disease and effect of antiviral drugs (including possible dosing changes, resistance emergence, adverse events and risk/benefit assessment, etc.)

Evaluate the effect of early use of antiviral drugs in high-risk patients.

Research priorities after a pandemic

Evaluate antiviral strategies; assess adverse events related to antivirals.

4.5.4.4 Sources[88, 89]

- United States Department of Health and Human Services; 2006 [updated March 30,2006; cited 18/09/2006]. HHS Pandemic Influenza Plan. Supplement 5: clinical guidelines. Available from: http://www.hhs.gov/pandemicflu/plan/
- United States Department of Health and Human Services; 2006 [updated March 30,2006; cited 18/09/2006]. HHS Pandemic Influenza Plan. Appendix G. Research activities. Available from: http://www.hhs.gov/pandemicflu/plan/

4.5.5 The Netherlands

4.5.5.1 NEEDS ASSESSMENT AND STOCKPILING

Basic assumptions

Attack rate + duration	25%, 9 weeks
Mortality rate	28/100 000
Groups most at risk	65 and older

	50%; 9 weeks
Moratlity rate	55/100 000
Groups most at risk	65 and older

Attack rate + duration	25%; 14 weeks
Assumptions	use of AV therapeutically
Mortality rate	15/100 000
Groups most at risk	65 and older

Attack rate + duration	25%; 12 weeks
Assumptions	vaccination of high risk groups
Mortality rate	7/100 000
Groups most at risk	65 and older

Attack rate + duration	50%; 12 weeks
Assumptions	vaccination of high risk groups
Mortality rate	14/100 000
Groups most at risk	65 and older

Explicit targets for use / strategies

Pandemic alert period (objective: containment)	
Treatment	Yes (all)
PEP	?
Prophylaxis	?
Established pandemic	
Treatment	Yes
PEP	No
Prophylaxis	No

At this moment: only therapeutic use. Objective: spread the pandemic in time. Cfr. 28.4

Planned stockpile

Oseltamivir : - (As per 15 March 2004) 225 700 treatment courses . - Intended (end of 2007): 5 000 000 courses . 16,491,461 (pop 2006) / 5000.000 (intended 2007) = +/- 30% . NB: the plan refers to buying a cheaper oseltamivir version (p 35, ???)

Explicit prioritization during pandemic if stockpile not sufficient

As per March 2004, stockpile +/- 230 000 courses:

Priority	Group	Strategy
	Flu in patients at risk for complications (patients with chronic and severe pulmonary or cardiac diseases, diabetes mellitus..)	T
	Flu in HCW directly involved in the care of patients with influenza or professionals supplying the resources for patient care)	T
	Flu in patients belonging to a specific pandemic risk group, if such a risk group exists and can be defined	T
	Flu requiring hospitalization	T
If/when stockpile expanded:		
	All patients with flu	T
	Patients with underlying disease (ex AIDS)	P
	Control outbreaks in residents of institutions (nursing homes and other chronic care facilities)	PEP

in patients with underlying disease leading to a greater risk of complications of influenza (e.g. AIDS) (needs to evaluated by medical professional)

department of nursing home with proven influenza in the department; only if the department can be well isolated

in specific pandemic risk groups and medical professionals during the period after vaccination with pandemic vaccine and in the period the pandemic is circulating in the Netherlands

	Treatment	prophylaxis
Start pandemic in Netherlands	Index patient	Household members and other contacts of the index patient; post-exposure prophylaxis
Full pandemic or massive introduction of the virus from other countries	Risk groups Professionals Specific pandemic risk groups	

4.5.5.2 SOURCES

- Ministerie van Volksgezondheid Welzijn en Sport. Beleidsdraaiboek Influenzapandemie. Landelijke Coördinatiestructuur Infectieziektebestrijdint (LCI); 2004 Juli 2004. Available from: http://www.infectieziekten.info/index.php3?lokatie=http%3A//www.infectieziekten.info/protocol.php3%3Fpagid%3D142
- Operationeel modeldraaiboek Influenzapandemie: http://www.infectieziekten.info/bestanden/protocollen/010704_Beleidsdraaiboek_influenzapandemie.doc

4.5.6 Switzerland

4.5.6.1 NEEDS ASSESMENT AND STOCKPILING

Basic assumptions

Attack rate (+ duration)	Adults: 25% of population Duration of pandemic wave: 8 – 12 weeks
Consultation rate	100% of influenza patients
Hospitalization rate	1 à 2,5 % of influenza patients
Intensive care	15% of hospitalized patients
Case fatality rate	0,4%
Mortality rate	0,1 %
Groups most at risk	seasonal influenza infants, persons > 65 yr, persons having a chronic illness or compromised immune system. Pandemic : unknown
Other assumptions	Absenteism: 10 %

Explicit targets for use

General targets :

- decrease of severity of individual illness (morbidity)
- decrease of mortality rate
- prevention of spreading of the new type virus during the pandemic alert phase
- protection of persons playing a key part in the struggle against the pandemic (prophylaxis)

Explicit targets:

Pandemic alert phase 3	
Treatment	Person with suspicion or confirmation of infection with the new type influenza virus
PEP	all persons having been in contact with an infected persons (without proper protection) all persons having been in contact with infected animals (without proper protection)
Prophylaxis	Persons involved in the struggle against epizoonoses.
Pandemic alert phase 4	
Treatment	Idem 3 + persons suspected of infection by a new type influenza virus by interhuman infection after confirmation of criteria
PEP	Idem 3 + Persons having been in contact with persons suspected of influenza
prophylaxis	Idem 3 + exposed health care workers
Pandemic alert phase 5	
Treatment	Idem 4
PEP	Idem 4
Prophylaxis	Idem 4
Pandemic alert phase 6	
Treatment	Idem 4
PEP	No prophylaxis for contacts
Prophylaxis	Health care workers

Planned stockpile

- pandemic alert phase 4: 10 000 packages
- pandemic alert phase 5: stock for 25% of the population
- total stock pile: population : 7 300 000
- treatments: for 25% of the population or 2 000 000 treatment courses(2X75 mg / d during 5 days)
- prophylaxis: for 250 000 persons (75mg / d during 6 weeks) = 1050000reserve stock pile: 10 % (or 306 000 courses)
- total: 3 366 000 of 46% of population

4.5.6.2 Clinical guidelines: Indications for treatment with antiviral drugs during a flu pandemic [88]

Diagnostic and treatment decision

Clinical definition of influenza-like illness (ILI):

- Seasonal flu: fever (> 38 °C), general feeling of illness, muscle pain, generalized pain. Sometimes: cough, rhinitis, joint pains.
- Avian flu: fever > 38°C, sneezing, sore throat, breathing difficulties, pneumonia, diarrhea.
- Pandemic flu: unknown. Hypothesis: clinical manifestations similar to seasonal flu

Indications for antivirals will be defined in phase 4

4.5.6.3 Surveillance, monitoring, research implying antivirals drugs[89]

Human surveillance and epidemiology

- Phase 1: registration and testing of new products against influenza
  - → Observation of side effect , interactions and resistance
- Phase 3: analyse clinical studies and recent data on efficacy and safety of antivirals
- Phase 4 - 6: monitoring of the use of antivirals
- Between pandemic waves: evaluate efficacy of antivirals and development of resistance. Adjust guidelines for use when necessary.
- After pandemic: evaluate efficacy and safety of antivirals

General remarks:

- Very detailed plan.
- Well underpinned.
- Clarifies areas of uncertainty – explains basis of decisions. I
- Contains a chapter on the ethical aspects.

4.5.6.4 Sources

Plan Suisse de pandémie Influenza 2006. Stratégies et mesures en preparation pour le cas d'une pandémie d'influenza. Département fédéral de l'interieur. Office fédéral de la santé publique. Suisse.[61]

4.5.7 Norway

4.5.7.1 NEEDS ASSESMENT AND STOCKPILING

Basic assumptions

Attack rate (+ duration)	Infection rate: 30 % over 6 months. 15% fall ill or become bedridden. Worst case scenario: 50% infection rate, 25 % fall ill or become bedridden.
Case-fatality rate	0,1-0,4% (700 – 3000 deaths in 700 000 cases of influenza)
Groups most at risk	See prioritisation
Other assumptions	Not specified

Explicit targets for use

General targets

satisfy the requirement of treatment of all persons In Norway who are taken ill with pandemic influenza

preventing the disease in certain priority groups

other anti-influenza medication for preventing the disease in approximately 300 000 persons in the course of six weeks

Pandemic alert period	All phases (pandemic phase in Norway : the state of disease that is described during the individual phase actually occurs in Norway or Norway maintains trade or cross border travel with a country in which the infectious disease exists)
Established pandemic	idem
Treatment	Yes
PEP	Yes
prophylaxis	Yes

Planned stockpile

1.4 millions packages, Oseltamivir (including powder for children) for 4,6 millions population (2006) = 30%

Explicit prioritisation if stockpile not sufficient

priority	Strategy	Target group
1	Primary prophylaxis	Continuous exposed health care personnel
2	Secondary prophylaxis	Close contacts to influenza diseased during the contagious period (ring-treatment of cases during the first period of the pandemic)
3	Treatment	Diseased persons with risk of complications
4	Treatment	Diseased and pregnant
5	Treatment	Diseased without risk of complications
6	Primary prophylaxis	Key personnel in leading positions and in selected societal services according to a close assessment of the present situation (health care system, veterinary system, pharmacies, energy sector, water sector, food supplies, renovation, public transport, telecommunications, personnel in fire departments and emergency servisc, plice, customs officers, people engaged in food safety, boarder control, people engaged in safety at word inclusive offshore stations, defence, civil defence, foreign services, humanitarian aid organisations, other key personnel in critical positions of civil society)

Priority category 6: amantadine if virus is sensitive. If the virus is amantadine resistant or in case of catastrophic pandemic influenza, it will be considered to prioritise putting certain key personnel on primary prophylaxis with oseltamivir instead of giving the drug to diseased people. This to prevent society from breaking down.

In a situation in which disease-provoking influenza virus among animals in Norway that could transmit to humans, people with high risk of exposure to this virus could be recommended to take Tamiflu as prophylactic treatment (medicines in this case obtained from ordinary pharmacies)

4.5.7.2 Clinical guidelines : Indications for treatment with antiviral drugs during a flu pandemic

Diagnostic and treatment decision

Not specified. WHO case definition will be followed (p24)

4.5.7.3 Surveillance, monitoring, research

The Norwegian Influenza Centre will collect samples of influenza virus types during and immediately after the outbreak of a pandemic and forwarding these straight away to WHO Collaborating Centres . Implementation of a weekly report on the epidemiological situation in the country throughout the influenza season to WHO in Geneva.

REMARK

The Norwegian plan contains an action plan for the different WHO phases. This part of the plan is only available in Norwegian.

4.5.7.4 Source

Norwegian National Influenza Pandemic Preparedness Plan. Norwegian Ministry of Health and Care Services. February 2006.

4.5.8 Spain

4.5.8.1 NEEDS ASSESSMENT AND STOCKPILING

Basic assumptions

Explicit targets for use / strategies

Objectives:

to minimize disease severity and the number of deaths and, secondly, to minimize the degree of social disruption

replenish AV reserves

revise, with updated information, plan for AV distribution and administration

Actions:

monitor the adverse effects and resistance continually

update use indications and management of cases

Planned stockpile

Not mentioned.

Explicit prioritization during pandemic if stockpile not sufficient

The initial identification of risk groups is based on previous years in which the rate of influenza disease was high and the experience of previous pandemics. The definition of "high risk groups" must be redefined after the onset of the pandemic based on epidemiological data available at each moment.

4.5.8.2 SOURCES

National Influenza Preparedness and Response Plan: http://www.msc.es/ciudadanos/enfLesiones/enfTransmisibles/docs/PlanGripeIngles.pdf

4.5.9 Slovak Republic

4.5.9.1 NEEDS ASSESSMENT AND STOCKPILING

Basic assumptions

Attack rate	35%
Case-fatality rate	NA
Groups most at risk	Health professionals: 50 000-60 000 (1%) Indiv at risk for severe course: 530 000-600 000 (10%) Key personnel (econ …): 170 000 (2.9%)
Other assumptions	-

Explicit targets for use / strategies

Objective:

to influence the spread until a vaccine becomes available

shorten the illness by 1.5-2 days

alleviate the course of the disease

markedly reduce complications

shorten the recovery time

help contain the virus spread

Planned stockpile

(275 000 – 550 000)

1 925 000 (= 35%).

(population: 5 500 000).

Explicit prioritization during pandemic if stockpile not sufficient

As soon as the first local, lab-verified outbreak has been identified, prophylactic AV shall be administered to contacts of ill persons provided that the epidemiological investigation suggests the possibility of containment of the focus, i.e. prevention and/or slowing down by the administration of the spread of the infection.

