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## **Summary Report**

# **Review on influenza antiviral medicinal products for potential use during pandemic**

## TABLE OF CONTENTS

<b>I. INTRODUCTION</b>	<b>3</b>
<b>II. OVERVIEW OF THE PROPERTIES OF AVAILABLE ANTIVIRAL AGENTS</b>	<b>4</b>
<b>A. Adamantane class (M2 inhibitors)</b>	<b>4</b>
Rimantadine	4
Amantadine	5
<b>B. Neuraminidase inhibitors</b>	<b>8</b>
Oseltamivir	8
Zanamivir	13
<b>III. GOALS OF ANTIVIRAL USE DURING INFLUENZA EPIDEMIC</b>	<b>16</b>
<b>IV. ANTIVIRAL DRUG USE – FACTORS WHICH MAY BE TAKEN INTO ACCOUNT</b>	<b>17</b>

## I. INTRODUCTION

Occasionally, emerging influenza A virus strains undergo major changes in their genes, especially in the neuraminidase (NA) and haemagglutinin (HA) genes. This may be due to an adaptation of an avian or porcine strain to the human host or to a genetic reassortment in a coinfection setting. The changes may provide the virus means for both increased infectivity and altered tissue distribution as well as a possibility to avoid detection by the host immune defence. Therefore, the new strains may have the capacity of causing severe worldwide pandemics. It is also possible that the past pandemic strains will re-emerge after being dormant for decades.

An influenza pandemic is a major acute threat to the public health, which warrants a concerted action for pandemic preparedness within the EU. A wider international collaboration under the auspices of WHO is crucial for the proper surveillance and timely execution of the pandemic plans.

Influenza antiviral medicinal products and pandemic influenza vaccines have a complementary role in the management of an influenza pandemic. In contrast to pandemic vaccines, influenza antivirals can be used from the very early phase of the influenza pandemic..

In May 2004, the DG Enterprise of the European Commission asked the scientific Committee for Human Medicinal Products (CHMP) of the EMEA to compile and review scientific information on antiviral medicinal products during an influenza pandemic. The CHMP conducted the review on the basis of the information obtained from the Marketing Authorisation Holders for amantadine, oseltamivir and zanamivir and from the literature. The recommendations were discussed in a workshop with European Experts held in February 2005. The review and the recommendations were submitted to the Commission in March 2005. The consensus reached at that time is summarised hereafter.

It should be noted that by no means should any of the following scientific guidance on the use of antivirals in a pandemic situation be regarded as introducing derogation(s) to the terms of existing marketing authorisation.

## II. OVERVIEW OF THE PROPERTIES OF AVAILABLE ANTIVIRAL AGENTS

There are four potential antiviral agents for a widespread use during an influenza pandemic, M2 inhibitors amantadine and rimantadine as well as neuraminidase inhibitors oseltamivir and zanamivir.

### A. Adamantane class (M2 inhibitors)

<b>Rimantadine</b>
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#### *Pharmacology*

Rimantadine inhibits the M2 membrane protein ion channel activity. This results in inhibition of the acidification of the virus interior which is required to promote fusion of the viral envelope with the endosome and for dissociation of the M1 matrix protein from the ribonucleoprotein complex (uncoating). Consequently, viral replication is blocked at an early stage of infection. Other effects may occur at later stages of the virus replication cycle.

Amantadine and Rimantadine differ significantly in their pharmacokinetics, with rimantadine achieving higher concentrations in respiratory secretions. The peak plasma concentration is obtained after 6 hours of oral administration in healthy adults. The single dose elimination half-life in this population is about 25 hours. In healthy elderly people, the elimination is somewhat prolonged and the average AUC values and peak concentration is 20 to 30 % higher than in healthy adults.

Following oral administration, rimantadine is extensively metabolised in the liver with less than 25 % of the dose excreted in the urine unchanged. In chronic liver disease, the pharmacokinetics of rimantadine are not appreciably altered, but in severe hepatic disorders AUC and elimination half-life time increase as apparent clearance is remarkably reduced. Renal insufficiency results in an increase in plasma metabolite concentrations and reduces apparent clearance of rimantadine.

Rimantadine does not interfere with the immunogenicity of inactivated influenza A vaccine. Interactions with other drugs like cimetidine, acetaminophen and aspirin lead to only minor changes in the pharmacokinetics of rimantadine but are mentioned in the official labelling of Flumadine® (rimantadine, registered in USA). The extent to which interaction studies have been performed remains unknown.

Flumadine® is contraindicated in patients with known hypersensitivity to drugs of the adamantane class, including rimantadine and amantadine.

Rimantadine is known to cross the placenta in mice and to be embryotoxic in rats at a high dose level. There are no adequate and well-controlled studies in pregnant women. Therefore, according to the Flumadine® label, rimantadine should be used during pregnancy only if the potential benefit justifies the risk to the foetus. However, without the possibility to assess the risk to the foetus, a recommendation to use rimantadine in pregnancy even during a pandemic is not possible. Rimantadine should not be administered to nursing mothers.

#### *Efficacy data*

According to a Cochrane review, 11 published treatment trials that were published between 1968 and 1986, trials were analysed by using the duration of fever (defined as a temperature of more than 37°C) as the common outcome measure. Compared to placebo, rimantadine significantly shortened the duration of fever by 1.27 days (95 % CI 0.77 to 1.77). The scarce available data suggest that amantadine and rimantadine have a comparable efficacy.

