SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Tamiflu. For information on changes after approval please refer to module 8B.

1. Introduction

Tamiflu is approved for the following indication:

> "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 of SPC).

Prevention of influenza

- 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 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 adolescents 13 years 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".

The active substance of Tamiflu, oseltamivir (Ro 64-0796), is a pro-drug of the active metabolite, oseltamivir carboxylate (Ro 64-0802). Oseltamivir has been investigated for its ability to inhibit neuraminidase activity in influenza A and B viruses. Oseltamivir is a selective inhibitor of influenza virus neuraminidase enzymes, which 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.

Tamiflu was originally tested as hard capsules for oral administration in strength of 75 mg. In order to extend the treatment to children and to patients who cannot swallow capsules, a powder for oral suspension containing 12 mg/ml of oseltamivir freebase was developed.

(a) Treatment options of influenza

In most cases, influenza is a self-limiting disease. Thus, a supportive and symptomatic therapy will be sufficient. Amantadine and rimantadine inhibit the function of the M2 protein of influenssa a virus. In some countries, amantadine is indicated for treatment and prophylaxis of influenza A in adults and in children. Amantadine should not be used during pregnancy. Amantadine has effects on the central nervous system, including dizziness, insomnia, and headache. Development of drug resistance is not uncommon. The first neuraminidase inhibitor zanamivir is indicated for the treatment of both influenza A and B in adults and children of age 12 and older. Zanamivir is relatively well tolerated but may cause severe bronchoconstriction in sensitive individuals. The efficacy of amantadine and zanamivir in the treatment of influenza is modest: the duration of the symptoms is shortened by 1-2 days. The treatment must be initiated within 48 hours of the onset of symptoms.

(b) Prophylaxis of influenza

Vaccination is the most important measure in the influenza prophylaxis. Unfortunately, the current use of the vaccination is not optimal even in the risk groups. Immunisation complements the immunity derived from natural infections. The status of immunity in the population modifies the epidemics and will explain the differential sensitivity of different age groups. The current split virion influenza

vaccines contain antigens from two influenza A strains and one influenza B strain. The relevant strains for the Northern hemisphere are selected each year on the basis of epidemiological data from the Southern hemisphere. New vaccines, such as live influenza vaccines are under development. However, there are some situations where vaccination is not possible or it is ineffective. In certain populations, such as the elderly and immunocompromised individuals, the response to the vaccination may be suboptimal. It is also possible that an antigenic drift will take place after the selection of the vaccine strains. This drift may significantly weaken the efficacy of the vaccine.

During a pandemia, it may be difficult to develop an effective vaccine in sufficient quantities. In these situations, other measures to prevent an influenza infection are needed.

2. Chemical, pharmaceutical and biological aspects

Composition

Tamiflu contains oseltamivir phosphate as the active substance and is presented in two pharmaceutical forms: hard capsules containing 75 mg oseltamivir, and a powder for oral suspension containing 12 mg/ml oseltamivir.

- **Hard capsules**

Each hard capsule consists of a grey opaque body bearing the imprint "ROCHE" and a light yellow opaque cap bearing the blue imprint "75mg", and contains 98.5 mg oseltamivir phosphate, corresponding to 75 mg of oseltamivir.

Other ingredients used in the formulation are pregelatinised starch, talc, povidone, croscarmellose sodium, and sodium stearyl fumarate. The capsule shell contains gelatin, iron oxides (red, yellow & black) (E172), titanium dioxide (E171), and the printing ink contains shellac, titanium dioxide (E171) and FD & C blue 2 (indigo carmine, E132).

The capsules are packaged in boxes, each containing 10 capsules in a blister pack (laminated PVC/PE/PVDC, sealed with aluminium foil).

- **Powder for oral suspension**

The powder for oral suspension is presented as a white to light yellow coloured granulate, which, when reconstituted forms a white to light yellow, opaque suspension.

Other ingredients in the formulation are sorbitol, sodium benzoate (preservative), sodium dihydrogen citrate, saccharin sodium, a proprietary Tutti Frutti flavour, xanthan gum and titanium dioxide.