Further spread across Slovakia: AV for all clinically ill patients; AV shall be applied to the most vulnarable population groups , including:

- HCW
- immunocompromised individuals
- chronically ill
- children and the elderly
- workers taking care of activities of economic relevance (i.e. professional exposure, maintenance of economic operation and public life)
- individuals at high risk of complications or death
- individuals who may become a potential source of infection

4.5.9.2 SURVEILLANCE, MONITORING, RESEARCH IMPLYING ANTIVIRAL DRUGS

Human surveillance and epidemiology

- monitoring of virus spread, monitoring of epidemiological, virological and clinical aspects
- preparation for the enlargement of lab capacities
- selection of the optimal diagnostic method, provision for diagnostic agents, coordination of laboratory diagnosis of infections at regional laboratories

Research priorities after a pandemic

- analysis of the impacts upon public health of the pandemic
- analysis of the impacts upon the operation of the state and its components of the pandemic
- recovery of the economy and the public lif

- recovery and transformation of pandemic bodies

4.5.9.3 SOURCES

Detailed plan of measures in case of an influenza pandemic in the Slovak Republic:
http://www.health.gov.sk/redsys/rsi.nsf/0/D2869A65B5F83280C12570EC00517352?OpenDocument

4.5.10 Czech Republic

4.5.10.1 NEEDS ASSESSMENT AND STOCKPILING

Basic assumptions

Explicit targets for use / strategies

At this moment: 50 000 doses: for the groups of active health care professionals as well as for security forces in order to manage the situation until a specific pandemic influenza vaccine is obtained. This reserve shall be the first step to protect the country against the risk of a pandemic and represents a partial supply of Tamiflu for the priority groups of people specified in the plan (i.e. for approximately 5% of the population.

Planned stockpile

(health care: 272 461 560 CZK

security, customs administration: 11 860 123 CZK

transport: 6 188 537 CZK

total: 592 878 000 CZK)

(population: 10 287 482)

at this moment: 50 000 doses: for the groups of active health care professionals as well as for security forces in order to manage the situation until a specific pandemic influenza vaccine is obtained. This reserve shall be the first step to protect the country against the risk of a pandemic and represents a partial supply of Tamiflu for the priority groups of people specified in the plan (i.e. for approximately 5% of the population).

Explicit prioritization during pandemic if stockpile not sufficient

Priority groups:

group 1a: persons at high risk due to their professional exposure to acute infections, who may easily spread influenza into other risk groups (out-patient health care facilities, long-term care facilities, nursing homes, other social care institutes, hygienic services)

group 1b: persons at a high risk of complications and death due to influenza (more than 65; patients in long-term, nursing homes, other social care services; patients with COPD, chronic vascular, cardiac and renal disease, diabetes; pts with HIV; pts with hemoproliferative diseases or neoplasias; pts using immunosuppressive agents; 6 months to 18 years; pts with chronic use of ASA; pts before and after transplantation; pts who have undergone splenectomy)

group 2: persons which may become a source of infection for the persons classified in groups 1a/b

group 3: persons working in key economic, defense, security sectors

Antiviral agents for prophylaxis will only be used for a very small indication group (persons who should be vaccinated but in whom vaccination is medically contraindicated) if a sufficient amount of vaccine for all high-risk and indication groups is available. Should the amount be insufficient, chemoprophylaxis will be provided free of charge primarily to the third indication group.

4.5.10.2 CLINICAL GUIDELINES: INDICATIONS FOR TREATMENT WITH ANTIVIRAL DRUGS DURING A FLU PANDEMIC

Chemoprophylaxis for maximum 3 weeks.

4.5.10.3 SURVEILLANCE, MONITORING, RESEARCH IMPLYING ANTIVIRAL DRUGS

4.5.10.4 SOURCES

Report on the fulfillment of the National Plan for Influenza Pandemics caused by a novel strain of the influenza virus (NPP) and on its further intent: http://www.eiss.org/documents/eiss_pandemic_plan_czech_republic.pdf

4.5.11 Germany

4.5.11.1 NEEDS ASSESSMENT AND STOCKPILING

Basic assumptions

Inhabitants of Germany by age group, special groups, and risk of influenza (2003 statistics).

Alters-gruppe	Bevölkerungsgruppe innerhalb der Altersgruppe	Anzahl Bevölkerung in der Altersgruppe	Risiko-gruppen-zugehö-rigkeit	Anzahl Bevölkerung in der Gruppe	in %
0-15		13.149.384	ja	**788.964**	6,0%
			nein	12.360.420	94,0%
16-60	Gesundheitswesen (GW)	3.800.000	ja	532.000	14,0%
			nein	3.268.000	86,0%
	öffentliche Ordnung (öÖ)	3.120.000	ja	436.800	14,0%
			nein	2.683.200	86,0%
	nicht GW, nicht öO	42.137.387	ja	**5.899.234**	14,0%
			nein	36.238.153	86,0%
> 60		20.328.015	ja	**9.554.167**	47,0%
			nein	**10.773.848**	53,0%
Gesamt		82.534.786		82.534.786	

GW= health care workers (HCW); öffentliche Ordnung= public order

Attack rate + duration	15%; 8 weeks
Specific mortality rate	48 000 deaths (58 /100 000)
Groups most at risk	NA
Other assumptions	with therapy of all ill patients: 24 000 fatalities less with prophylaxis of professionals: 4 800 fatalities less

Attack rate + duration	30%; 8 weeks
mortality rate	96 000 deaths (110 /100 000)
Groups most at risk	NA
Other assumptions	with therapy of all ill patients: 48 000 fatalities less with prophylaxis of professionals: 9 600 fatalities less

Attack rate + duration	50%; 8 weeks
mortality rate	160 273 deaths (190 /100 000)
Groups most at risk	NA
Other assumptions	with therapy of all ill patients: 80 000 fatalities less with prophylaxis of professionals: 16 000 fatalities less

(population: 82 534 786)

Explicit targets for use / strategies

To diminish mortality and morbidity and to control the influenza on health care.

No possibility for prophylaxis for the entire population because of reasons of capacity (production), logistics and finances.

Treatment:

All patients who are seriously ill, who are at high for complications and who present within 48 hours after the onset of symptoms, have priority. Priority groups can change during the pandemic.

HCW and personnel in charge of public order are a second priority group.

In the beginning of the pandemic, postexposure-prophylaxis from contacts can be done.

Longtermprophylaxis can be done for special professionals, until vaccine is available and until 2 weeks after vaccination: HCW in hospital and nursing homes, because they have a greater risk of infection and they can be a source of infection, and persons in charge of public order.

Planned stockpile

Yes.

Explicit prioritization during pandemic if stockpile not sufficient

All patients who are seriously ill, who are at high risk for complications and who present within 48 hours after the onset of symptoms, have priority. Priority groups can change during the pandemic.

HCW and personnel responsible for public order are a second priority group.

One should start to supply a stock of antivirals for these priority populations in order to allow for postexposure prophylaxis.

4.5.11.2 CLINICAL GUIDELINES: INDICATIONS FOR TREATMENT WITH ANTIVIRAL DRUGS DURING A FLU PANDEMIC

Description of seasonal influenza, with some aspects of 1918 added.

Zanamivir as therapy for adults and children 12 years and older (inhalation therapy).

Oseltamivir as therapy for adults and children of 1 year and older, and as prophylaxis for adults and children of 12 years and older. Because of the way of administration, lower costs and usefulness in prophylaxis, oseltamivir is the first choice product. Amantadin is second choice for prophylaxis if stockpile of oseltamivir is not sufficient.

4.5.11.3 SURVEILLANCE, MONITORING, RESEARCH IMPLYING ANTIVIRAL DRUGS

Human surveillance and epidemiology

Cfr. 33.3

Antiviral drug development

Research priorities during a pandemic

Research concerning:

- incubation
- symptoms
- mortality, descriptive epidemiology, survival analysis
- exclusion of bioterroristic attack
- serologic and epidemiologic study of contacts
- manifestation index
- number of complications (pneumonia)
- number of visits to medicine
- number of hospitalisations
- infection rate in different situations
- viral shedding
- number of complications in risk groups:
- elderly
- chronically ill
- infants, children
- pregnant women
- efficacy of AV: therapy vs. prophylaxis

Research priorities after a pandemic

4.5.11.4 SOURCES

Nationaler Influenzapandemieplan:

http://www.rki.de/cln_011/nn_879788/DE/Content/InfAZ/I/Influenza/Influenzapandemieplan.html

4.5.12 Belgium

4.5.12.1 NEEDS ASSESSMENT AND STOCKPILING

Basic assumptions

Attack rate up to 30%.

Explicit targets for use / strategies

Only treatment, no prophylactic use because of:

- economic reasons
- unknown side-effects of use of NAI during more than 6 weeks
- ethical reasons (which subgroup of the population has the right to use NA prophylactically, and which not?)

Planned stockpile

3 million treatment courses (2.7 million Tamiflu, 300000 Relenza) = 30% of the population.

Explicit prioritization during pandemic if stockpile not sufficient

Treatment of all ill people is foreseen. No specific prioritization.

4.5.12.2 SOURCES

http://www.influenza.be/nl/operationeel-plan_nl.asp

4.5.13 France

4.5.13.1 NEEDS ASSESSMENT AND STOCKPILING

Basic assumptions

9 to 21 million ill people (depending on attack rate), in absence of treatment and hygienic measures. Population 2006: 60.9 million.

Explicit targets for use / strategies

Planned stockpile

Treatment for about 25% of the population.

At the end of 2005: 14 million treatment courses available (13.8 million Tamiflu and 200000 Relenza).

Explicit prioritization during pandemic if stockpile not sufficient

Can change during the pandemic (epidemiology, pathogenecity, resistance).

Priority for treatment. Zanamivir only for treatment for persons aged 12 years and older who have no difficulties to understand the way how to use it and who can be observed during treatment. Oseltamivir is first choice in treatment.

Prophylactic use depends on characteristics of the virus, epidemiologic data, efficacy of treatment and available amount of stockpile.

4.5.13.2 SOURCES

Assemblée Nationale de la République Française. Rapport fait au nom de la mission d'information sur la grippe aviaire: mesures préventives. TOME III « Plan pandémie » : une stratégie de gestion de crise. 2006

4.6 APPENDIX 6. SUMMARY OF PRODUCT CHRACTERISTICS FOR TAMIFLU (OSELTAMIVIR) AND RELENZA (ZANAMIVIR)

The summaries of product characteristics were received in November 2006 from the regulatory departments of the marketing authorisation holders and have been copied here for information only.

4.6.1 TAMIFLU (oseltamivir) - Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 75 mg capsule, hard.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 98.5 mg oseltamivir phosphate, corresponding to 75 mg of oseltamivir.

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard

The hard capsule consists of a grey opaque body bearing the imprint "ROCHE" and a light yellow opaque cap bearing the imprint "75 mg". Imprints are blue.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza in adults and children one year of age or older who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms. This indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A (see Section 5.1).

Prevention of influenza

- Post exposure prevention in adults and children one year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

- The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in adults and children one year of age or older.

Tamiflu is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations taking into consideration variability of epidemiology and the impact of the disease in different geographical areas and patient populations.

4.2 Posology and method of administration

Tamiflu capsules and Tamiflu suspension are bioequivalent formulations, 75 mg doses can be administered as either one 75 mg capsule or by administering one 30 mg dose plus one 45 mg dose of suspension. Adults, adolescents or children (>40 kg) who are unable to swallow capsules may receive appropriate doses of Tamiflu suspension.

The safety and efficacy of Tamiflu in children less than one year of age have not been established (see Section 5.3).

Treatment of influenza

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

For adults and adolescents 13 years or older the recommended oral dose is 75 mg oseltamivir twice daily, for 5 days.

For children one year or older, Tamiflu oral suspension is available. For children with body weight above 40 kg, capsules may be prescribed at the adult dosage of 75 mg twice daily for 5 days.

Prevention of influenza

Post exposure prevention

For adults and adolescents 13 years or older, the recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days. Therapy should begin as soon as possible within two days of exposure to an infected individual.

Children weighing > 40 kg, who are able to swallow capsules, may also receive prevention with a 75 mg capsule once daily for 10 days as an alternative to the recommended dose of Tamiflu suspension.

Prevention during an influenza epidemic in the community: The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to six weeks.

Special populations

Hepatic impairment

No dose adjustment is required either for treatment or for prevention, in patients with hepatic dysfunction

Renal impairment

Treatment of influenza: Dose adjustment is recommended for adults with severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	Recommended dose for treatment
>30 (ml/min)	75 mg twice daily
>10 to ≤30 (ml/min)	75 mg once daily or 30 mg suspension twice daily
≤10 (ml/min)	Not recommended
dialysis patients	Not recommended

Prevention of influenza: Dose adjustment is recommended for adults with severe renal impairment as detailed in the table below

Creatinine clearance	Recommended dose for prevention
>30 (ml/min)	75 mg once daily
>10 to ≤30 (ml/min)	75 mg every second day or 30 mg suspension once daily
≤10 (ml/min)	Not recommended
dialysis patients	Not recommended

Elderly

No dose adjustment is required, unless there is evidence of severe renal impairment.

4.3 Contraindications

Hypersensitivity to oseltamivir phosphate or to any of the excipients.

4.4 Special warnings and special precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses.

The safety and efficacy of oseltamivir for the treatment and prevention of influenza in children of less than one year of age have not been established (see Section 5.3).

No information is available regarding the safety and efficacy of oseltamivir in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalisation.

The safety and efficacy of oseltamivir in either treatment or prevention of influenza in immunocompromised patients have not been established.

Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see Section 5.1).

Tamiflu is not a substitute for influenza vaccination. Use of Tamiflu must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as Tamiflu is administered. Tamiflu should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community.