The Cochrane review identified several reports published between 1966 and 1990 on the prophylactic use of rimantadine. The study results were analysed according to the comparison of oral rimantadine to placebo and oral amantadine to oral rimantadine. Comparisons were stratified on the basis of whether participants had received vaccination or not. Rimantadine prevented 72 % (95 % CI –8% to 92 %) of the influenza and influenza-like illnesses and 35 % (95 % CI –20 to 65 %) of influenza-like illnesses. Whilst these results were not statistically significant ( $p = 0.07$  and  $p = 0.17$ , respectively), the estimates were based on only 688 individuals, and are of very similar magnitude to those for amantadine. Rimantadine seemed efficacious also in the vaccinated population. When comparing amantadine and rimantadine, there was no evidence of a difference in efficacy.

#### Sensitivity of different influenza strains

Rimantadine has no effect on influenza type B virus infection. The *in vitro* susceptibility covers the three antigenic subtypes, i.e., H1N1, H2N2, H3N2, that have been isolated from man.

#### Viral resistance

Amino acid replacement in the transmembrane domain of M2 leads to resistance to amantadine and rimantadine. Such rimantadine-resistant strains of influenza A have emerged among freshly isolated epidemic strains in closed settings where rimantadine has been used, but such strains have only rarely been isolated from specimens collected as part of routine influenza surveillance. Resistant viruses have been shown to be transmissible and to cause typical influenza illness. Analyses of some of the 2004 H5N1 viruses isolated from poultry and humans in Asia have shown that the viruses were resistant to amantadine and rimantadine.

#### Adverse effect profile

Rimantadine lacks the central nervous system effects seen with amantadine. The pharmacokinetic properties of rimantadine may account for its more favourable side effect profile compared to amantadine. The adverse effect profile of rimantadine includes the gastrointestinal system, the skin and the respiratory tract.

#### Regulatory status

Medicinal products containing rimantadine have been approved nationally.

It should be noted that no information was provided by the marketing authorisation holders (MAHs) of rimantadine within EU for the purpose of this assessment.

### **Amantadine**

#### Pharmacology

Amantadine inhibits the M2 membrane protein ion channel activity. This results in inhibition of the acidification of the virus interior which is required to promote fusion of the viral envelope with the endosome and for dissociation of the M1 matrix protein from the ribonucleoprotein complex (uncoating). Consequently, viral replication is blocked at an early stage of infection. Other effects may occur at later stages of the virus replication cycle.

Amantadine is absorbed well with oral bioavailability of 62-93% in the young and 53-100% in the elderly, based on published data. The time to attain peak plasma concentrations varies from 2 to 6 hours and the elimination half-life is relatively long, 12-16h.

Amantadine is not metabolised and is excreted unchanged in urine. Thus, the plasma half-life of amantadine is considerably prolonged in patients with impaired renal function (justifying dose

adjustment in case of renal impairment) and the half-life of amantadine in elderly men after multiple doses is almost double that in young men. Average half-lives of 8.3 and 13 days have been recorded in patients on chronic haemodialysis.

Interactions with anticholinergic agents, several classes of medicinal products affecting CNS, combination diuretics, as well as with quinine and quinidine have been described. The product information on interactions may differ among the member states. Amantadine does not impair the immune response to the conventional influenza vaccine. The effect on (live) influenza vaccination is unknown.

Amantadine has not been studied in pregnant women. According to Marketing Authorisation Holders, there is no evidence of malformations or foetal toxicity due to amantadine in humans. However, claims of isolated reports on malformations have appeared in the literature although causality remains unknown. Anyway, based on animal embryotoxicity and teratogenesis studies, the use of amantadine is not recommended during pregnancy. Amantadine is not recommended during lactation, because the drug is excreted into human breast milk

### Efficacy data

Only limited clinical information is available. Most of the clinical trials were performed between 1960 and 1980. Thus, these studies have neither been conducted nor assessed according to the current regulatory standards. The assessment is mainly based on the Cochrane review "Amantadine and rimantadine for preventing and treating influenza A in adults updated in 2004".

Influenza A treatment indication of amantadine in the EU varies between the member states. The treatment (and prophylaxis) indication is for adults, adolescents and children or for adults and adolescents only, depending on the member state.

The recommended dose varies from 200mg daily for healthy adults to 50-100mg daily for children. The dose is adjusted according to the renal function. The recommended duration is up to 10 days for treatment and up to 8 weeks for prophylaxis.

Amantadine treatment of adults without concomitant diseases is estimated to shorten the disease with fever by approximately one day. Data on the use in patients with chronic diseases are scarce. There is no strong evidence for the prevention of influenza-associated complications. Amantadine will not impair the efficacy of conventional influenza vaccines.

No data on the use of amantadine for treatment of pandemic influenza were submitted for review by the CHMP.

The indication for prophylaxis for amantadine varies within the EU. Amantadine is often recommended for patients with risk factors for influenza complications. The recommended daily dose for prophylaxis is the same as for treatment but the dosing is for longer periods. In the pooled analysis of all placebo-controlled studies of prophylaxis, the protection against influenza was approximately 61%. Data of the use of amantadine for prophylaxis of influenza A in children were of questionable quality.

### Sensitivity of different influenza strains

Amantadine inhibits human H1N1, H2N2 and H3N2 subtypes of influenza A. Amantadine (as well as rimantadine) does not inhibit influenza B. Antiviral activity has been demonstrated *in vitro* in cell culture at concentrations from 0.01 to 1.5 mg/ml (0.05-7.5 mM).

Amantadine has been used for prophylaxis during the pandemics in 1968 caused by H3N2 and in 1977 caused by H1N1 influenza virus strain.

Avian and equine subtypes of influenza A are also sensitive. Recent H5N1 strains of “bird flu” are resistant to M2 inhibitors (amantadine and rimantadine).

The level of phenotypic resistance is high, usually with  $\geq 100$ -fold reductions in susceptibility.

#### Viral resistance

In human influenza viruses, resistance is due to point mutation in the M gene. It has been also observed that a co-infection in mice with a mixture of amantadine-resistant and amantadine-sensitive strains of influenza virus resulted in the transfer of amantadine-resistance to a sensitive strain by reassortment.