The primary container is a 100 ml amber glass bottle with a tamper-evident child-resistant screw closure. This is supplied with a plastic adaptor, a plastic graduated syringe/oral dispenser and a plastic measuring cup (CE marked).

After reconstitution as directed, with 52 ml of water, the usable volume of oral suspension allows for the retrieval of 10 doses, each of 75 mg oseltamivir.

Active substance

Oseltamivir phosphate, (3R,4R,5S)-4-acetylamino-5-amino-3-(1-ethylpropoxy)1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1), is a highly water soluble and non-hygroscopic pro-drug of the active metabolite, oseltamivir carboxylate. It has not yet been described in any pharmacopoeia.

A second polymorph may be formed under extreme circumstances, which are not encountered during synthesis of the drug substance or manufacture of the finished product. This is therefore unlikely to be clinically relevant, especially considering the high solubility of the active substance.

The starting material in the synthesis of oseltamivir phosphate is the epoxide, Ro 64-0792, which itself is synthesised in five steps from either (-)-shikimic acid or (-)-quinic acid, both of which are derived from biological sources (plant or fermentation origin). Shikimic acid originates from star anise or fermentation (using genetically engineered E. coli) and quinic acid from cinchona bark. There are three chiral centres and particular attention has been paid to the control of stereochemistry. The chirality of the epoxide starting material has been confirmed, and mechanistic, spectroscopic and

X-ray structure analysis have shown that oseltamivir phosphate, as used in the pre-clinical and clinical development program and intended for marketing, is in the 3R, 4R, 5S configuration.

TSE letters of certification from the manufacturers of fermentative (-)-shikimic acid are provided. The manufacturers of (-)-shikimic acid confirm that no materials of animal origin are used in the production of (-)-shikimic acid.

The active substance specification includes tests for appearance and identity (IR or NIR, HPLC, presence of phosphate) and tests and limits for assay (HPLC), impurities (specified, unspecified and total), residual organic solvents (acetone, ethanol, n-heptane & for reworked material only, methylene chloride), heavy metals, water and specific optical rotation.

All methods in the specification have been satisfactorily described and all the key methods validated. The limits have been justified by reference to batch analyses data, which confirm both compliance with the proposed specification and consistency between batches.

One related substance, a 2-azido compound arising from the route of synthesis, was found to be mutagenic when present in levels exceeding 0.03%. The active substance passed the Ames test when this related substance was not present. However, the pre-clinical assessment concludes that any genotoxic or carcinogenic potential due to the minute quantities this 2-azido compound actually found can probably be discounted, and therefore this impurity is not clinically relevant in the amounts found in routine production. In general the active substance appears to be of high purity. The most recent lots of active substance manufactured were recorded as having a total impurity content of approximately 0.2%. Satisfactory batch analysis records have been provided, generated by validated methods, to indicate that this purity will be consistently achieved from batch to batch.

Stability data for the active substance for up to 36 months are available for registration batches. No remarkable changes have occurred between 24 and 36 months storage. The Applicant has provided an undertaking that they will submit updated stability data for production batches in order to confirm the claimed retest period of 36 months, when these data become available.

Other ingredients

- **Hard capsules**

All excipients used to manufacture oseltamivir phosphate capsules comply with the appropriate monographs of the current PhEur.

The applicant declares that the sodium stearyl fumarate used is not of animal origin, and TSE certificates are provided for the PhEur gelatine used in the manufacture of capsule shells.

Satisfactory specifications are provided for the primary packaging materials.

- **Powder for oral suspension**

All excipients used to manufacture oseltamivir phosphate capsules comply with the appropriate monographs of the current PhEur except sodium dihydrogen citrate, which is tested according to an FAO nutrition paper. Although sorbitol is tested according to the monograph of the current PhEur the specification includes an additional test for residual glucose (HPLC), which is limited to a maximum of 0.03 % for stability purposes. (Refer to stability section below.)