Severe renal impairment

Dose adjustment is recommended for both treatment and prevention in adults with severe renal insufficiency. There are no data concerning the safety and efficacy of oseltamivir in children with renal impairment (see Sections 4.2 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see Section 5.2), suggest that clinically significant drug interactions via these mechanisms are unlikely.

No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid , a potent inhibitor of the anionic pathway of renal tubular secretion results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway suggesting that oseltamivir interaction with this pathway is weak.

Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone.

No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetyl-salicylic acid, cimetidine or with antacids (magnesium and aluminium hydroxides and calcium carbonates).

4.6 Pregnancy and lactation

There are no adequate data from the use of oseltamivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see Section 5.3). Oseltamivir should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. It is not known whether oseltamivir or the active metabolite are excreted in human milk. Oseltamivir should be used during lactation only if the potential benefit for the mother justifies the potential risk for the nursing infant.

4.7 Effects on ability to drive and use machines

Tamiflu has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

Treatment of influenza in adults and adolescents: A total of 2107 patients participated in phase III studies in the treatment of influenza. The most frequently reported undesirable effects were nausea, vomiting and abdominal pain. The majority of these events were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. All events that were reported commonly, (i.e. at an incidence of at least 1 %, irrespective of causality) in subjects receiving oseltamivir 75 mg twice daily, are included in the table below.

Treatment of influenza in elderly: In general, the safety profile in the elderly patients was similar to adults aged up to 65 years: the incidence of nausea was lower in oseltamivir treated elderly persons (6.7 %) than in those taking placebo (7.8 %) whereas the incidence of vomiting was higher in those who received oseltamivir (4.7 %) than among placebo recipients (3.1 %).

The adverse event profile in adolescents and in the patients with chronic cardiac and/or respiratory disease was qualitatively similar to that of healthy young adults.

Prevention of influenza In prevention studies, where the dosage of oseltamivir was 75 mg once daily for up to 6 weeks,, adverse events reported more commonly in subjects receiving oseltamivir compared to subjects receiving placebo (in addition to the events listed in the table below) were: Aches and pains, rhinorrhoea, dyspepsia and upper respiratory tract infection. There were no clinically relevant differences in the safety profile of the elderly subjects, who received oseltamivir or placebo, compared with the younger population.

Most Frequent Adverse Events in Studies in Naturally Acquired Influenza

System Organ Class	Adverse Event	Treatment		Prevention	
		Placebo (N=1050)	Oseltamivir 75 mg twice daily (N=1057)	Placebo (N=1434)	Oseltamivir 75 mg once daily (N=1480)
Gastrointestinal Disorders	Vomiting [2]	3.0 %	8.0 %	1.0 %	2.1 %
	Nausea [1, 2]	5.7 %	7.9 %	3.9 %	7.0 %
	Diarrhoea	8.0 %	5.5 %	2.6 %	3.2 %
	Abdominal Pain	2.0 %	2.2 %	1.6 %	2.0 %
Infections and Infestations	Bronchitis	5.0 %	3.7 %	1.2 %	0.7 %
	Bronchitis acute	1.0 %	1.0 %	-	-
General Disorders	Dizziness	3.0 %	1.9 %	1.5 %	1.6 %
	Fatigue	0.7 %	0.8 %	7.5 %	7.9 %
Neurological Disorders	Headache	1.5 %	1.6 %	17.5 %	20.1 %
	Insomnia	1.0 %	1.0 %	1.0 %	1.2 %

[1] Subjects who experienced nausea alone; excludes subjects who experienced nausea in association with vomiting.
[2] The difference between the placebo and oseltamivir groups was statistically significant.

Treatment of influenza in children: A total of 1032 children aged 1 to 12 years (including 695 otherwise healthy children aged 1 to 12 years and 334 asthmatic children aged 6 to 12 years) participated in phase III studies of oseltamivir given for the treatment of influenza. A total of 515 children received treatment with oseltamivir suspension. Adverse events occurring in greater than 1 % of children receiving oseltamivir are listed in the table below. The most frequently reported adverse event was vomiting. Other events reported more frequently by oseltamivir treated children included abdominal pain, epistaxis, ear disorder and conjunctivitis. These events generally occurred once, resolved despite continued dosing and did not cause discontinuation of treatment in the vast majority of cases.

Most Frequent Adverse Events in Studies in Naturally Acquired Influenza in Children [Adverse Events Occurring On Treatment in >1% of Paediatric Patients]

	Treatment[a]				Treatment[b]		Prevention[b]	
Adverse Event	**Placebo N=517**		**Oseltamivir 2 mg/kg bid N=515**		**Oseltamivir 30 to 75 mg[c] N=158**		**Oseltamivir 30 to 75 mg[c] N=99**	
Vomiting	48	(9.3%)	77	(15.0%)	31	(19.6%)	10	(10.1%)
Diarrhoea	55	(10.6%)	49	(9.5%)	5	(3.2%)	1	(1.0%)
Otitis media	58	(11.2%)	45	(8.7%)	2	(1.3%)	2	(2.0%)
Abdominal pain	20	(3.9%)	24	(4.7%)	3	(1.9%)	3	(3.0%)
Asthma (including aggravated)	19	(3.7%)	18	(3.5%)	-		1	(1.0%)
Nausea	22	(4.3%)	17	(3.3%)	10	(6.3%)	4	(4.0%)
Epistaxis	13	(2.5%)	16	(3.1%)	2	(1.3%)	1	(1.0%)
Pneumonia	17	(3.3%)	10	(1.9%)	-		-	
Ear disorder	6	(1.2%)	9	(1.7%)	-		-	
Sinusitis	13	(2.5%)	9	(1.7%)	-		-	
Bronchitis	11	(2.1%)	8	(1.6%)	3	(1.9%)	-	
Conjunctivitis	2	(0.4%)	5	(1.0%)	-		-	
Dermatitis	10	(1.9%)	5	(1.0%)	1	(0.6%)	-	
Lymphadenopathy	8	(1.5%)	5	(1.0%)	1	(0.6%)	-	
Tympanic membrane disorder	6	(1.2%)	5	(1.0%)	-		-	

[a] Pooled data from Phase III trials of Tamiflu treatment of naturally acquired influenza.
[b] Uncontrolled study comparing treatment (twice-daily dosing for 5 days) with prevention (once-daily dosing for 10 days).
[c] 30 to 75 mg = age-based dosing (see Section 5.1).

Adverse events included are: all events reported in the treatment studies with a frequency ≥1% in the oseltamivir 2 mg/kg bid group.

In general, the adverse event profile in the children with asthma was qualitatively similar to that of otherwise healthy children.

Prevention of influenza in children

Paediatric patients aged 1 to 12 years participated in a post exposure prevention study in households, both as index cases (n=134) and as contacts (n=222). Gastrointestinal events, particulary vomiting were the most frequently reported,. The adverse events were consistent with those previously observed (see table above).

Observed during clinical practice: The following adverse reactions have been reported during postmarketing use of oseltamivir: dermatitis, rash, eczema, urticaria, angioneurotic oedema, hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, as well as very rare reports of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Additionally, there are very rare reports of hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness.

4.9 Overdose

There is no experience with overdose. However, the anticipated manifestations of acute overdose would be nausea, with or without accompanying vomiting,

and dizziness. Patients should discontinue the treatment in the event of overdose. No specific antidote is known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral

ATC code: J05AH02

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published trials.

Reduced sensitivity of viral neuraminidase: There has been no evidence for emergence of drug resistance associated with the use of Tamiflu in clinical studies conducted to date in post exposure (7 days), post exposure within household groups (10 days) and seasonal (42 days) prevention of influenza.

The risk of emergence of drug resistance in clinical use in the treatment of influenza has been extensively examined. In all clinical studies in naturally acquired infection 0.32% (4/1245) of adults and adolescents and 4.1% (19/464, range 0-19% in individual studies) of children aged 1-12 were found to transiently carry influenza virus with decreased neuraminidase susceptibility to oseltamivir carboxylate. The emergence of resistance may be higher in young children and in children who had immunosuppression or who were under-exposed to oseltamivir. Patients carrying resistant virus cleared it normally and showed no clinical deterioration. Rare cases of oseltamivir-resistant virus strains in patients who were not confirmed to have been exposed to oseltamivir have been reported. All resistant genotypes are disadvantaged compared to the corresponding wild-type isolate and are likely to be less contagious in man. Thus far, there is no evidence for resistance in influenza B *in vitro* or in clinical trials.

Treatment of influenza infection

Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population which included both influenza-positive and-negative subjects (ITT) primary efficacy was reduced proportional to the number of influenza-negative individuals. In the overall treatment population influenza infection was confirmed in 67 % (range 46 % to 74 %) of the recruited patients. Of the elderly subjects, 64 % were influenza positive and of those with chronic cardiac and/or respiratory disease 62 % were influenza positive. In all

phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents aged 13 years and older:. Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥37.8 °C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2413) enrolled into treatment studies oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95 % CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95 % CI 4.0 – 4.4 days) (p ≤0.0001).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1063) in the placebo group to 8.6 % (116/1350) in the oseltamivir treated population (p = 0.0012).

Treatment of influenza in high risk populations:

The median duration of influenza illness in elderly subjects (≥ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In the influenza-positive elderly, oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics, from 19 % (52/268) in the placebo group to 12 % (29/250) in the oseltamivir treated population (p = 0.0156).

In influenza-positive patients with chronic cardiac and/or respiratory disease the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17% (22/133) in the placebo group and 14 % (16/118) in the oseltamivir treated population (p = 0.5976).

Treatment of influenza in children: In a study of otherwise healthy children (65 % influenza-positive), aged 1 to 12 years (mean age 5.3 years), who had fever (≥37.8° C) plus either cough or coryza, 67 % of influenza-positive patients were infected with influenza A and 33 % with influenza B. Oseltamivir treatment , started within 48 hours of onset of symptoms, significantly reduced the time to freedom from illness (defined as the simultaneous return to normal health and activity and alleviation of fever, cough and coryza,) by 1.5 days (95 % CI 0.6 - 2.2 days, p < 0.0001) compared to placebo. Oseltamivir reduced the incidence of acute otitis media from 26.5 % (53/200) in the placebo group to 16 % (29/183) in the oseltamivir treated children (p = 0.013).

A second study was completed in 334 asthmatic children aged 6 to 12 years old of which 53.6 % were influenza-positive. In the oseltamivir treated group the median duration of illness was not reduced significantly. By day 6 (the last day of treatment) FEV_1 had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo (p = 0.0148) in this population.

Treatment of influenza B infection: Overall 15 % of the influenza-positive population were infected by influenza B, proportions ranging from 1 to 33 % in individual studies. The median duration of illness in influenza B infected subjects did not differ significantly between the treatment groups in individual studies. Data from 504 influenza B infected subjects were pooled across all studies for analysis. Oseltamivir reduced the time to alleviation of all symptoms by 0.7 days (95 % CI 0.1 – 1.6 days; p = 0.022) and the duration of fever (≥37.8° C), cough

and coryza by one day (95 % CI 0.4 – 1.7 days; p <0.001)), compared to placebo.

Prevention of influenza

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory confirmed influenza. The virulence of influenza epidemics is not predictable and varies within a region and from season to season, therefore the number needed to treat (NNT) in order to prevent one case of influenza illness varies.

Post-exposure prevention: A study in contacts (12.6 % vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily, was started within 2 days of onset of symptoms in the index case and continued for seven days. Influenza was confirmed in 163 out of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12 %) in the placebo group to 2/205 (1 %) in the oseltamivir group (92 % reduction, (95 % CI 6 – 16), p ≤0.0001). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95 % CI 9 – 12) and was 16 (95 % CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and children aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20% (27/136) in the group not receiving prevention to 7% (10/135) in the group receiving prevention (62.7% reduction, [95% CI 26.0-81.2]; p= 0.0042). In households of influenza infected index cases, there was a reduction in the incidence of influenza from 26% (23/89) in the group not receiving prevention to 11% (9/84) in the group receiving prevention (58.5% reduction, [95% CI 15.6-79.6; p=0.0114].

According to subgroup analysis in children at 1-12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21/111) in the group not receiving prevention to 7 % (7/104) in the group receiving (64.4 % reduction, (95 % CI 15.8-85.0); p= 0.0188). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15/70) in the group not receiving prevention to 4 % (2/47) in the group receiving prevention (80.1 % reduction, (95 % CI 22.0-94.9); p = 0.0206). The NNT for the total paediatric population was 9 (95 % CI 7-24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTII) respectively.

Prevention during an influenza epidemic in the community: In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25/519 (4.8 %) in the placebo group to 6/520 (1.2 %) in the oseltamivir group (76 % reduction, (95 % CI 1.6 – 5.7); p = 0.0006) during a community outbreak of influenza. The NNT in this study was 28 (95 % CI 24 – 50).

A study in elderly residents of nursing homes, where 80 % of participants received vaccine in the season of the study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4 %) in the placebo group to 1/276 (0.4 %) in the oseltamivir group (92 % reduction, (95 % CI 1.5 – 6.6) ; p = 0.0015. The NNT in this study was 25 (95 % CI 23 – 62).

Specific studies have not been conducted to assess of the reduction in the risk of complications.