It has been estimated that the overall frequency of phenotypic amantadine resistance for both H1N1 and H3N2 among influenza virus isolates in the UK 1968-1999 was 2.3%. In mice and chicken resistance was obtained after one to three passages. In humans, the influenza A virus resistance to amantadine (rimantadine) occurs within 2 to 5 days of treatment, illustrating the rapidity with which resistant virus can replace sensitive virus during treatment. Drug resistant virus appears when amantadine is used for treatment in about 30% of patients. Limited data show that drug-resistant virus was higher in treated children (up to 80%). This may be related to more intense and prolonged virus replication in children, which could be due to the absence of pre-existing immunity.

Amantadine (and rimantadine)-resistant viruses are able to transmit the disease. Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa. Cross-resistance with the neuraminidase inhibitors does not occur.

#### Clinical significance of resistant strains

Resistant viruses can transmit the disease but have not been found to be more virulent than sensitive ones. Transmission of resistant strains can result in failures of influenza prophylaxis in family members and in nursing home contacts. The frequency of amantadine prophylaxis failures proven to be due to resistant variants in nursing home outbreaks in published studies was 0.5-2.4%. The increasing use of amantadine in China raises further concerns as regards the emergence of amantadine-resistant variants. Prolonged shedding of drug-resistant influenza virus in a hospital setting may have implications in terms of nosocomial infections.

#### Adverse effect profile and contraindications

The product information varies between the member states. In France, the product information mentions the following common adverse effects: dizziness, insomnia and nervousness. More rarely depression, anxiety, hallucination, confusion, nausea, anorexia, dry mouth, constipation, ataxia, orthostatic hypotension, headache are noted. Livedo reticularis and peripheral oedema have been observed in prolonged treatment. Exceptionally psychosis, urinary retention, dyspnoea, fatigue, rash, vomiting, weakness, slurred speech, vision disorders, convulsions, leucopenia, neutropenia, eczema, oculogyric episodes occurred.

In France, amantadine is contra-indicated in the following situations: hypersensitivity, concomitant use with neuroleptic anti-emetic drugs is contra-indicated due to antagonism effect, children below one year of age due to the absence of specific data, and pregnancy due to the lack of clinical experience. The Marketing Authorisation Holder also contraindicates as follows: hypersensitivity to the product, severe renal failure, history of convulsions, history of gastric ulcerations, and severe heart disease.

#### Quality aspects related to pandemic use

The only available possibility for stockpiling would be the authorised formulation (tablets). No information on the preparation of a magistral formulation is known. It seems that amantadine bulk

material itself shows excellent stability, but this needs to be further confirmed by reliable stability data. The current shelf life of the film coated tablets is 5 years, when stored below 25°C.

### Regulatory status

Medicinal products containing amantadine have been approved nationally.

## **B. Neuraminidase inhibitors**

<b>Oseltamivir</b>
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### Clinical uses

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.

Post exposure prevention in adults and adolescents 13 years of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

The appropriate use of oseltamivir 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 adolescents 13 years of age or older.

Oseltamivir (Tamiflu®) has been shown to be effective in post-exposure prophylaxis in children older than one year although a regulatory approval for the use in the paediatric population is still pending in the EU. The safety and efficacy of Tamiflu in children less than one year of age have not been established.

For treatment of adults and adolescents 13 years or older as well as for children weighing more than 40kg, the recommended oral dose is 75 mg oseltamivir twice daily, for 5 days. For children weighing 40kg or less, the dosing is modified by the weight.

In individuals at 13 years or older the recommended dose of oseltamivir for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for at least 7 days. The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to six weeks.

### Pharmacology

Oseltamivir phosphate is an orally administered prodrug that, after absorption *in vivo*, is metabolised into oseltamivir carboxylate (OC), the clinically active metabolite. OC binds to highly conserved amino acid residues in the active site of neuraminidase, which is one of the two major surface glycoprotein antigens of influenza viruses. In influenza-infected host cells, newly formed viruses are transported to the cell membrane. The progeny viruses remain attached to the cell membrane until they are cleaved from the surface by the proteolytic activity of the viral neuraminidase. Prevention of this neuraminidase activity results in clustering of the newly formed viruses onto the surface of the host cells, thereby preventing further transmission of the viruses into adjacent cells. Prevention of the neuraminidase activity therefore effectively interrupts the virus life cycle and eventually aborts the influenza infection.

The absolute bioavailability of active oseltamivir after oral administration of the prodrug is 74-85%. There is no significant effect of food on the oral bioavailability of oseltamivir. The T<sub>max</sub> of the active drug is 1.5-5h. The estimated average volume of distribution of the active metabolite of oseltamivir is 23 -26 L, a volume equivalent to extra cellular body fluid. Thus, oseltamivir carboxylate is distributed

to the potential sites of influenza virus replication. The binding of the oseltamivir carboxylate to human plasma protein is negligible.

Conversion of the prodrug to the active metabolite is predominantly due to hepatic esterase activity. No further metabolism of the parent or active molecules has been detected in man, and the *in vitro* studies indicated no interaction with cytochrome P450 isoenzymes. Oseltamivir carboxylate (the active compound) has a mean apparent elimination half-life of 6.3 h. Oseltamivir is eliminated mainly via kidneys in the form of the active drug.

The average C<sub>max</sub> and AUC are lower in children as compared to adults. Pharmacokinetic studies of oseltamivir in the elderly have shown that plasma concentrations of the prodrug and the active drug were similar to those of younger adults.

Accumulation of active oseltamivir is seen in patients with decreased renal function. A three-fold increase in AUC is seen in individuals with a creatinine clearance of < 30 ml/min and two-fold in individuals with a clearance of 31-60 ml/min.