The qualitative composition of the "Tutti Frutti, Permaseal 11900-31" flavour and a satisfactory specification is presented. Satisfactory specifications are also provided for the primary packaging materials.

Product development and finished product

The product was initially formulated as hard capsules (75 mg), but in order to facilitate the treatment of both children and patients who cannot swallow capsules, a powder for oral suspension (containing 12 mg/ml of oseltamivir free base) was developed.

- **Hard capsules**

These are conventional release hard gelatin capsules, the contents of which are manufactured by a wet granulation process using conventional pharmaceutical technology. All the manufacturing processes and in-process controls are satisfactorily described. During process development the lubricant sodium

stearyl fumarate was used as a surrogate marker for homogeneity, however, this has been justified by several reasons, including that it is the component of lowest concentration in the formulation.

The product specification contains the relevant tests and limits for a product of this type. Tests include appearance, identification of the active substance (HPLC & TLC), assay (HPLC), limits for impurities (specified, unspecified and total impurities of 0.6% max. at release and 0.8% max. over the claimed shelf-life). In addition there are also tests for uniformity of fill-mass (PhEur), dissolution, identification of colorants and microbial limits (PhEur).

The analytical methods are described and suitably validated, in accordance with current guidelines.

Batch analysis records indicate satisfactory product uniformity.

- **Powder for oral suspension**

Preservative efficacy data from during development support the selection of 0.1% sodium benzoate as the preservative system.

After reconstitution of the powder (30 g) with the stated amount of water (52 ml), followed by vigorously shaking for approximately 15 seconds, the volume of the resulting suspension in the bottle is 75 ml. The 15-second shaking time has been proven to be sufficient to obtain a homogeneous distribution of both oseltamivir phosphate and sodium benzoate in the resulting suspension. During development only minimal settling was observed in the reconstituted suspension stored for up to 17 days. This settling is considered negligible, since under user conditions the reconstituted suspension is to be administered either twice a day for 5 days, or once a day for at least 7 days, with shaking prior to each administration, and a uniform product was demonstrated to be obtained under these conditions (as defined in the instructions of the SPC and patient leaflet).

A compatibility study demonstrates the compatibility of the oral dispenser with the formulation and the suitability for its intended use.

The manufacturing processes for the powder for oral suspension are satisfactorily described, and the in-process controls and their specifications have been justified.

The product specification contains the relevant tests and limits for a product of this type. Tests include appearance (before and after reconstitution), identification of the active substance (HPLC and TLC), preservative and colorant, assay of active substance (HPLC), sodium benzoate (lower limit justified by preservative efficacy test data), limits for impurities (specified, unspecified (0.3% at release) and total impurities (1.0% at release)), pH, microbial quality. The limits of the impurities are justified by the safety studies.

The analytical methods are described and suitably validated, in accordance with current guidelines.

- **Hard capsules & Powder for oral suspension**

The Applicant has provided an undertaking that they will review the specifications of both pharmaceutical forms when the final shelf-life stability data become available for the validation batches.

Stability of the Product

- **Hard capsules**

Degradation products increased only very slightly at normal and intermediate storage conditions, and moderately at accelerated testing conditions. The stability data are in accordance with ICH/CPMP guidelines and confirm the proposed shelf-life of 36 months for the product, with no special precautions for storage.

- **Powder for oral suspension**

There are differences between the active substance degradation in the hard capsules and the powder for oral suspension. During storage of the latter, a moderate increase in degradation was observed under normal and intermediate storage conditions, and a strong non-linear increase of degradation was found under accelerated storage conditions. Two main degradation products, Ro 68-7010 and Ro 69-4458, have been identified in the powder for oral suspension. Ro 68-7010 is the reaction

product of oseltamivir phosphate with residual glucose in the excipient sorbitol, and Ro 69-4458 is formed by degradation of Ro 68-7010.

The stability data provided confirm the proposed shelf-life of 24 months when stored below 30°C.