5.2 Pharmacokinetic properties

Absorption

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5 % relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution

The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular oseltamivir carboxylate distributes to all sites of influenza virus spread.

The binding of the oseltamivir carboxylate to human plasma protein is negligible (approximately 3 %).

Metabolism

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In-vitro* studies demonstrated, that neither oseltamivir, nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination

Absorbed oseltamivir is primarily (>90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds glomerular filtration rate (7.5 l/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Renal impairment

Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see Section 4.2.

Hepatic impairment

In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see Section 4.2).

Elderly

Exposure to the active metabolite at steady state was 25 to 35 % higher in elderly (age 65 to 78 years) compared to adults less than 65 years of age, given

comparable doses of oseltamivir. Half–lives observed in the elderly were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for elderly patients unless there is evidence of severe renal impairment (creatinine clearance below 30 ml/min) (see Section 4.2).

Children

The pharmacokinetics of oseltamivir have been evaluated in single dose pharmacokinetic studies in children aged one to 16 years. Multiple dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the prodrug and its active metabolite faster than adults, resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults, receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children over 12 years of age are similar to those in adults.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of Tamiflu in its adopted therapeutic indications.

Teratology studies have been conducted in rats and rabbits at doses of up to 1500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal development were observed. A rat fertility study up to a dose of 1500 mg/kg/day demonstrated no adverse effects on either sex. In pre- / post-natal rat studies, prolonged parturition was noted at 1500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. It is not known whether oseltamivir or the active metabolite are excreted in human milk, but extrapolation of the animal data provides estimates of 0.01 mg/day and 0.3 mg/day for the respective compounds.

A potential for skin sensitisation to oseltamivir was observed in a "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active ingredient showed erythema after challenging the induced animals. Reversible irritancy of rabbits' eyes was detected.

In a two-week study in unweaned rats a single dose of 1000 mg/kg oseltamivir phosphate to 7-day old pups resulted in deaths associated with unusually high exposure to the pro-drug. However, at 2000 mg/kg in 14-day old unweaned pups, there were no deaths or other significant effects. No adverse effects occurred at 500 mg/kg/day administered from 7 to 21 days *post partum.* .In a single-dose investigatory study of this observation in 7-, 14- and 24-day old rats, a dose of 1000 mg/kg resulted in brain exposure to the pro-drug that suggested, respectively, 1500-, 650-, and 2-fold the exposure found in the brain of adult (42-day old) rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinized starch (derived from maize starch), talc, povidone, croscarmellose sodium, and sodium stearyl fumarate. The capsule shell contains gelatin, yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172) and titanium dioxide (E171). The printing ink contains shellac, titanium dioxide (E171) and FD and C Blue 2 (indigo carmine, E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

One box contains 10 capsules in a triplex blister pack (PVC/PE/PVDC, sealed with aluminium foil).

6.6 Instructions for use and handling and disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited

6 Falcon Way

Shire Park

Welwyn Garden City

AL7 1TW

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 June 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 12 mg/ml powder for oral suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder for oral suspension, containing 39.4 mg oseltamivir phosphate per 1 g filling mixture.

The reconstituted suspension contains 12 mg oseltamivir per ml.

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension

The powder is a granulate or clumped granulate with a white to light yellow colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza in adults and children one year of age or older who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms. This indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A (see Section 5.1).

Prevention of influenza

Post exposure prevention in adults and children one year of age or older following a contact with clinically diagnosed influenza case when influenza virus is circulating in the community.

The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in adults and children one year of age or older.

Tamiflu is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations taking into consideration variability of epidemiology and the impact of the disease in different geographical areas and patient populations.

4.2 Posology and method of administration

Tamiflu suspension and Tamiflu capsules are bioequivalent formulations, 75 mg doses can be administered as either one 75 mg capsule or by administering one 30 mg dose plus one 45 mg dose of suspension. Adults, adolescents or children (>40 kg) who are able to swallow capsules may receive appropriate doses of Tamiflu capsules.

The safety and efficacy of Tamiflu in children less than one year of age have not been established (see Section 5.3).

Treatment of influenza

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

For adults and adolescents 13 years or older the recommended oral dose is 75 mg oseltamivir twice daily, for 5 days

For children of 1 to 12 years of age: The recommended dose of Tamiflu oral suspension is indicated in the table below. The following weight adjusted dosing regimens are recommended for children one year or older:

Body Weight	Recommended dose for 5 days
≤15 kg	30 mg twice daily
>15 kg to 23 kg	**45 mg twice daily**
>23 kg to 40 kg	**60 mg twice daily**
>40 kg	**75 mg twice daily**

For dosing an oral dispenser with 30 mg, 45 mg, and 60 mg graduations is provided in the box. For accurate dosing the oral dispenser supplied should be used exclusively.

Prevention of influenza

Post exposure prevention

For adults and adolescents 13 years or older, the recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days. Therapy should begin as soon as possible within two days of exposure to an infected individual.

Children weighing >40 kg, who are able to swallow capsules, may also receive prevention with a 75 mg capsule once daily for 10 days as an alternative to the recommended dose of Tamiflu suspension.

The recommended prophylactic dose of Tamiflu suspension for children one year or older is:

Body Weight	Recommended dose for 10 days
≤15 kg	30 mg once daily
>15 kg to 23 kg	**45 mg once daily**
>23 kg to 40 kg	**60 mg once daily**
>40 kg	**75 mg once daily**

For dosing an oral dispenser with 30 mg, 45 mg, and 60 mg graduations is provided in the box. For accurate dosing the oral dispenser supplied should be used exclusively.

It is recommended that Tamiflu powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient (see Section 6.6)

Prevention during an influenza epidemic in the community: The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to six weeks.

Special populations

Hepatic impairment

No dose adjustment is required either for treatment or for prevention, in patients with hepatic dysfunction.

Renal impairment

Treatment of influenza: Dose adjustment is recommended for adults with severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	Recommended dose for treatment
>30 (ml / min)	75 mg twice daily
>10 to ≤ 30 (ml / min)	75 mg once daily or 30 mg suspension twice daily
≤10 (ml / min)	Not recommended
dialysis patients	Not recommended

Prevention of influenza: Dose adjustment is recommended for adults with severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for prevention
>30 (ml / min)	75 mg once daily
>10 to ≤ 30 (ml / min)	75 mg every second day or 30 mg suspension once daily
≤10 (ml / min)	Not recommended
dialysis patients	Not recommended

Elderly

No dose adjustment is required, unless there is evidence of severe renal impairment.

4.3 Contraindications

Hypersensitivity to oseltamivir phosphate or to any of the excipients.

4.4 Special warnings and special precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses.

The safety and efficacy of oseltamivir for the treatment and prevention of influenza in children of less than one year of age have not been established (see Section 5.3).

No information is available regarding the safety and efficacy of oseltamivir in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalisation.

The safety and efficacy of oseltamivir in either treatment or prevention of influenza in immunocompromised patients have not been established.

Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see Section 5.1).

Tamiflu is not a substitute for influenza vaccination. Use of Tamiflu must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as Tamiflu is administered. Tamiflu should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community.

Severe renal impairment

Dose adjustment is recommended for both treatment and prevention in adults with severe renal insufficiency. There are no data concerning the safety and efficacy of oseltamivir in children with renal impairment (see Sections 4.2 and 5.2).

This medicinal product contains 26 g of sorbitol. One dose of 45 mg oseltamivir administered twice daily delivers 2.6 g of sorbitol. For subjects with hereditary fructose intolerance this is above the recommended daily maximum limit of sorbitol.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see Section 5.2) suggest that clinically significant drug interactions via these mechanisms are unlikely.

No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway suggesting that oseltamivir interaction with this pathway is weak. Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetyl-salicylic acid, cimetidine or with antacids (magnesium and aluminium hydroxides and calcium carbonates).

4.6 Pregnancy and lactation

There are no adequate data from the use of oseltamivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see Section 5.3). Oseltamivir should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. It is not known whether oseltamivir or the active metabolite are excreted in human milk. Oseltamivir should be used during lactation only if the potential benefit for the mother justifies the potential risk for the nursing infant.

4.7 Effects on ability to drive and use machines

Tamiflu has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

Treatment of influenza in adults and adolescents: A total of 2107 patients participated in phase III studies in the treatment of influenza. The most frequently reported undesirable effects were nausea, vomiting and abdominal pain. The majority of these events were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. All events that were reported commonly, (i.e. at an incidence of at least 1 %, irrespective of causality) in subjects receiving oseltamivir 75 mg twice daily, are included in the table below.

Treatment of influenza in elderly: In general, the safety profile in the elderly patients was similar to adults aged up to 65 years: the incidence of nausea was lower in oseltamivir treated elderly persons (6.7 %) than in those taking placebo (7.8 %) whereas the incidence of vomiting was higher in those who received oseltamivir (4.7 %) than among placebo recipients (3.1 %).

The adverse event profile in adolescents and in the patients with chronic cardiac and/or respiratory disease was qualitatively similar to that of healthy young adults.

Prevention of influenza. In prevention studies, where the dosage of oseltamivir was 75 mg once daily for up to 6 weeks, adverse events reported more commonly in subjects receiving oseltamivir compared to subjects receiving placebo (in addition to the events listed in the table below) were: Aches and pains, rhinorrhoea, dyspepsia and upper respiratory tract infection. There were no clinically relevant differences in the safety profile of the elderly subjects, who received oseltamivir or placebo, compared with the younger population.

Most Frequent Adverse Events in Studies in Naturally Acquired Influenza

System Organ Class	Adverse Event	Treatment		Prevention	
		Placebo (N = 1050)	Oseltamivir 75 mg twice daily (N = 1057)	Placebo (N = 1434)	Oseltamivir 75 mg once daily (N = 1480)
Gastrointestinal Disorders	Vomiting [2]	3.0 %	8.0 %	1.0 %	2.1 %
	Nausea [1, 2]	5.7 %	7.9 %	3.9 %	7.0 %
	Diarrhoea	8.0 %	5.5 %	2.6 %	3.2 %
	Abdominal Pain	2.0 %	2.2 %	1.6 %	2.0 %
Infections and Infestations	Bronchitis	5.0 %	3.7 %	1.2 %	0.7 %
	Bronchitis acute	1.0 %	1.0 %	-	-
General Disorders	Dizziness	3.0 %	1.9 %	1.5 %	1.6 %
	Fatigue	0.7 %	0.8 %	7.5 %	7.9 %
Neurological Disorders	Headache	1.5 %	1.6 %	17.5 %	20.1 %
	Insomnia	1.0 %	1.0 %	1.0 %	1.2 %

[1] Subjects who experienced nausea alone; excludes subjects who experienced nausea in association with vomiting.

2 The difference between the placebo and oseltamivir groups was statistically significant.

Treatment of influenza in children: A total of 1032 children aged 1 to 12 years (including 695 otherwise healthy children aged 1 to 12 years and 334 asthmatic children aged 6 to 12 years) participated in phase III studies of oseltamivir given for the treatment of influenza. A total of 515 children received treatment with oseltamivir suspension. Adverse events occurring in greater 1 % of children receiving oseltamivir are listed in the table below. The most frequently reported adverse event was vomiting. Other events reported more frequently by oseltamivir treated children included abdominal pain, epistaxis, ear disorder and conjunctivitis. These events generally occurred once, resolved despite continued dosing and did not cause discontinuation of treatment in the vast majority of cases.

Most Frequent Adverse Events in Studies in Naturally Acquired Influenza in Children [Adverse Events Occurring On Treatment in >1% of Paediatric Patients]

	Treatment[a]				Treatment[b]		Prevention[b]	
Adverse Event	**Placebo N=517**		**Oseltamivir 2 mg/kg bid N=515**		**Oseltamivir 30 to 75 mg[c] N=158**		**Oseltamivir 30 to 75 mg [c] N=99**	
Vomiting	48	(9.3%)	77	(15.0%)	31	(19.6%)	10	(10.1%)
Diarrhoea	55	(10.6%)	49	(9.5%)	5	(3.2%)	1	(1.0%)
Otitis media	58	(11.2%)	45	(8.7%)	2	(1.3%)	2	(2.0%)
Abdominal pain	20	(3.9%)	24	(4.7%)	3	(1.9%)	3	(3.0%)
Asthma (including aggravated)	19	(3.7%)	18	(3.5%)	-		1	(1.0%)
Nausea	22	(4.3%)	17	(3.3%)	10	(6.3%)	4	(4.0%)
Epistaxis	13	(2.5%)	16	(3.1%)	2	(1.3%)	1	(1.0%)
Pneumonia	17	(3.3%)	10	(1.9%)	-		-	
Ear disorder	6	(1.2%)	9	(1.7%)	-		-	
Sinusitis	13	(2.5%)	9	(1.7%)	-		-	
Bronchitis	11	(2.1%)	8	(1.6%)	3	(1.9%)	-	
Conjunctivitis	2	(0.4%)	5	(1.0%)	-		-	
Dermatitis	10	(1.9%)	5	(1.0%)	1	(0.6%)	-	
Lymphadenopathy	8	(1.5%)	5	(1.0%)	1	(0.6%)	-	
Tympanic membrane disorder	6	(1.2%)	5	(1.0%)	-		-	

[a] Pooled data from Phase III trials of Tamiflu treatment of naturally acquired influenza.
[b] Uncontrolled study comparing treatment (twice-daily dosing for 5 days) with prevention (once-daily dosing for 10 days).
[c] 30 to 75 mg = age-based dosing (see Section 5.1).