No significant interactions have been demonstrated between oseltamivir and any other substances investigated. Similarly, oseltamivir will not interact with vaccination with the inactivated intramuscularly administered vaccine. Theoretically, the use of oseltamivir concomitantly with vaccination with the live intranasally administered vaccine could impair the immunogenicity of the vaccine, but no data on such an interaction are available.

#### Efficacy data

- Treatment

In a pooled analysis of the placebo-controlled clinical trials, the time to alleviation of illness was reduced by approximately one day among the oseltamivir recipients (100.6 h versus 124.5 h) when the treatment was started within 36 h of the onset of symptoms. The median duration of fever was reduced by 36% (44 h versus 69 h). Oseltamivir treatment has been shown to result in significant shortening of the period to cessation of virus shedding.

Subgroup analyses of clinical trials have shown that oseltamivir significantly reduces the duration of illness with the exception of patients with chronic co-morbid diseases. Oseltamivir is effective irrespective of the influenza vaccination status of the patients. In children, the median duration of influenza illness was reduced by 26% (101 h versus 137 h) when oseltamivir treatment was started within 48 h of the onset of illness.

In a pooled analysis of all placebo-controlled trials among adults and adolescents, oseltamivir has been shown to reduce the incidence of influenza-related lower respiratory tract infections (mainly bronchitis) resulting in antibiotic therapy by 55% (4.6% versus 10.3%), and overall antibiotic use for any reason by 27% (14.0% versus 19.1%). Hospitalisation for any cause was reduced among the oseltamivir recipients (0.7% versus 1.7%).

In children aged 1-12 years, oseltamivir treatment reduced the development of acute otitis media as a complication by 44% (12% versus 21%). The incidence of antibiotic prescriptions was also significantly lower among oseltamivir recipients than among the placebo recipients (31% versus 41%).

#### Treatment of pandemic and/or avian influenza

There are no data on the use of oseltamivir in a real pandemic situation. Very limited data are available on the use of oseltamivir for treatment of influenza caused by H5N1 strains that are related to the potential pandemic strains. In animal studies, the efficacy of oseltamivir has been demonstrated against H5N1 viruses that circulated in Hong Kong in 1997. No animal data are available on the efficacy of oseltamivir against the recent drifted strains of H5N1 viruses. However, *in vitro* studies indicate that oseltamivir is likely to be effective also against the current strains of H5N1 viruses and

other avian viruses with a pandemic potential (e.g. H9N2, H7N7). Animal studies have also indicated that the avian influenza viruses may be shed for longer periods than normal epidemic viruses. If true during a pandemic, there would be a need to use oseltamivir for longer periods than 5 days for treating the patients.

- Prophylaxis

Oseltamivir is indicated for the prophylaxis of influenza in adults and children aged 13 years and older.

Oseltamivir administered once daily has been shown to be effective both in seasonal prophylaxis among healthy persons and in post-exposure prophylaxis within families. In seasonal prophylaxis, the duration of medication has been up to 6 weeks, and in the post-exposure prophylaxis it has been 7-10 days.

In seasonal prophylaxis among healthy adults, the protective efficacy of oseltamivir against laboratory-confirmed influenza was 74%, and against culture-proven influenza 87%. Even higher protection was observed in a study of 6-week seasonal prophylaxis among frail elderly subjects in residential home care setting; the protective efficacy against laboratory-confirmed influenza was 92%. In addition, the protective efficacy among elderly persons who had been vaccinated against influenza was 91%.

In post-exposure prophylaxis in the family setting, the overall protective efficacy of oseltamivir among the contacts (aged >12 years) of an influenza-positive index case was 89%. In another post-exposure prophylaxis study that included also children aged 1 year or older, the protective efficacy was 68%.

Impact on the non-clinical infections, infectivity and immunogenicity

An important feature of oseltamivir prophylaxis is that it does not prevent influenza infection *per se*, but works by preventing further transmission of newly formed viruses into adjacent cells. Therefore, oseltamivir prophylaxis does not suppress the antibody response to influenza infection if a subject acquires influenza during the prophylactic period.

Experience on pandemic use/use for avian influenza

There are no data on the use of oseltamivir prophylaxis in a real pandemic situation. There are no properly controlled clinical studies in humans with respect to the current avian influenza strains. The prophylactic efficacy of oseltamivir was tested recently against a 2004 clinical isolate of the current avian influenza strain in a mouse model of influenza and significantly reduced the mortality against a lethal challenge of the virus at a dosage equivalent to the approved human dose. Survival was increased further with a prolonged treatment regimen. During the 2003 avian influenza H7N7 outbreak in the Netherlands, oseltamivir prophylaxis with the recommended dose of 75 mg once daily seemed to be effective to protect poultry workers and their close contacts.

Sensitivity of different influenza strains

Nine different types of influenza neuraminidases (N1-N9) are currently known to exist. With few exceptions, only influenza viruses with N1 and N2 have circulated among humans during the past century. In addition to documented efficacy against strains with N1 or N2, oseltamivir has been shown to be potent *in vitro* against influenza virus neuraminidases N3-N9.

Three distinct influenza pandemics occurred in the 20<sup>th</sup> century. The most devastating of them was the pandemic of 1918-20. This pandemic was caused by an H1N1 influenza virus. Oseltamivir has been shown to effectively inhibit recombinant influenza viruses possessing the haemagglutinin and neuraminidase of the 1918 strains of influenza both *in vitro* and *in vivo* in mice. The other pandemic

strains H2N2 (1957), H3N2 (1968), and H1N1 (1977) are also inhibited *in vitro* and/or *in vivo* by oseltamivir.