The proposed in-use shelf-life, following reconstitution as directed in the SPC, is 10 days at 2°C- 8°C (in a refrigerator), and this has been supported by the appropriate physical, chemical and microbial data.

Preservative efficacy testing has been carried out on bottles which have been stored for 18 months at 26°C/60% RH and then reconstituted for 10 days. The results demonstrate the satisfactory antimicrobial efficacy of the preservative, as the requirements of PhEur were met. This is in accordance with the levels of sodium benzoate determined in the same samples.

3. Toxico-pharmacological aspects

Pharmacodynamics

- *In vitro* studies

In vitro antiviral assays (plaque reduction, virus yield, or cytopathic effect) of influenza viruses of active oseltamivir were mainly performed using Madin-Darby canine kidney (MDCK) cells. Active oseltamivir inhibited *in vitro* the influenza neuraminidases with Ki and IC50 values in the nanomolar range (0.06 – 1 ng/ml), but had little or no activity against other neuraminidases from other sources (human liver, rat liver or uterus or two bacterial and parainfluenza and Newcastle disease neuraminidases). Clinical isolates and laboratory strains of A-type virus seem to be more sensitive than B-type viruses to active oseltamivir. Ki value for a resistant mutant enzyme was >27000x above the value obtained for a wild type enzyme.

- *In vivo* studies

In vivo studies used highly virulent viruses to infect mice. Effects of lethal intranasal doses of mouse-adapted influenza A (H1N1, H3N2) and B were inhibited dose-dependently. Other animal models tested *in vivo* were ferrets and chickens. In ferrets, symptoms of disease caused by clinical isolates (A/H1N1 or A/H3N2 or B) were slightly relieved by oseltamivir doses that give the exposure comparable to that observed in clinical trials. Chickens infected by a highly pathogenic avian influenza A virus (H7N7) and treated with 10 or 100 mg/kg oseltamivir (Ro 64-0796) had lower virus titres and a slightly improved survival in the high dose group only.

Resistance-linked point mutations have been found, one of which was found only in clinical samples. All mutations are near to the active site of the neuraminidase enzyme and may thus modify substrate-enzyme binding. Viruses carrying resistance mutations to active oseltamivir in their neuraminidase were less virulent in mice and ferrets.

Thus far, resistant influenza B viruses have not been found in in vitro studies or among clinical isolates.

- General and safety pharmacology programme
- *Central nervous system*

Acute or chronic effects of oseltamivir and active oseltamivir (Ro-640802) were marginal. In an acute study, two mice had convulsions following a 250-mg/kg intravenous bolus injection. Severe vomiting occurred in a few marmosets at high dose level. Therefore, both oseltamivir and active oseltamivir were tested in a receptor-ligand binding assay that included CNS receptors known to be involved in nausea and emesis. Neither compound had a significant effect on any receptor at concentrations of up to 10 mM (3 mg/ml). In isolated guinea pig ileum samples, neither compound affected the basal tone of the ileum. Thus, the reason for oseltamivir-induced nausea and vomiting remains unknown.

No specific alerts rose in safety pharmacology studies specifically designed to examine the effects of test drug on the CNS of rodents; effects on general behaviour, spontaneous locomotory activity, pentylenetetrazole-induced convulsions and hexobarbital-induced sleeping time in mice, as well as the response to a painful stimulus and effects on respiratory rate and body temperature in rats.

- *Cardiovascular system*

A preliminary cardiovascular safety study *in vivo* was carried out in anaesthetised dogs: delay in cardiac repolarisation associated with intravenously administered active oseltamivir (dose 100 mg/kg) was observed. Aconfirmatory study in six male and six female conscious dogs found statistically significant increase in the QT interval associated with decreased HR. After corrections QT/HR rate with the Van de Water and Friedica's formula, no statistical effects on heart rate, QTc interval or any other ECG parameter or wave-form existed. *In vitro* studies in isolated sheep Purkinje fibres or rabbit Purkinje fibres (with positive controls; sotalol, cisapride and sparfloxacin, after artificial stimulation by 0.2 or 1.0 Hz) could not confirm the *in vivo* findings in anesthetised dogs. The effects of oseltamivir on potassium currents using recombinant hERG channels expressed in mammalian cells were studied (with cisapride, sparfloxacin and terfenadine as positive controls); no significant change in potassium current at any concentration was observed. Thus, there appears not to be a preclinical safety signal for cardiac toxicity.