Adverse events included are: all events reported in the treatment studies with a frequency ≥1% in the oseltamivir 2 mg/kg mg bid group.

In general, the adverse event profile in the children with asthma was qualitatively similar to that of otherwise healthy children.

Prevention of influenza in children

Paediatric patients aged 1 to 12 years participated in a post exposure prevention study in households, both as index cases (n=134) and as contacts (n=222). Gastrointestinal events, particulary vomiting were the most frequently reported. The adverse events were consistent with those previously observed (see table above).

Observed during clinical practice: The following adverse reactions have been reported during postmarketing use of oseltamivir: dermatitis, rash, eczema, urticaria, angioneurotic oedema , hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, as well as very rare reports of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Additionally, there are very rare reports of hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness.

4.9 Overdose

There is no experience with overdose. However, the anticipated manifestations of acute overdose would be nausea, with or without accompanying vomiting, and dizziness. Patients should discontinue the treatment in the event of overdose. No specific antidote is known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral

ATC code: J05AH02

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells and the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1nM to 1.3nM, and for influenza B was 2.6nM. Higher IC50 values for influenza B, up to a median of 8.5nM, have been observed in published trials.

Reduced sensitivity of viral neuraminidase: There has been no evidence for emergence of drug resistance associated with the use of Tamiflu in clinical studies conducted to date in post exposure (7 days), post exposure within household groups (10 days) and seasonal (42 days) prevention of influenza.

The risk of emergence of drug resistance in clinical use in the treatment of influenza has been extensively examined. In all clinical studies in naturally acquired infection 0.32% (4/1245) of adults and adolescents and 4.1% (19/464, range 0-19% in individual studies) of children aged 1-12 were found to transiently carry influenza virus with decreased neuraminidase susceptibility to oseltamivir carboxylate. The emergence of resistance may be higher in young children and in children who had immunosuppression or who were under-exposed to oseltamivir. Patients carrying resistant virus cleared it normally and showed no clinical deterioration. Rare cases of oseltamivir-resistant virus strains in patients who were not confirmed to have been exposed to oseltamivir have been reported. All resistant genotypes are disadvantaged compared to the corresponding wild-type isolate and are likely to be less contagious in man. Thus far, there is no evidence for resistance in influenza B *in vitro* or in clinical trials.

Treatment of influenza infection

Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population which included both influenza-positive and -negative subjects (ITT) primary efficacy was reduced proportional to the number of influenza negative individuals. In the overall treatment population influenza infection was confirmed in 67 % (range 46 % to 74 %) of the recruited patients. Of the elderly subjects, 64 % were influenza positive and of those with chronic cardiac and/or respiratory disease 62 % were influenza positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents aged 13 years and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥37.8°C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2413) enrolled into treatment studies oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95 % CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95 % CI 4.0 – 4.4 days) (p ≤0.0001).

The proportion of subjects who developed specified lower respiratory tract complications(mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1063) in the placebo group to 8.6 % (116/1350) in the oseltamivir treated population (p = 0.0012).

Treatment of influenza in high risk populations:

The median duration of influenza illness in elderly subjects (≥ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In the influenza-positive elderly, oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics, from 19 % (52/268) in the placebo group to 12 % (29/250) in the oseltamivir treated population (p = 0.0156).

In influenza-positive patients with chronic cardiac and/or respiratory disease the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17 % (22/133) in the placebo group and 14 % (16/118) in the oseltamivir treated population (p = 0.5976).

Treatment of influenza in children: In a study of otherwise healthy children (65% influenza-positive), aged 1 to 12 years (mean age 5.3 years), who had fever (≥ 37.8°C) plus either cough or coryza, 67 % of influenza-positive patients were infected with influenza A and 33 % with influenza B. Oseltamivir treatment started within 48 hours of onset of symptoms, significantly reduced the duration of time to freedom from illness (defined as the simultaneous return to normal health and activity and alleviation of fever, cough and coryza) by 1.5 days (95 % CI 0.6 - 2.2 days, p < 0.0001) compared to placebo. oseltamivir reduced the incidence of acute otitis media from 26.5 % (53/200) in the placebo group to 16 % (29/183) in the oseltamivir treated children (p = 0.013).

A second study was completed in 334 asthmatic children aged 6 to 12 years old of which 53.6 % were influenza-positive. In the oseltamivir treated group the median duration of illness was not reduced significantly. By day 6 (the last day of treatment) FEV_1 had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo (p = 0.0148) in this population.

Treatment of influenza B infection: Overall 15 % of the influenza-positive population were infected by influenza B, proportions ranging from 1 to 33 % in individual studies. The median duration of illness in influenza B infected subjects did not differ significantly between the treatment groups in individual studies. Data from 504 influenza B infected subjects were pooled across all studies for analysis. oseltamivir reduced the time to alleviation of all symptoms by 0.7 days (95 % CI 0.1 – 1.6 days; p = 0.022) and the duration of fever (≥ 37.8° C), cough and coryza by one day (95 % CI 0.4 - 1.7 days; p < 0.001)), compared to placebo.

Prevention of influenza

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory confirmed influenza. The virulence of influenza epidemics is not predictable and varies within a region and from season to season, therefore the number needed to treat (NNT) in order to prevent one case of influenza illness varies.

Post-exposure prevention: A study in contacts (12.6 % vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily, was started within 2 days of onset of symptoms in the index case and continued for seven days. Influenza was confirmed in 163 out of 377 index cases. oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12 %) in the placebo group to 2/205 (1 %) in the oseltamivir group (92 % reduction, (95% CI 6 – 16), p ≤0.0001). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95 % CI 9 – 12) and was 16 (95 % CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and children aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20% (27/136) in the group not receiving prevention to 7% (10/135) in the group receiving prevention (62.7% reduction, [95% CI 26.0-81.2]; p= 0.0042). In households of influenza infected index cases, there was a reduction in the incidence of influenza from 26% (23/89) in the group not receiving prevention to 11% (9/84) in the group receiving prevention (58.5% reduction, [95% CI 15.6-79.6; p=0.0114].

According to subgroup analysis in children at 1-12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21/111) in the group not receiving prevention to 7 % (7/104) in the group receiving (64.4 % reduction, (95 % CI 15.8-85.0); p= 0.0188). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15/70) in the group not receiving prevention to 4 % (2/47) in the group receiving prevention (80.1 % reduction, (95 % CI 22.0-94.9); p= 0.0206). The NNT for the total paediatric population was 9 (95 % CI 7-24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTII) respectively.

Prevention during an influenza epidemic in the community: In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25/519 (4.8 %) in the placebo group to 6/520 (1.2 %) in the oseltamivir group (76 % reduction, 95 % CI 1.6 – 5.7); p = 0.0006) during a community outbreak of influenza. The NNT in this study was 28 (95 % CI 24 – 50).

A study in elderly residents of nursing homes, where 80 % of participants received vaccine in the season of the study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from

12/272 (4.4 %) in the placebo group to 1/276 (0.4 %) in the oseltamivir group (92 % reduction, (95 % CI 1.5 – 6.6); p = 0.0015). The NNT in this study was 25 (95 % CI 23 – 62).

Specific studies have not been conducted to assess of the reduction in the risk of complications.

5.2 Pharmacokinetic properties

Absorption

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5 % relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution

The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular oseltamivir carboxylate distributes to all sites of influenza virus spread.

The binding of the oseltamivir carboxylate to human plasma protein is negligible (approximately 3 %).

Metabolism

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In-vitro* studies demonstrated, that neither oseltamivir, nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination

Absorbed oseltamivir is primarily (>90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds glomerular filtration rate (7.5 l/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Renal impairment

Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see Section 4.2.

Hepatic impairment

In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see Section 4.2).

Elderly

Exposure to the active metabolite at steady state was 25 to 35 % higher in elderly (age 65 to 78 years) compared to adults less than 65 years of age, given comparable doses of oseltamivir. Half–lives observed in the elderly were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for elderly patients unless there is

evidence of severe renal impairment (creatinine clearance below 30 ml/min) (see Section 4.2).

Children

The pharmacokinetics of oseltamivir have been evaluated in single dose pharmacokinetic studies in children aged one to 16 years. Multiple dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the prodrug and its active metabolite faster than adults, resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults, receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children over 12 years of age are similar to those in adults.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of Tamiflu in its adopted therapeutic indications.

Teratology studies have been conducted in rats and rabbits at doses of up to 1500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal development were observed. A rat fertility study up to a dose of 1500 mg/kg/day demonstrated no adverse effects on either sex. In pre- / post-natal rat studies, prolonged parturition was noted at 1500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. It is not known whether oseltamivir or the active metabolite are excreted in human milk, but extrapolation of the animal data provides estimates of 0.01 mg/day and 0.3 mg/day for the respective compounds.

A potential for skin sensitisation to oseltamivir was observed in a "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active ingredient showed erythema after challenging the induced animals. Reversible irritancy of rabbits' eyes was detected.

In a two-week study in unweaned rats a single dose of 1000 mg/kg oseltamivir phosphate to 7-day old pups resulted in deaths associated with unusually high exposure to the pro-drug. However, at 2000 mg/kg in 14-day old unweaned pups, there were no deaths or other significant effects. No adverse effects occurred at 500 mg/kg/day administered from 7 to 21 days *post partum*. .In a single-dose investigatory study of this observation in 7-, 14- and 24-day old rats, a dose of 1000 mg/kg resulted in brain exposure to the pro-drug that suggested, respectively, 1500-, 650-, and 2-fold the exposure found in the brain of adult (42-day old) rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420), sodium dihydrogen citrate (E331(a)), xanthan gum (E415), sodium benzoate (E211), saccharin sodium (E954), titanium dioxide (E171) and tutti frutti flavour (including maltodextrins (maize), propylene glycol, arabic gum

E414 and natural identical flavouring substances) (mainly consisting of banana, pineapple and peach flavour).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After reconstitution, the suspension should not be used for longer than 10 days.

6.4 Special precautions for storage

Do not store above 30°C.

After reconstitution, store the suspension at 2°C- 8°C (in a refrigerator).

6.5 Nature and contents of container

Carton containing a 100 ml amber glass bottle (with child-resistant plastic screw cap) with 30 g of powder for oral suspension, a plastic adapter, a plastic oral dispenser and a plastic measuring cup). After reconstitution with 52 ml of water, the usable volume of oral suspension allows for the retrieval of a total of 10 doses of 75 mg oseltamivir.

6.6 Instructions for use and handling and disposal

It is recommended that Tamiflu oral suspension should be reconstituted by the pharmacist prior to its dispensing to the patient.

Preparation of Oral Suspension

1. Tap the closed bottle gently several times to loosen the powder.

2. Measure 52 ml of water by filling the measuring cup to the indicated level (measuring cup included in the box).

3. Add all 52 ml of water into the bottle, recap the bottle and shake the closed bottle well for 15 seconds.

4. Remove the cap and push the bottle adapter into the neck of the bottle.

5. Close the bottle tightly with the cap (on the top of the bottle adapter). This will make sure that the bottle adapter fits in the bottle in the right position.

Tamiflu powder for suspension will appear as an opaque and white to light yellow suspension after reconstitution.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited

6 Falcon Way

Shire Park

Welwyn Garden City

AL7 1TW

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 June 2002

10. DATE OF REVISION OF THE TEXT

4.6.2 RELENZA (zanamivir) - Summary of Product Characteristics

Name of the Medicinal Product

Relenza 5mg/dose, inhalation powder, pre-dispensed.

Qualitative and Quantitative Composition

Each pre-dispensed quantity of inhalation powder (one blister) contains 5 mg zanamivir. Each delivered inhalation (the amount that leaves the mouthpiece of the Diskhaler) contains 4.0mg zanamivir.

For excipients, see section 6.1.

Pharmaceutical Form

Inhalation powder, pre-dispensed.

Clinical Particulars

Therapeutic indications

Treatment of influenza

Relenza is indicated for treatment of both influenza A and B in adults and children (≥ 5 years) who present with symptoms typical of influenza when influenza is circulating in the community.

Prevention of influenza

Relenza is indicated for post-exposure prophylaxis of influenza A and B in adults and children (≥ 5 years) following contact with a clinically diagnosed case in a household (see section 5.1 for children aged 5-11 years). In exceptional circumstances, Relenza may be considered for seasonal prophylaxis of influenza A and B during a community outbreak (e.g. in case of a mismatch between circulating and vaccine strains and a pandemic situation).

Relenza is not a substitute for influenza. The appropriate use of Relenza for prevention of influenza should be determined on a case-by-case basis depending on the circumstances and the population requiring protection.

The use of antivirals for the treatment and prevention of influenza should take into consideration official recommendations, the variability of epidemiology, and the impact of the disease in different geographical areas and patient populations.

Posology and method of administration

Treatment of influenza

Treatment should begin as soon as possible and within 48 hours after onset of symptoms for adults, and within 36 hours after onset of symptoms for children.

Relenza is for administration to the respiratory tract by oral inhalation only, using the Diskhaler device provided. One blister should be utilised for each inhalation.