*In vitro*, oseltamivir has been shown to be effective against H5N1 strains isolated during the initial human outbreak in Hong Kong in 1997 as well as recently (in 2004) isolated H5N1 strains in Vietnam. *In vivo*, the efficacy of oseltamivir against H5N1 viruses has been demonstrated mainly in a mouse model of influenza infection. Orally administered oseltamivir effectively prevented the death of mice infected with H5N1/97 viruses and recently oseltamivir prevented the death of mice infected with H5N1/04, obtained from a clinical case in Vietnam. Oseltamivir treatment has also been shown to reduce mortality in chickens infected with another highly pathogenic avian influenza strain, H7N7, which recently caused a human outbreak in the Netherlands.

#### Viral resistance

Viral resistance to oseltamivir may develop by alteration of the amino acid composition of neuraminidase. Resistant strains have been generated *in vitro* and such strains have also been found in a small proportion of patients during or after treatment with oseltamivir. Oseltamivir-resistant strains have also been detected in individuals not exposed to oseltamivir. Mutations in the viral neuraminidase gene can be generated *in vitro* by repeated passages in the presence of low concentrations of oseltamivir. In clinical trials among adults and children older than 13 years, the incidence of development of resistant strains has been very low, 0.33%. However, in studies among children, the corresponding rate has been 4.0%- 18%. The high rate of oseltamivir-resistance in children treated with oseltamivir is of concern and should be monitored carefully.

#### Clinical significance and surveillance of resistant strains

For time being, the clinical significance of oseltamivir-resistant strains of influenza appears to be limited because of reduced infectivity, replicative ability, and pathogenicity of the resistant strains. The significance of the resistant strains observed in individuals who were not exposed to oseltamivir is unclear at the present. The decreased virulence and low rates of transmission have been shown in the ferret and mouse models with resistant strains carrying the mutation R292K or H274Y. With respect to the E119V mutation, the results are conflicting. Some studies in mice and ferrets have demonstrated a low infectivity of the resistant strain, but in a recent ferret study the infectivity and transmissibility of the resistant strain was comparable with the wild-type strain. No data are yet available for the newly detected resistant strain with the N294S mutation.

The development of viral resistance is possible and might have a substantial impact on the clinical usefulness of oseltamivir. Therefore, a global surveillance network called the Neuraminidase Inhibitor Susceptibility Network (NISN) has been set up in collaboration with the World Health Organization (WHO) to monitor the possible emergence of viral resistance. The NISN monitors the situation globally, with particular emphasis on countries in which the neuraminidase inhibitors are used most frequently.

#### Adverse effect profile and contraindications

Hypersensitivity to oseltamivir is the only listed contraindication. The most frequently reported adverse effects during oseltamivir treatment both in adults and children are nausea and vomiting. In pre-licensing clinical trials, the rate of these adverse effects has been approximately 5% units greater than the corresponding rates in placebo recipients. Discontinuation of the treatment because of side effects has been very rare. Serious skin reactions, including Stevens-Johnson syndrome and erythema multiforme have been reported rarely. Additionally, there are rare reports of hepatobiliary system disorders including hepatitis and elevated liver enzymes in patients with influenza-like illness.

There are no adequate data from the use of oseltamivir in pregnant women. In pre-licensing animal studies, no evidence of foetal toxicity or teratogenicity was observed. In rodents, oseltamivir has been shown to be secreted into milk. There is no information on secretion into breast milk in humans.

According to the approved product information in EU, oseltamivir should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus. Furthermore, oseltamivir should be used during lactation only if the potential benefit for the mother justifies the potential risk for the nursing infant.

#### Quality aspects related to pandemic use

Two dosage forms are commercialized:

- capsules 75 mg oseltamivir with a shelf life of 5 years.
- powder for reconstitution : 12 mg/ml oseltamivir with a shelf-life of 24 months, reconstituted solution: 10 days stored at 2 to 8°C.

A magistral formulation is proposed for oseltamivir (API system).

The proposed magistral formulation consists of an oral solution containing 19.70 mg/ml of bulk oseltamivir phosphate (API; Tamiflu grade) (corresponding to 15.0 mg/ml base), 1mg/ml sodium benzoate (EP or food grade) and water (EP purified or potable water can be used). Sodium benzoate was chosen as antimicrobial preservative as it dissolves rapidly in water, is well tolerated, is well established for oral solutions and is also as food grade readily available.

The method of preparation is well described and rather simple and can be prepared either in a pharmacy, in a hospital or in a suitable laboratory. There are no formal specifications (acceptance criteria + test methods) proposed by the MAH as the necessary equipment for quality control is not necessarily available in a hospital or in a pharmacy. This can be accepted in a pandemic situation as no quality control is performed in pharmacies when preparing other magistral preparations. The manufacturer will not supply the dosing device. Thus, no data on accuracy were presented. Member states will have to make sure that an adequate device is put at the disposal of the user/patient (part of stockpiling).

Data are presented to demonstrate the efficacy of the antimicrobial preservative sodium benzoate. The MAH does not test according to the Eu.Ph. standard test but according to a published low level challenge test using the same strains that are recommended Eu.Ph. The method proposed by the company to test the efficacy of the preservative is acceptable as it simulates more the in-use conditions than the EP test. The provided results demonstrate acceptable microbiological stability.

The chemical / physical stability has been studied in the magistral preparation stored at 5°C and 25°C in colourless glass bottles, PET bottles and HDPE bottles. The following use up conditions were proposed and are supported by data:

- 3 weeks if stored not above 25°C
- 6 weeks if stored at 5°C

The MAH has prepared a guide (*API User Manual*) on how to prepare the magistral solution for the oseltamivir phosphate.

The API user manual is comprehensive and very helpful in preparing the magistral solution. It has some advantages compared to the commercialised capsules formulation: cost, a shorter manufacturing cycle, availability, administration to children, even if from a logistic point of view the capsules are easier to dispense to the patient.