- *Gastrointestinal system*

No gastrointestinal damage was found in repeated dose studies in marmoset, dogs, rats or mice at relevant dose levels. Two mid dose (2 x 100 mg/kg/day) group male marmosets and one low dose (2 x 25 mg/kg/day) group female were found to have osteomalacia. According to the applicant, marmosets are prone to this condition in the laboratory, due to their large requirement for vitamin D3.

Pharmacokinetics

The oral absorption of active oseltamivir has not been studied in humans but its low bioavailability in rat and marmoset (< 5%) suggests a low bioavailability also in humans. Absorption of oseltamivir is high (>70%) in all species.

Pharmacokinetic characteristics changed with age. A particularly high exposure to oseltamivir was found in 7-day old rats with increased mortality in 7-day old rats at high dose levels; for example, AUC(0-24h) after a 500 mg/kg dose was 335 µg.h/ml compared to only 74 µg.h/ml in adult animals.

Distribution of drug-related material in animals after oral administration of oseltamivir results in high levels in the lung, gastrointestinal tract, kidney and liver being 3-6 times that of blood. Active oseltamivir has also been measured in bronchoalveolar fluid of rats at similar levels to those of plasma. Penetration of the drug to central nervous system is low (25% of plasma) and foetal exposure is 15 - 20% of that of the mother, in terms of AUC, in both rats and rabbits. Binding of active oseltamivir to plasma proteins is <4% and that of oseltamivir (prodrug) is moderate in several species.

In a dog study, plasma concentrations of both oseltamivir and active oseltamivir were comparable after a single 75 mg dose of capsules or oral suspension. Cytochrome P450-mediated biotransformation reactions of oseltamivir have not been observed in ferrets and primates, including man. The relative rate of hydrolysis of the pro-drug - enzyme activity found in the cytoplasm of the hepatocyte is man >> marmoset >> ferret and the bioavailability of the active oseltamivir is in the same order. Differences in human hepatic esterases have been demonstrated. *In vitro,* studies show quite a wide range in enzyme activity, which might potentially arise through pharmacogenetic differences or disease. Despite this wide range in enzyme activity, a 75 mg oral dose of oseltamivir has been shown to generate a consistent systemic exposure to active oseltamivir (Ro 64-0802), with little inter-subject variability.

No inhibition of the biotransformation of specific substrates of the major forms of cytochrome P450 (CYP1A, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP4A) by oseltamivir or the active compound was observed when a pool of human liver microsomes (10 livers) was used.

The excretion of active oseltamivir is 99% renal in man and predominantly into urine in all other species as well. The renal clearance in man is about 2.5 times that of glomerular filtration rate (GFR) suggesting that tubular secretion will occur. Human organic ion transporter type 1 (hOAT1) is a major component of active tubular secretion in the kidney. Probenecid inhibited this transporter when it had been transfected into Chinese hamster ovary cells (Ki = 4.3 mM), but no effects were seen with active oseltamivir (Ki = 45000 mM) or amoxicillin (Ki = 7600 mM). Other disposition mediators were not tested.

If chronic toxicity tests result with no hepatic, kidney and other specific organ toxicity, the more detailed evaluation of disposition mediators (such as BAEP (bile acid excretory pump), MPR1-7, *ABC*-cassette) can be omitted. However, interaction with P-glycoprotein has been investigated. Good substrates of P-gp such as cyclosporin, saquinavir and ritonavir effectively inhibited P-gp mediated efflux of oseltamivir. This could increase the oral absorption of the pro-drug into the gut-wall and hence into the systemic circulation but, as its absorption is already 80-85%, the maximum rise in systemic exposure would be less than 25% . The weak affinity of oseltamivir for P-gp means that it will have no affect on the P-gp-mediated efflux of drugs such as saquinavir and cyclosporin. The active oseltamivir, Ro 64-0802, does not interact to any measurable extent with P-gp.