The recommended dose of Relenza for treatment of influenza in adults and children from the age of 5 years is two inhalations (2 x 5 mg) twice daily for five days, providing a total daily inhaled dose of 20 mg.

Inhaled drugs, e.g. asthma medication, should be administered prior to administration of Relenza (see section 4.4).

Prevention of influenza

Post-exposure prophylaxis

The recommended dose of Relenza for prevention of influenza, following close contact with an individual, is two inhalations (2 x 5 mg) once daily for 10 days. Therapy should begin as soon as possible and within 36 hours of exposure to an infected person.

Seasonal prophylaxis

The recommended dose of Relenza for prevention of influenza during a community outbreak is 2 inhalations (2 x 5 mg) once daily for up to 28 days.

*Impaired Renal or Hepatic Function***:** No dose modification is required. (See section 5.2).

Elderly patients: No dose modification is required. (See section 5.2).

Contraindications

Hypersensitivity to any ingredient of the preparation (see Pharmaceutical Particulars, 6.1 List of excipients).

Special warnings and special precautions for use

Due to the limited number of patients with severe asthma or with other chronic respiratory disease, patients with unstable chronic illnesses or immunocompromised patients (see Section 5.1) who have been treated, it has not been possible to demonstrate the efficacy and safety of Relenza in these groups. Due to limited and inconclusive data, the efficacy of Relenza in the prevention of influenza in the nursing home setting has not been demonstrated. The efficacy of zanamivir for the treatment of elderly patients $\geqq$ 65 years has also not been established (see section 5.1).

There have been very rare reports of patients being treated with Relenza who have experienced bronchospasm and/or decline in respiratory function which may be acute and/or serious. Some of these patients did not have any previous history of respiratory disease. Any patients experiencing such reactions should discontinue Relenza and seek medical evaluation immediately.

Due to the limited experience, patients with severe asthma require a careful consideration of the risk in relation to the expected benefit, and Relenza should not be administered unless close medical monitoring and appropriate clinical facilities are available in case of bronchoconstriction. In patients with persistent asthma or severe COPD, management of the underlying disease should be optimised during therapy with Relenza.

Should zanamivir be considered appropriate for patients with asthma or chronic obstructive pulmonary disease, the patient should be informed of the potential risk of bronchospasm with Relenza and should have a fast acting bronchodilator available. Patients on maintenance inhaled bronchodilating therapy should be advised to use their bronchodilators before taking Relenza (see section 4.2).

Relenza is not a substitute for influenza vaccination and the use of Relenza must not affect the evaluation of individuals for annual vaccination. The protection against influenza only lasts as long as Relenza is administered. Relenza should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza is circulating in the community.

Relenza is effective only against illness caused by influenza viruses. There is no evidence for the efficacy of Relenza in any illness caused by agents other than influenza viruses.

Interaction with other medicinal products and other forms of interaction

Zanamivir is not protein bound and not hepatically metabolised or modified. Clinically significant drug interactions are unlikely. Zanamivir, when given for 28 days, did not impair the immune response to influenza vaccine.

Pregnancy and lactation

Pregnancy: The safe use of Relenza during pregnancy has not been established.

In rats and rabbits zanamivir has been shown to cross the placenta. High doses of zanamivir were not associated with malformations in rats or rabbits and only minor alterations were reported. The potential risk for humans is unknown. Relenza should not be used in pregnancy unless the expected benefit to the mother is thought to outweigh any possible risk to the foetus.

Lactation: In rats zanamivir has been shown to be secreted into milk. There is no information on secretion into breast milk in humans.

The use of zanamivir is not recommended in mothers who are breast feeding.

Effects on ability to drive and use machines

None known

Undesirable effects

There have been rare reports of patients with previous history of respiratory disease (asthma, COPD) and very rare reports of patients without previous history of respiratory disease, who have experienced acute bronchospasm and/or serious decline in respiratory function after use of Relenza (see section 4.4).

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

Immune system disorders

Very rare: allergic-type reaction including facial and oropharyngeal oedema

Respiratory, thoracic and mediastinal disorders:

Very rare: bronchospasm, dyspnea, throat tightness or constriction

Skin and subcutaneous tissue disorders:

Very rare: rash, urticaria

Overdose

Accidental overdose is unlikely due to the physical limitations of the presentation, the route of administration and the poor oral bioavailability (2 to 3%) of zanamivir. Doses of zanamivir up to 64 mg/day (approximately 3 times the maximum daily recommended dose) have been administered by oral inhalation (by nebuliser) without adverse effects. Additionally, systemic

exposure by intravenous administration of up to 1200 mg/day for five days showed no adverse effect.

Pharmacological Properties

Pharmacodynamic properties

ATC code J05AH01

Mechanism of action

Zanamivir is a selective inhibitor of neuraminidase, the influenza virus surface enzyme. Neuraminidase inhibition occurred in vitro at very low zanamivir concentrations (50% inhibition at 0.64nM – 7.9nM against influenza A and B strains). Viral neuraminidase aids the release of newly formed virus particles from infected cells, and may facilitate access of virus through mucus to epithelial cell surfaces, to allow viral infection of other cells. The inhibition of this enzyme is reflected in both *in vitro* and *in vivo* activity against influenza A and B virus replication, and encompasses all of the known neuraminidase subtypes of influenza A viruses.

The activity of zanamivir is extracellular. It reduces the propagation of both influenza A and B viruses by inhibiting the release of infectious influenza virions from the epithelial cells of the respiratory tract. Influenza viral replication occurs in the superficial epithelium of the respiratory tract. The efficacy of topical administration of zanamivir to this site has been confirmed in clinical studies. To date, virus with reduced susceptibility to zanamivir has not been detected in samples obtained pre and post treatment from patients in clinical studies.

Cross-resistance has been observed between some zanamivir-resistant and some oseltamivir-resistant influenza virus mutants generated in vitro. No studies have been performed to assess risk of emergence of cross-resistance during clinical use.

Clinical experience

Treatment of influenza

Relenza alleviates the symptoms of influenza and reduces their median duration by 1.5 days (range 0.25 – 2.5 days) in adults as detailed in the table below. The efficacy of Relenza has been demonstrated in otherwise healthy adults when treatment is initiated within 48 hours, and in otherwise healthy children when treatment is initiated within 36 hours, after the onset of symptoms. No treatment benefit has been documented for patients with afebrile disease (< 37.8°C).

Six key Phase III randomised, placebo-controlled, parallel-group, multicentre treatment studies (NAIB3001, NAIA3002, NAIB3002, NAI30008, NAI30012 and NAI30009) have been conducted with zanamivir for the treatment of naturally acquired influenza A and B. Study NAI30008 recruited only patients with asthma (n=399), COPD (n=87), or asthma and COPD (n=32), study NAI30012 recruited only elderly (≥65 years) patients (n=358) and study NAI30009 (n=471) recruited paediatric patients, 5-12 years. The Intent to Treat population of these six studies comprised 2942 patients of which 1490 received 10 mg zanamivir b.i.d by oral inhalation. The primary endpoint was identical for all six Phase III studies, i.e. time to alleviation of clinically significant signs and symptoms of influenza. For all six phase III studies, alleviation was defined as no fever, i.e. temperature <37.8◦C and feverishness score of 'none'('same as normal/none' in NAI30012), and headache, myalgia, cough and

sore throat recorded as 'none' ('same as normal/none' in NAI30012) or 'mild' and maintained for 24 hours.

Comparison of Median Time (Days) to Alleviation of Influenza Symptoms: Influenza Positive Population

Study	**Placebo**	**Zanamivir** 10mg inhaled twice daily	**Difference in Days**	**(95% CI)** **p-value**
NAIB3001	n=160 6.0	n=161 4.5	1.5	(0.5, 2.5) 0.004
NAIA3002	n=257 6.0	n=312 5.0	1.0	(0.0, 1.5) 0.078
NAIB3002	n=141 7.5	n=136 5.0	2.5	(1.0, 4.0) <0.001
Combined analysis of NAIB3001, NAIA3002, and NAIB3002	n=558 6.5	n=609 5.0	1.5	(1.0, 2.0) <0.001
Asthma/COPD study				
NAI30008	n=153 7.0	n=160 5.5	1.5	(0.5, 3.25) 0.009
Elderly study				
NAI30012	n=114 7.5	n=120 7.25	0.25	(-2.0 to 3.25) 0.609
Paediatric study				
NAI30009	n=182 5.0	n=164 4.0	1.0	(0.5, 2.0) <0.001

The median time to alleviation of influenza symptoms in elderly subjects (≥ 65 years) and in children aged 5-6 years, was not significantly reduced.

In the Intent to Treat (ITT) population the difference in time to alleviation of symptoms was 1.0 day (95% CI: 0.5 to 1.5) in the combined analysis of NAIB3001, NAIA3002 and NAIB3002, 1.0 day (95% CI: 0 to 2) in study NAI30008, 1.0 day (95% CI –1.0 to 3.0) in study NAI30012 and 0.5 days (95% CI: 0 to 1.5) in study NAI30009. There are limited data in high risk children.

In a combined analysis of patients with influenza B (n=163), including 79 treated with zanamivir, a 2.0 day treatment benefit was observed (95%CI: 0.50 to 3.50).

In the pooled analysis of 3 phase III studies in influenza positive, predominantly healthy adults, the incidence of complications was 152/558 (27%) in placebo recipients and 119/609 (20%) in zanamivir recipients (relative risk zanamivir:placebo 0.73; 95% CI 0.59 to 0.90, p=0.004). In study NAI30008 enrolling patients with asthma and COPD the incidence of complications was 56/153 (37%) in influenza-positive placebo recipients and 52/160 (33%) in influenza positive zanamivir recipients (relative risk zanamivir:placebo 0.89; 95% CI: 0.65 to 1.21, p=0.520). In study NAI30012 enrolling elderly patients the incidence of complications was 46/114 (40%) in influenza positive placebo recipients and 39/120 (33%) in influenza positive zanamivir recipients (relative risk zanamivir:placebo 0.80, 95% CI: 0.57 to 1.13, p=0.256). In the paediatric study NAI30009, the incidence of complications was 41/182 (23%) in influenza-positive placebo recipients and 26/164 (16%) in influenza-positive zanamivir recipients (relative risk zanamivir:placebo 0.70; 95% CI: 0.45 to 1.10, p=0.151).

In a placebo controlled study in patients with predominantly mild/moderate asthma and/or Chronic Obstructive Pulmonary Disease (COPD) there was no clinically significant difference between zanamivir and placebo in forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEFR) measured during treatment or after the end of treatment.

Prevention of influenza

The efficacy of Relenza in preventing naturally occurring influenza illness has been demonstrated in two post-exposure prophylaxis studies in households and two seasonal prophylaxis studies during community outbreaks of influenza. The primary efficacy endpoint in these studies was the incidence of symptomatic, laboratory-confirmed influenza, defined as the presence of two or more of the following symptoms: oral temperature 37.8°C or feverishness, cough, headache, sore throat, and myalgia; and laboratory confirmation of influenza by culture, PCR, or seroconversion (defined as a 4-fold increase in convalescent antibody titer from baseline).

Post exposure prophylaxis

Two studies assessed post-exposure prophylaxis in household contacts of an index case. Within 1.5 days of onset of symptoms in an index case, each household (including all family members ≥5 years of age) was randomized to Relenza 10 mg or placebo inhaled once daily for 10 days. In the first study only, each index case was randomized to the same treatment (Relenza or placebo) as the other household members. In this study, the proportion of households with at least one new case of symptomatic influenza was reduced from 19% (32 of 168 households) with placebo to 4% (7 of 169 households) with Relenza (79% protective efficacy; 95% CI: 57% to 89%, p<0.001). In the second study, index cases were not treated and the incidence of symptomatic influenza was reduced from 19% (46 of 242 households) with placebo to 4% (10 of 245 households) with Relenza (81% protective efficacy; 95% CI: 64% to 90%, p<0.001). Results were similar in the subgroups with influenza A or B. In these studies, which included a total of 2128 contact cases, 553 children were aged 5-11 years, of which 123 children were 5-6 years. The incidence of symptomatic laboratory confirmed influenza in the 5 to 6-year-old group (placebo vs. zanamivir) was 4/33 (12%) vs. 1/28 (4%) in the first study and 4/26 (15%) vs. 1/36 (3%) in the second study, which seems to be consistent with older age categories. However, as the studies were not powered to establish protective efficacy in individual age categories, a formal subgroup analysis has not been performed.

Seasonal Prophylaxis

Two seasonal prophylaxis studies assessed Relenza 10 mg versus placebo inhaled once daily for 28 days during community outbreaks. In the first study, which involved unvaccinated, otherwise healthy adults aged ≥ 18 years, the incidence of symptomatic influenza was reduced from 6.1% (34 of 554) with placebo to 2.0% (11 of 553) with Relenza (67% protective efficacy; 95% CI: 39% to 83%, p<0.001). The second study involved community-dwelling subjects aged ≥ 12 years at high risk of complications from influenza, where 67% of participants had received vaccine in the season of the study. High risk was defined as subjects ≥ 65 years of age and subjects with chronic disorders of the pulmonary or cardiovascular systems or with diabetes mellitus. In this study, the incidence of symptomatic influenza was reduced from 1.4% (23 of 1,685) with placebo to 0.2% (4 of 1,678) with Relenza (83% protective efficacy; 95% CI: 56% to 93%, p<0.001).