However, if the API model is chosen, the procedures for preparing the solution and dispensing it to users/patients have to be organised carefully.

The capsule model has a longer shelf life than the powder for reconstitution formulation but probably shorter than the bulk substance intended for the magistral formulation. In contrast to the magistral formulation, the use of capsules is supported by the full regulatory package and extensive clinical experience. The logistics of distribution are less complicated when commercial packages are used.

However, its use will be more expensive and the rate of production (to obtain sufficient stocks) is slower. Capsules are not suitable for use by small children.

### Regulatory status

Medicinal products containing oseltamivir (Tamiflu) have been approved centrally within the European Union by the European Commission. Please see the European Public Assessment Report (EPAR). [hyperlink to the Tamiflu EPAR on the website](#).

## **Zanamivir**

### Clinical uses

Zanamivir is indicated for treatment of influenza A and B in adults and adolescents aged  $\geq 12$  years at a dose of 10mg twice daily for five days. Zanamivir is not yet approved for prophylaxis in EU.

### Pharmacology

Zanamivir is another selective inhibitor of influenza neuraminidase (NA), the influenza virus surface glycoprotein enzyme. In principle, the presumed mechanism of action is the same as for oseltamivir (see above). The activity of the drug is a result of the replacement of a hydroxyl group at the C-4 atom by a guanidine group. The interaction of the guanidino group with two framework residues Glu 119 and Glu 227 results in tight affinity of zanamivir for the active site of the enzyme.

The oral bioavailability of zanamivir is low (2%, range 1-5%). Therefore, it is administered topically to airways using a specifically designed breath-activated device for inhaling powder, Diskhaler.

The two major sites of deposition immediately following dosing were the oropharynx and the lungs (mean 77.6% and 13.2%, respectively). Thereafter, the inhaled zanamivir was rapidly eliminated via the oesophagus to the stomach and the intestines. The estimated zanamivir concentration in this area would be at least 1868ng/mL, which is approximately 1400 times the neuraminidase IC<sub>50</sub>. In the worst case scenario, there should still be approximately 140 times the neuraminidase IC<sub>50</sub> at the peripheral lung. Measurable zanamivir levels have been demonstrated in nasal cavity after oral inhalation. The observed levels were in excess of the median zanamivir neuraminidase IC<sub>50</sub> of 0.9ng/mL for at least 12h post-dose.

The systemic exposure to zanamivir is low, less than 30% of the administered dose. It is not metabolised but is primarily excreted unchanged via the kidneys. Thus, renal or hepatic dysfunction will not influence the dosing. The dose does not need to be modified in the elderly or in children.

Zanamivir is not protein bound and not metabolised or modified in the liver. Clinically significant drug interactions are unlikely. Zanamivir, when given for 28 days, does not impair the immune response to the conventional influenza vaccine. The effect on live influenza vaccination is unknown.

The safe use of zanamivir in 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 significant malformations in the rat and rabbit. Zanamivir should not be used in pregnancy unless the expected benefit to the mother is thought to outweigh any possible risk to the foetus.

In rats, zanamivir has 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.

### Efficacy data

- Treatment

The results of the pivotal phase III studies, all double-blind and placebo-controlled, demonstrated that inhaled zanamivir, at a dose of 10mg twice daily for 5 days, was efficacious in the treatment of

influenza A and B, reducing the median time to alleviation of symptoms by 1.5 days. The duration of viral shedding is also shortened. The studies mostly enrolled younger, otherwise healthy subjects but high-risk subjects were also included. A shortening (1.5 days) of the time to alleviation of the disease was observed in a study of patients with respiratory disease. The treatment effect has been demonstrated in patients in whom the treatment was initiated within 48 hours after the onset of clinical symptoms. In a combined analysis of four phase III trials, complications were significantly reduced from 29% of placebo patients to 22% of zanamivir patients. Use of antibiotics for treatment of complications was reduced from 19% of placebo to 14% of zanamivir patients. The use of zanamivir is not expected to impair the effect of conventional influenza vaccines.

- Prophylaxis

Zanamivir is approved in 19 markets for prophylaxis at a dose of 10mg once daily during the period of exposure risk.

Studies have been conducted in a number of different settings, including communities, nursing homes and households. In the phase III studies, subjects received study medication for 10 (household prophylaxis) – 28 days (community prophylaxis), depending of the type of prophylaxis. The efficacy in the community prophylaxis studies ranged between 60% and 83%. The efficacy in the post-exposure prophylaxis in households was 79-81%. Studies in nursing homes suggested a protective efficacy of 29%-56%.

#### Sensitivity of influenza strains to zanamivir

*In vitro*: 50% inhibition at 0.64nM-7.9nM against influenza A and B. Within the frame of the NA inhibitor susceptibility network (NISON) over 1000 of clinical influenza isolates recovered from 1996 to 1999 have been tested and the mean zanamivir IC<sub>50</sub>s were 0.76, 1.82 and 2.28 for the subtypes H1N1, H3N2 and influenza B, respectively. There was no evidence of naturally occurring resistance to zanamivir in any of the isolates. Further 2691 isolates have been tested during the post-approval period (see below).

It is suggested that NA inhibitors would be effective against the 1918 pandemic virus. Investigators have generated recombinant influenza viruses possessing the 1918 HA, NA and M segments. The other pandemic strains H2N2 (1957), H3N2 (1968), and H1N1 (1977) were also inhibited in both tissue culture and in mice by zanamivir.

*In vitro* studies have demonstrated that zanamivir is able to inhibiting the different neuraminidase subtypes. The inhibitory profile was somewhat different from the profile of oseltamivir.

Data from animal models suggest that zanamivir is effective against the A/Hong Kong/156/ 97 (H5N1) virus that caused fatal illness in Hong Kong in 1997. Intranasally administered zanamivir protects mice against lethal challenge with A/HK/156/97 (H5N1) influenza virus, reducing viral replication in the lungs (by approximately 2 log<sub>10</sub>) and reducing morbidity and mortality compared with untreated mice.

Other studies showed that zanamivir partially protects chickens from A/chick/Victoria/1/85 (H7N7), but failed to protect chickens against other highly virulent viruses of NA subtypes N1, N2, N3, N7, N8, although there is *in vitro* activity against the neuraminidase enzyme for these sub-types. This discrepancy may be due the fact that some influenza strains are able to replicate outside the respiratory tract where zanamivir is not available. However, studies in a mouse model using avian H5N1, H6N1 and H9N2 strains showed that intranasal zanamivir significantly reduced viral titres in the lungs and completely blocked the spread of virus to the brain, with the conclusion that systemic spread may be related to the level of virus replication in the lungs.

#### Mechanisms of viral resistance

*In vitro* studies have shown that mutations in both the haemagglutinin and neuraminidase are associated with resistance development over prolonged passage. Resistance mutations in the NA result in reduced affinity of NA for the inhibitor. Resistance mediated by HA mutations has been attributed to reductions in the affinity of HA for the sialylated glycoconjugates, thereby reducing the dependence of viral replication on NA activity. The clinical significance of HA mutations is unknown. Interestingly, some strains that are resistant to oseltamivir have retained sensitivity to zanamivir.

#### Clinical significance and surveillance systems of viral resistance

A global neuraminidase inhibitor susceptibility network (NISN) has monitored susceptibility of influenza isolates circulating world wide before the introduction of the neuraminidases (1997-1999) and following approval. The susceptibility of 2691 isolates from 1999- 2002, post-licensure of the neuraminidases, was monitored and only three isolates (0.1%) had resistance-associated mutations. The clinical use of zanamivir is still relatively limited but, for time being, zanamivir-resistant viruses have not been isolated from immunocompetent individuals who have received zanamivir.

#### Adverse effect profile and contraindications

The only contraindication is hypersensitivity to the product. Zanamivir was well tolerated in the adult/adolescent treatment studies. The most commonly reported AEs were typical of the signs and symptoms of influenza and occurred with similar frequency in the zanamivir and placebo groups. However, inhalation of the zanamivir has been rarely associated with bronchospasm that may be severe in patients with bronchial asthma and chronic obstructive pulmonary disease.

#### Quality aspects related to pandemic use

Relenza Rotadisk 5 mg is registered via Mutual Recognition procedure in the old member states and via national procedures in the new member states. There is no difference in the Diskhaler and Rotadisk blister packs supplied to the EU and non EU-market. The key specifications for release and end of life are very similar for most markets.

Shelf-life: 3 years (stored at  $\leq 30^{\circ}\text{C}$ ) but may be extended to 5 years.

According to the marketing authorisation holder, the manufacturing capacity has been created to meet demand of expected pandemic stockpiling.

In case of a pandemic situation (import of non EU stock), it may be possible to return the stock to a registered packaging site in the EU for repackaging and release of the packs. A batch specific variation is to be submitted and approved by the relevant authority to allow importation and immediate use of the packs.

Due to the formulation (powder for inhalation) and the need for a device, there is no magistral formulation available.

#### Regulatory status

Medicinal products containing zanamivir (Relanza) have been approved via the Mutual Recognition procedure within the European Union.

### III. GOALS OF ANTIVIRAL USE DURING INFLUENZA PANDEMIC

Influenza antiviral medicinal products and pandemic influenza vaccines have a complementary role in the management of an influenza pandemic. In contrast to pandemic vaccines, influenza antivirals can be used from the very early phase of the influenza pandemic.

The estimates of efficacy of the influenza antivirals in a pandemic situation are largely based on their use in treatment and prophylaxis of seasonal influenza epidemics. However, the epidemiological pattern, the disease severity and demographics of patients of the pandemic influenza may be different. These differences may have implications for the optimal posology of the antivirals. Nevertheless, the goals for the use of antivirals and vaccines should be the reduction of morbidity and mortality due to the influenza infection.

The usefulness of antivirals for treatment of influenza is restricted by the need to initiate treatment within two days of the onset of clinical symptoms. Even then, the treatment effect is modest and uncertain against the pandemic strains. Early treatment of a large number of patients in a pandemic situation requires a well functioning distribution system.

Thus, successful use of antivirals during a pandemic cannot be based on treatment of symptomatic disease alone because of their limited efficacy, risk of viral resistance and the availability of the products (stocks and logistics of early treatment). Based on currently available clinical data and on results of modelling studies, it appears that targeted prophylaxis of influenza will be a feasible approach to the use of influenza antivirals during an influenza pandemic:

- For certain groups of individuals who are essential for the key functions of the society (e.g. health care workers, decision makers, police, firemen etc.), long-term prophylaxis should be considered in the very early phase of the pandemic and until a vaccine becomes available.
- For the general population, prompt treatment of index cases combined with prophylactic use by their close contacts (post-exposure prophylaxis) is a useful approach to mitigate the effects of the pandemic and to slow down the progression of the pandemic at the time when an effective vaccine is not available. In certain circumstance of the early phase of the pandemic, containment of the disease may be possible.

A wider long-term prophylactic use of antivirals will have a major impact on the size of the necessary stocks as well as on the distribution system. The feasibility of this approach remains uncertain.

Factors which might be taken into account in the choice of antiviral product(s) may be based on the pharmacological properties of the available agents, possibilities to use them in different groups of individuals, as well as on practical aspects related to the stockpiling and distribution. In spite of the uncertainty, the recommendation takes notice of the current epidemiological situation, i.e. the widespread infection of domestic and wild animals by the H5N1 strain of influenza virus (“bird flu”) – a potential ancestor of a pandemic.