Due to limited and inconclusive data, the efficacy of Relenza in the prevention of influenza in the nursing home setting has not been established.

Pharmacokinetic properties

Absorption: Pharmacokinetic studies in humans have shown that the absolute oral bioavailability of the drug is low (mean (min, max) is 2%(1%, 5%)). Similar studies of orally inhaled zanamivir indicate that approximately 10-20% of the dose is systemically absorbed, with serum concentrations generally peaking within 1-2 hours. The poor absorption of the drug results in low systemic concentrations and therefore there is no significant systemic exposure to zanamivir after oral inhalation. There is no evidence of modification in the kinetics after repeated dosing with oral inhaled administration.

Distribution: After oral inhalation, zanamivir is widely deposited at high concentrations throughout the respiratory tract, thus delivering the drug to the site of influenza infection. Following a single 10mg dose the concentrations of zanamivir were measured in induced sputum. Zanamivir concentrations of 337 (range 58-1593) and 52 (range 17-286) fold above the median viral neuraminidase IC_{50} were measured at 12h and 24h respectively. The high concentrations of zanamivir in the respiratory tract will result in the rapid onset of inhibition of the viral neuraminidase. The major immediate site of deposition is the oropharynx (mean 78%) from where zanamivir was rapidly eliminated to the GI-tract. The early deposition in total lungs ranged between 8 and 21%.

Metabolism: Zanamivir has been shown to be renally excreted as unchanged drug, and does not undergo metabolism. *In vitro* studies demonstrated that zanamivir did not affect the activity of a range of probe substrates for cytochrome P450 isoenzymes (CYP1A/2, A6, 2C9, 2C18, 2D6, 2E1, 3A4) in human hepatic microsomes, nor did it induce cytochrome P450 expression in rats, suggesting that metabolic interactions between zanamivir and other drugs are unlikely *in vivo*.

Elimination: The serum half-life of zanamivir following administration by oral inhalation ranges from 2.6 to 5.05 hours. It is entirely excreted unchanged in the urine. Total clearance ranges from 2.5 to 10.9 L/h as approximated by urinary clearance. Renal elimination is completed within 24 hours.

Patients with renal impairment: Inhaled zanamivir results in approximately 10%-20% of the inhaled dose being absorbed. In the severe renal impairment group from the single IV zanamivir dose trial subjects were sampled after a dose of 2 mg or twice to four times the expected exposure from inhalation. Using the normal dosing regimen (10mg bid), the predicted exposure at Day 5 is 40 fold lower than what was tolerated in healthy subjects after repeated iv administration. Given the importance of local concentrations, the low systemic exposure, and the previous tolerance of much higher exposures no dose adjustment is advised.

Patients with hepatic impairment: Zanamivir is not metabolised, therefore dose adjustment in patients with hepatic impairment is not required.

Elderly patients: At the therapeutic daily dose of 20mg, bioavailabilty is low (10-20%), and as a result there is no significant systemic exposure of patients to zanamivir. Any alteration of pharmacokinetics that may occur with age is unlikely to be of clinical consequence and no dose modification is recommended.

Paediatric patients: In an open-label single-dose study the pharmacokinetics of zanamivir was evaluated in 16 paediatric subjects, aged 6 to 12 years, using dry powder (10 mg) inhalation formulation (Diskhaler device). The systemic exposure was similar to 10 mg of inhaled powder in adults, but the variability was large in all age groups and more pronounced in the youngest children. Five

patients were excluded due to undetectable serum concentrations at all time points or 1.5 hours post-dose, suggesting inadequate drug delivery.

Preclinical safety data

General toxicity studies did not indicate any significant toxicity of zanamivir. Zanamivir was not genotoxic and no clinically relevant findings were observed in long term carcinogenicity studies in rats and mice.

Pharmaceutical Particulars

List of excipients

Lactose monohydrate (which contains milk protein).

Incompatibilities

Not applicable

Shelf-life

5 years

Special precautions for storage

Do not store above 30°C.

Nature and content of container

Relenza inhalation powder is packed in a circular aluminium foil disk (a Rotadisk) with four regularly distributed blisters. An inspiration driven inhaler made of plastic (a Diskhaler) is used for administration of doses (the contents of 2 blisters constitute a dose) from these foil disks, and is provided in the pack.

The pack contains 1 or 5 foil disks and a Diskhaler.

Instructions for use and handling, and disposal (if appropriate)

The inhaler (Diskhaler) is loaded with a disk containing inhalation powder packed in individual blisters. These blisters are pierced when the inhaler is used, and with a deep inhalation the powder can then be inhaled through the mouthpiece down into the respiratory tract. Detailed instructions for use are enclosed in the pack.

Marketing Authorisation Holder

GlaxoSmithKline AB

Box 263

431 23 Mölndal

Marketing Authorisation Number(s)

14997

Date of First Authorisation/Renewal of the Authorisation

1999-02-09 / 2004-02-09

Date of Revision of the Text

23 August 2006

5 REFERENCES

1. Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. Health Technol Assess. 2003;7(35):iii-iv, xi-xiii, 1-170.
2. Jefferson T. Influenza vaccination: policy versus evidence. BMJ. 2006;333(7574):912-5.
3. Taubenberger JK, Reid AH, Lourens RM, Wang R, Jin G, Fanning TG. Characterization of the 1918 influenza virus polymerase genes. Nature. 2005;437(7060):889-93.
4. Juckett G. Avian influenza: preparing for a pandemic. Am Fam Physician. 2006;74(5):783-90.
5. Ellis JS, Alvarez-Aguero A, Gregory V, Lin YP, Hay A, Zambon MC. Influenza AH1N2 viruses, United Kingdom, 2001-02 influenza season. Emerg Infect Dis. 2003;9(3):304-10.
6. Lin YP, Gregory V, Bennett M, Hay A. Recent changes among human influenza viruses. Virus Res. 2004;103(1-2):47-52.
7. Beigel JH, Farrar J, Han AM, Hayden FG, Hyer R, de Jong MD, et al. Avian influenza A (H5N1) infection in humans. N Engl J Med. 2005;353(13):1374-85.
8. EMEA. Pandemic influenza crisis management plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals. 2006Available from: http://www.emea.europa.eu/pdfs/human/vwp/21430106en.pdf
9. Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med. 2005;353(13):1363-73.
10. Fagan HB, Moeller AH. What is the best antiviral agent for influenza infection? Am Fam Physician. 2004;70(7):1331-2.
11. Hayden FG. Antiviral resistance in influenza viruses--implications for management and pandemic response. N Engl J Med. 2006;354(8):785-8.
12. de Jong MD, Tran TT, Truong HK, Vo MH, Smith GJD, Nguyen VC, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. N Engl J Med. 2005;353(25):2667-72.
13. Moscona A. Oseltamivir resistance--disabling our influenza defenses. N Engl J Med. 2005;353(25):2633-6.
14. Matheson NJ, Symmonds-Abrahams M, Sheikh A, Shepperd S, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev. 2003(3):CD002744.
15. Ambrozaitis A, Gravenstein S, van Essen GA, Rubinstein E, Balciuniene L, Stikleryte A, et al. Inhaled Zanamivir Versus Placebo for the Prevention of Influenza Outbreaks in an Unvaccinated Long-term Care Population. J Am Med Dir Assoc. 2005;6(6):367-74.
16. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. Chest. 2006;129(1):174-81.
17. Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet. 2006;367(9507):303-13.
18. Boivin G, Goyette N, Hardy I, Aoki F, Wagner A, Trottier S. Rapid antiviral effect of inhaled zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults. J Infect Dis. 2000;181(4):1471-4.

19. Sato M, Hosoya M, Kato K, Suzuki H. Viral shedding in children with influenza virus infections treated with neuraminidase inhibitors. Pediatr Infect Dis J. 2005;24(10):931-2.

20. Nicholson KG, Aoki FY, Osterhaus AD, Trottier S, Carewicz O, Mercier CH, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. Lancet. 2000;355(9218):1845-50.

21. Puhakka T, Lehti H, Vainionpaa R, Jormanainen V, Pulkkinen M, Sharp S, et al. Zanamivir: a significant reduction in viral load during treatment in military conscripts with influenza. Scand J Infect Dis. 2003;35(1):52-8.

22. Monto AS, Webster A, Keene O. Randomized, placebo-controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. J Antimicrob Chemother. 1999;44 Suppl B:23-9.

23. Lalezari J, Campion K, Keene O, Silagy C. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. Arch Intern Med. 2001;161(2):212-7.

24. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med. 2003;163(14):1667-72.

25. Johnston SL, Ferrero F, Garcia ML, Dutkowski R. Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. Pediatr Infect Dis J. 2005;24(3):225-32.

26. Murphy K. Efficacy and safety of inhaled zanamivir for the treatment of influenza in patients with asthma or chronic obstructive pulmonary disease: A double-blind, randomised, placebo-controlled, multicentre study. Clinical Drug Investigation. 2000;20(5):337-49.

27. Hedrick JA, Barzilai A, Behre U, Henderson FW, Hammond J, Reilly L, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. Pediatr Infect Dis J. 2000;19(5):410-7.

28. Whitley RJ, Hayden FG, Reisinger KS, Young N, Dutkowski R, Ipe D, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J. 2001;20(2):127-33.

29. Peters PH, Jr., Gravenstein S, Norwood P, De Bock V, Van Couter A, Gibbens M, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. J Am Geriatr Soc. 2001;49(8):1025-31.

30. Ambrozaitis A VEG, Rubinstein E. Inhaled zanamivir versus placebo for the prevention of influenza outbreaks in an unvaccinated long-term care population. J Am Geriatr Soc. 2001;49(4):S130-S131.

31. NHG-standpunt. Voorschrijven van virusremmers bij (vogel)griep. 2005

32. Deonandan R. Oseltamivir and Zanamivir for the Prevention of influenza. Canadian Agency for Drugs and Technologies in Health; 2006

33. NICE. TA67 Flu prevention - amantadine and oseltamivir. London: 2003Available from: http://www.nice.org.uk/page.aspx?o=TA67

34. NICE. TA 58 Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza. London: 2003Available from: http://www.nice.org.uk/guidance/TA58

35. Domus Medica. Preventie van Influenza.Aanbeveling voor goede medische praktijkvoering. 2005Available from: www.domusmedica.be

36. Uhnoo I, Linde A, Pauksens K, Lindberg A, Eriksson M, Norrby R, et al. Treatment and prevention of influenza: Swedish recommendations. Scand J Infect Dis. 2003;35(1):3-11.

37. Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas RA. Prevention and Control of Influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR-10):1-42.

38. Wutzler P, Kossow KD, Lode H, Ruf BR, Scholz H, Vogel GE, et al. Antiviral treatment and prophylaxis of influenza in primary care: German recommendations. J Clin Virol. 2004;31(2):84-91.

39. Ministère de la santé de la famille et des personnes handicapées - Direction génerale de la santé. Avis du conseil supérieur d'hygiène publique de France relatif à la prophylaxie chez les personnes à risque lors d'une épidémie de grippe dans une collectivité, en période de circulation du virus grippal. 16 January 2004. 2004

40. Infectieziektenbestrijding LCr. LCI protocol influenza (j10-j11). Utrecht: 2003

41. Anonymous.Weekly epidemiological record. 7 April 2006; 81(14): 129-136. Available from: www.who.int/wer

42. Langley JM, Faughnan ME. Prevention of influenza in the general population. CMAJ. 2004;171(10):1213-22.

43. Langley JM, Faughnan ME, Canadian Task Force on Preventive Health C. Prevention of influenza in the general population: recommendation statement from the Canadian Task Force on Preventive Health Care. CMAJ. 2004;171(10):1169-70.

44. Infectieziektebestrijding LCr. LCI protocol influenza (j10-j11) Bijlage IV: Influenza in verpleeg- en verzorgingshuizen. 2004

45. WHO; 2006.WHO Rapid Advice Guidelines on pharmacological managment of humans infected with avian influenza A (H5N1) virus. Available from: www.WHO.int/medicines/publications/WHO_PSM_PAR_2006.6.pdf

46. Tran TH, Nguyen TL, Nguyen TD, Luong TS, Pham PM, Nguyen vVC, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. N Engl J Med. 2004;350(12):1179-88.

47. Chotpitayasunondh T, Ungchusak K, Hanshaoworakul W, Chunsuthiwat S, Sawanpanyalert P, Kijphati R, et al. Human disease from influenza A (H5N1), Thailand, 2004. Emerg Infect Dis. 2005;11(2):201-9.

48. Anonymous. Human cases of influenza A (H5N1) infection in eastern Turkey, December 2005-January 2006. Weekly Epidemiological Record. 27 October 2006; 43: 410-416. Available from: www.who.int/wer

49. Yen H-L, Monto AS, Webster RG, Govorkova EA. Virulence may determine the necessary duration and dosage of oseltamivir treatment for highly pathogenic A/Vietnam/1203/04 influenza virus in mice. J Infect Dis. 2005;192(4):665-72.

50. Leneva IA, Roberts N, Govorkova EA, Goloubeva OG, Webster RG. The neuraminidase inhibitor GS4104 (oseltamivir phosphate) is efficacious against A/Hong Kong/156/97 (H5N1) and A/Hong Kong/1074/99 (H9N2) influenza viruses. Antiviral Res. 2000;48(2):101-15.