## **IV. ANTIVIRAL DRUG USE– FACTORS WHICH MAY BE TAKEN INTO ACCOUNT**

### **What are the properties of the different antivirals available?**

Both the M2-inhibitors and the neuraminidase inhibitors are potentially useful in a pandemic situation. However, none of them provide an ideal solution to antiviral therapy of influenza. Thus, the availability of more than one agent would be useful in order to cope with special and unexpected circumstances, such as emergence of resistant strains. The dependence of only one provider makes the pandemic plans vulnerable.

The emergence of resistant influenza virus strains is more common during amantadine than during neuraminidase inhibitor treatment. Amantadine-resistant strains are generally susceptible for neuraminidase inhibitors and *vice versa*. There is not a complete cross-resistance to the neuraminidase inhibitors. Monitoring of viral resistance should take place during a pandemic.

In a pandemic situation, zanamivir may not be the preferred agent due to its mode of administration (inhalation with a device). The use of amantadine is hampered by its limited efficacy for the current candidate pandemic influenza virus strains, emergence of drug resistance and by its adverse effect profile and possible drug-drug interactions. However, it may be useful for prophylaxis in a healthy population provided that the influenza virus strain is not resistant.

Please refer to the Annex for Properties of the relevant influenza antiviral medicinal products.

### **Which formulation of oseltamivir should be used?**

Two commercial oseltamivir formulations {75mg capsules and a powder for reconstitution as an oral suspension (12 mg/ml)} and one magistral formulation (oseltamivir phosphate dissolved in water to a concentration of 15 mg/ml) can be made available for pandemic use. Currently, the manufacturing process of commercial oseltamivir formulation may last for longer than a year. The capsules are not suitable for smaller children (difficult to swallow, no possibility for accurate dosing) whereas the powder for oral solution has a relatively short shelf life (2 years). Results suggest that the magistral formulation is bioequivalent with the commercial formulations.

### **What amount of antivirals could be needed?**

The estimation of the necessary stocks will depend on the selected pandemic strategy and the availability of a vaccine against the pandemic strain. The type of a pandemic influenza virus strain and the characteristics of the pandemic must be considered in the estimates. Thus, the dose and duration of treatment will have to be further defined in order to determine the amount of products needed. Unfortunately, the optimal duration of prophylaxis during a pandemic is not known, but it is possible that periods exceeding the recommended duration of the normal seasonal prophylaxis (6-8 weeks) will be needed. Modelling of influenza pandemics should be further developed and refined. Such models may be valuable in estimation of the impact of the pandemic, including the amount of antivirals needed.

### **What scientific aspects should be considered in relationship to stockpiling?**

The active ingredient of oseltamivir (bulk oseltamivir phosphate) that has a retest period of at least 5 years with a possibility of extension after re-testing can be used for stockpiling. However, the capacity of local health care systems to formulate and distribute magistral formulations has to be taken into account. Furthermore, the possibilities of interpandemic use of the magistral formulation should be explored in order to rotate the stocks. Interpandemic use would also test and improve the distribution system. Smaller amounts of the commercial formulations can be stockpiled for special circumstances. Thus, oseltamivir is preferred for large scale stockpiling. Stockpiling of other agents on a smaller scale could be considered in order to cope with unexpected events, such as drug resistance or supply problems.

## ANNEX

### Properties of the relevant influenza antiviral medicinal products

Property	Amantadine	Oseltamivir	Zanamivir
<b>Mode of action</b>	M2 ion channels blockade	Neuraminidase inhibition	Neuraminidase inhibition
<b>Adverse effects</b>	Common-uncommon: CNS effects, nausea, vomiting, palpitation Rare. Cardiac arrhythmias, seizures	Common: Nausea, vomiting, headache Rare to very rare: hypersensitivity skin reactions hepatitis, elevated liver enzymes	Very rare: bronchospasm
<b>Warnings (some variation at the member state level)</b>	Prostatic hypertrophy Narrow angle glaucoma Agitation and confusion History of seizure, psychosis or delirium Severe hepatic or renal dysfunction	Hypersensitivity reactions	Bronchospasm
<b>Use during pregnancy</b>	Not recommended	Only if the risk of infection exceeds the risk to the foetus	Only if the risk of infection exceeds the risk to the foetus
<b>Use in children</b>	Very limited data	Used in children from one year of age Not recommended for children < 12 Mo	Limited data on children Not suitable for children <5 years
<b>Contraindications (some variation at the member state level)</b>	Hypersensitivity to the product Severe renal failure History of convulsions History of gastric ulcerations Severe heart disease	Hypersensitivity to the product Use in children under one year of age not recommended	Hypersensitivity to the product
<b>Drug-drug interactions</b>	Anticholinergic agents Several medicinal products affecting CNS Combination diuretics Quinine, quinidine	Not known	Not known
<b>Effect: treatment prophylaxis</b>	Modest Good initially, may be lost due to resistance	Modest Good	Modest Good
<b>Route of administration</b>	Oral	Oral	Inhalation with a device
<b>Site of action</b>	Systemic	Systemic	Respiratory tract
<b>Effect on past pandemic strains</b>	Yes ( <i>in vitro and in vivo</i> )	Yes ( <i>in vitro</i> )	Yes ( <i>in vitro</i> )
<b>Effect on H5N1 “bird flu” strains</b>	Questionable	Yes ( <i>in vitro</i> , experimental <i>in vivo</i> ) Probably clinically	Yes ( <i>in vitro</i> , experimentally <i>in vivo</i> )
<b>Resistance</b>	Common in treatment	Rare (except in treatment of children)	Rare
<b>Formulations</b>	Tablets	Capsules, powder for solution, a magistral formulation (oral solution)	Powder for inhalation