51. Gubareva LV, McCullers JA, Bethell RC, Webster RG. Characterization of influenza A/HongKong/156/97 (H5N1) virus in a mouse model and protective effect of zanamivir on H5N1 infection in mice. J Infect Dis. 1998;178(6):1592-6.

52. Leneva IA, Goloubeva O, Fenton RJ, Tisdale M, Webster RG. Efficacy of zanamivir against avian influenza A viruses that possess genes encoding H5N1 internal proteins and are pathogenic in mammals. Antimicrob Agents Chemother. 2001;45(4):1216-24.

53. Li KS, Guan Y, Wang J, Smith GJD, Xu KM, Duan L, et al. Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. Nature. 2004;430(6996):209-13.

54. Le QM, Kiso M, Someya K, Sakai YT, Nguyen TH, Nguyen KHL, et al. Avian flu: isolation of drug-resistant H5N1 virus. Nature. 2005;437(7062):1108.

55. WHO; 2005 [updated March 2005.; cited 30/09/2006]. WHO global influenza preparedness plan. The role of WHO and recommendations for national measures before and during pandemics - March 2005. Available from: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5/en/index.html

56. Enserink M. Oseltamivir becomes plentiful--but still not cheap. Science. 2006;312(5772):382-3.

57. United States Department of Health and Human Services. HHS Pandemic Influenza Plan - Appendix D: NVAC/ACIP Recommendations for Prioritization of Pandemic Influenza Vaccine and NVAC Recommendations on Pandemic Antiviral Drug Use. 2006 March 30,200618/09/2006. Available from: http://www.hhs.gov/pandemicflu/plan/appendixd.html

58. The European Centre for Disease Prevention and Control. Influenza National Pandemic Plans. 2006Available from: http://www.ecdc.eu.int/Health_topics/Pandemic_Influenza/Pandemic_Planning.html

59. Central Intelligence Agency. World Fact Book. 2006Available from: https://www.cia.gov/cia/publications/factbook/geos/ca.html

60. Australian government - Department of Health and Aging. The Australian Health Management Plan for Pandemic Influenza. 2006Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/ohp-pandemic-ahmppi.htm

61. Office fédéral de la santé publique. Division des maladies transmissibles. Plan suisse de pandémie Influenza 2006. 2006Available from: http://www.bag.admin.ch/influenza/01120/01134/03058/index.html?lang=fr

62. Australian government - Department of Health and Aging. Preparing for an Influenza Pandemic - A Practical Guide for Medical Practitioners. 2005 June 6, 20050/10/2006. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pubhlth-pandemic-gp.htm

63. Uscher-Pines L, Omer SB, Barnett DJ, Burke TA, Balicer RD. Priority Setting for Pandemic Influenza: An Analysis of National Preparedness Plans. PLoS Med. 2006;3(10).

64. Public Health Agency of Canada. Canadian Pandemic Influenza Plan. 2004Available from: http://www.phac-aspc.gc.ca/cpip-pclcpi/

65. Longini IM, Jr., Halloran ME, Nizam A, Yang Y. Containing pandemic influenza with antiviral agents. Am J Epidemiol. 2004;159(7):623-33.

66. Wu JT, Riley S, Fraser C, Leung GM. Reducing the impact of the next influenza pandemic using household-based public health interventions. PLoS Med. 2006;3(9):e361.

67. Ferguson NM, Cummings DAT, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. Nature. 2006;442(7101):448-52.

68. Longini IM, Jr, Nizam A, Xu S, Ungchusak K, Hanshaoworakul W, Cummings DAT, et al. Containing pandemic influenza at the source. Science. 2005;309(5737):1083-7.

69. Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev. 2006;3:CD001265.

70. Kashiwagi S, Kudoh S, Watanabe A, Yoshimura I. [Efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir for prophylaxis against influenza--placebo-controlled double-blind multicenter phase III trial]. Kansenshogaku Zasshi. 2000;74(12):1062-76.

71. Lin JT, Yu XZ, Cui DJ, Chen XY, Zhu JH, Wang YZ, et al. A multicentre, randomized, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population. Curr Med Res Opin. 2006;22(1):75-82.

72. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Lancet. 1998;352(9144):1877-81.

73. Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner D, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. BMJ. 2003;326(7401):1235.

74. Makela MJ, Pauksens K, Rostila T, Fleming DM, Man CY, Keene ON, et al. Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomized, double-blind, placebo-controlled European study. J Infect. 2000;40(1):42-8.

75. Hayden FG, Osterhaus AD, Treanor JJ, Fleming DM, Aoki FY, Nicholson KG, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. GG167 Influenza Study Group. N Engl J Med. 1997;337(13):874-80.

76. Hayden FG, Gubareva LV, Monto AS, Klein TC, Elliot MJ, Hammond JM, et al. Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. N Engl J Med. 2000;343(18):1282-9.

77. Welliver R, Monto AS, Carewicz O, Schatteman E, Hassman M, Hedrick J, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. JAMA. 2001;285(6):748-54.

78. Hayden FG, Treanor JJ, Fritz RS, Lobo M, Betts RF, Miller M, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. JAMA. 1999;282(13):1240-6.

79. Schilling M, Povinelli L, Krause P, Gravenstein M, Ambrozaitis A, Jones HH, et al. Efficacy of zanamivir for chemoprophylaxis of nursing home influenza outbreaks. Vaccine. 1998;16(18):1771-4.

80. Monto AS, Robinson DP, Herlocher ML, Hinson JM, Jr., Elliott MJ, Crisp A. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. JAMA. 1999;282(1):31-5.

81. Kaiser L, Henry D, Flack NP, Keene O, Hayden FG. Short-term treatment with zanamivir to prevent influenza: results of a placebo-controlled study. Clin Infect Dis. 2000;30(3):587-9.

82. Australian government - National Health and Medical Research Council. Outcomes of funding rounds. Details of the successful NHMRC funding recipients. 20062006 10/10/2006. Available from: http://nhmrc.gov.au/funding/funded/outcomes/index.htm

83. Australian government - Department of Health and Aging. The Australian Health Management Plan for Pandemic Influenza. Appendix 1: access to the Australian national medical stockpile during an influenza pandemic. 2006Available from:

http://www.health.gov.au/internet/wcms/publishing.nsf/Content/ohp-pandemic-ahmppi.htm

84. Meltzer MI, Cox NJ, Fukuda K. The economic impact of pandemic influenza in the United States: priorities for intervention. Emerg Infect Dis. 1999;5(5):659-71.

85. UK Health Departments; 2005 [updated 2005; cited September 21]. Influenza pandemic contingency plan (October 2005 edition). Available from: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4121735&chk=Z6kjQY

86. Department of Health U. UK operational framework for stockpiling, distributing and using antiviral medicines in the event of pandemic influenza. 2005 September 2005.Available from: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4119491&chk=T/Iaww

87. British Infection Society, British Thoracic Society, Health Protection Agency, Department of Health U; 2006 [updated 6 June 2006; cited September 2006]. Clinical guidelines for patients with an influenza like illness during an influenza pandemic.Version 10.5 March 2006. Available from: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4121753&chk=ZXKxus

88. United States Department of Health and Human Services; 2006 [updated March 30,2006; cited 18/09/2006]. HHS Pandemic Influenza Plan. Supplement 5: clinical guidelines. Available from: http://www.hhs.gov/pandemicflu/plan/

89. United States Department of Health and Human Services; 2006 [updated March 30,2006; cited 18/09/2006]. HHS Pandemic Influenza Plan. Appendix G. Research activities. Available from: http://www.hhs.gov/pandemicflu/plan/

This page is left intentionally blank.

Dépôt légal : D/2006/10.273/66

KCE reports

1. Efficacité et rentabilité des thérapies de sevrage tabagique. D/2004/10.273/2.
2. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale (Phase 1). D/2004/10.273/4.
3. Utilisation des antibiotiques en milieu hospitalier dans le cas de la pyélonéphrite aiguë. D/2004/10.273/6.
4. Leucoréduction. Une mesure envisageable dans le cadre de la politique nationale de sécurité des transfusions sanguines. D/2004/10.273/8.
5. Evaluation des risques préopératoires. D/2004/10.273/10.
6. Validation du rapport de la Commission d'examen du sous financement des hôpitaux. D/2004/10.273/12.
7. Recommandation nationale relative aux soins prénatals: Une base pour un itinéraire clinique de suivi de grossesses. D/2004/10.273/14.
8. Systèmes de financement des médicaments hospitaliers: étude descriptive de certains pays européens et du Canada. D/2004/10.273/16.
9. Feedback: évaluation de l'impact et des barrières à l'implémentation – Rapport de recherche: partie 1. D/2005/10.273/02.
10. Le coût des prothèses dentaires. D/2005/10.273/04.
11. Dépistage du cancer du sein. D/2005/10.273/06.
12. Etude d'une méthode de financement alternative pour le sang et les dérivés sanguins labiles dans les hôpitaux. D/2005/10.273/08.
13. Traitement endovasculaire de la sténose carotidienne. D/2005/10.273/10.
14. Variations des pratiques médicales hospitalières en cas d'infarctus aigu du myocarde en Belgique. D/2005/10.273/12
15. Evolution des dépenses de santé. D/2005/10.273/14.
16. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale. Phase II : développement d'un modèle actuariel et premières estimations. D/2005/10.273/16.
17. Evaluation des montants de référence. D/2005/10.273/18.
18. Utilisation des itinéraires cliniques et guides de bonne pratique afin de déterminer de manière prospective les honoraires des médecins hospitaliers: plus facile à dire qu'à faire.. D/2005/10.273/20
19. Evaluation de l'impact d'une contribution personnelle forfaitaire sur le recours au service d'urgences. D/2005/10.273/22.
20. HTA Diagnostic Moléculaire en Belgique. D/2005/10.273/24, D/2005/10.273/26.
21. HTA Matériel de Stomie en Belgique. D/2005/10.273.28.
22. HTA Tomographie par Emission de Positrons en Belgique. D/2005/10.273/30.
23. HTA Le traitement électif endovasculaire de l'anévrysme de l'aorte abdominale (AAA). D/2005/10.273.33.
24. L'emploi des peptides natriurétiques dans l'approche diagnostique des patients présentant une suspicion de décompensation cardiaque. D/2005/10.273.35
25. Endoscopie par capsule. D2006/10.273.02.
26. Aspects médico-légaux des recommandations de bonne pratique médicale. D2006/10.273/06.
27. Qualité et organisation des soins du diabète de type 2. D2006/10.273/08.
28. Recommandations provisoires pour les évaluations pharmacoéconomiques en Belgique. D2006/10.273/11.
29. Recommandations nationales Collège d'oncologie : A. cadre général pour un manuel d'oncologie B. base scientifique pour itinéraires cliniques de diagnostic et traitement, cancer colorectal et cancer du testicule. D2006/10.273/13.
30. Inventaire des bases de données de soins de santé. D2006/10.273/15.
31. Health Technology Assessment : l'antigène prostatique spécifique (PSA) dans le dépistage du cancer de la prostate. D2006/10.273/18.
32. Feedback: évaluation de l'impact et des barrières à l'implémentation - Rapport de recherche: partie II. D2006/10.273/20.
33. Effets et coûts de la vaccination des enfants Belges au moyen du vaccin conjugué antipneumococcique. D2006/10.273/22.
34. Trastuzumab pour les stades précoces du cancer du sein. D2006/10.273/24.

35. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale – Phase III : affinement des estimations. D2006/10.273/27.
36. Traitement pharmacologique et chirurgical de l'obésité. Prise en charge résidentielle des enfants sévèrement obèses en Belgique. D/2006/10.273/29.
37. Health Technology Assessment Imagerie par Résonance Magnétique. D/2006/10.273/33.
38. Dépistage du cancer du col de l'utérus et recherche du Papillomavirus humain (HPV). D/2006/10.273/36
39. Evaluation rapide de technologies émergentes s'appliquant à la colonne vertébrale : remplacement de disque intervertébral et vertébro/cyphoplastie par ballonnet. D/2006/10.273/39.
40. Etat fonctionnel du patient: un instrument potentiel pour le remboursement de la kinésithérapie en Belgique? D/2006/10.273/41.
41. Indicateurs de qualité cliniques. D/2006/10.273/44.
42. Etude des disparités de la chirurgie élective en Belgique. D/2006/10.273/46.
43. Mise à jour de recommandations de bonne pratique existantes. D/2006/10.273/49.
44. Procédure d'évaluation des dispositifs médicaux émergeants. D/2006/10.273/51.
45. HTA Dépistage du Cancer Colorectal : état des lieux scientifique et impact budgétaire pour la Belgique. D/2006/10.273/54.
46. Health Technology Assessment. Polysomnographie et monitoring à domicile des nourrissons en prévention de la mort subite. D/2006/10.273/60.
47. L'utilisation des médicaments dans les maisons de repos et les maisons de repos et de soins Belges. D/2006/10.273/62
48. Lombalgie chronique. D/2006/10.273/64.
49. Médicaments antiviraux en cas de grippe saisonnière et pandémique. Revue de littérature et recommandations de bonne pratique. D/2006/10.273/66.