Multiple dose pharmaco/toxicokinetic studies were carried out in rats, mice, rabbit, ferrets and dogs. Peak concentrations of oseltamivir were usually observed between 0.5 and 1 hour after dosing with those of active oseltamivir, one or two hours later. Species-dependent variation in the pharmacokinetis of oseltamivir was observed. There was a tendency for the maximum concentrations of the active drug to appear later at high doses, suggesting that its rate of formation was saturable.

Toxicology

Acute and special toxicity studies were conducted in rats, mice, rabbits and guinea pigs. Teratogenic potential was evaluated in rats and rabbits. The selection of animal models is appropriate.

- *Single dose toxicity:*

Acute toxicity studies in mice and rats (adults and juvenile) administered orally, suggested a maximum non-lethal dose of 2000 mg/kg of Ro 64-0796/002. No drug-related deaths or adverse toxicological effects were observed.

- *Repeat dose toxicity:*

The main repeated dose studies with oseltamivir were carried out in the rat (27 weeks) and marmoset (39-weeks)

Rats

In a two-week oral toxicity study, in adult and juvenile (unweaned 7-20 days of age) Sprague-Dowley rats receiving Ro 64-0796/001, the no edverse effect level (NOAEL) of Ro 64-0796/002 was found to be 500 mg/kg/day.

In a main four-week study, groups of weaned 21 to 49 day old rats, the NAOEL of Ro 64-0796/002 was 500 mg/kg/day. In an adult rat study of similar duration the NOAEL was 250 mg/kg/day. At 1500 mg/kg/day cortico-medullary mineralisation and associated changes were found in the kidneys.

A 27-week oral toxicity study was conducted in Sprague-Dawley CD rats at doses of 0, 50, 200 or 1000 mg/kg/day of the pro-drug, Ro 64-0796/002. Increased incidences of mild cortico-medullary mineralisation and chronic progressive nephropathy were observed histologically at 1000 mg/kg/day. These changes were not reversible after two or six months without treatment.

Although some minor disturbances were noted for occasional clinical pathology parameters at 50 and 200 mg/kg/day, significant toxicologic/pathologic changes were related to the kidneys and confined to the high-dose group.

Marmosets

In a thirty nine-week oral (gavage) toxicity study, Ro 64-0796/002 was administered to groups of marmosets at dose levels of 50, 200 and 1000 mg/kg/day each given as two daily doses of 25, 100 or 500 mg/kg/dose, approximately 2 hours apart. The only significant dose-related adverse effect was post dosing emesis and salivation.

A four-week oral study in marmosets at doses of up to 2 x 500 (=1000) mg/kg/day also demonstrated good tolerance in all groups.

Mice

Groups of mice received 50, 250, 500, 1000 or 1500 mg/kg/day of Ro 64-0796/002 for 4 weeks. The doses were chosen in view of the good overall tolerance in rat and marmoset studies. There was one

death in the 1500 mg/kg/day group due to renal lesions (a combination of cortico-medullary mineralisation, tubular dilation and papillary necrosis). At high dose levels, males showed slight increases in hemoglobin concentration, RBC count and packed cell volume. No changes were observed in females. Microscopically, there was a slight increase in minor focal nephropathy at doses of 500 or 1000 mg/kg/day. Renal papillary necrosis and segmental atrophy were observed in isolated animals in the 500, 1000 or 1500 mg/kg/day dose groups.

- *Genotoxicity/Mutagenicity*

No mutagenic potential was observed with or without metabolic rat "S9" mix in Ames' test, with five *Salmonella typhimurium* tester strains. No induction of TK-mutants was found in a mouse lymphoma *tk+/-* test by active oseltamivir. No chromosomal aberrations were observed with Oseltamivir as tested in human lymphocytes. Mouse micronucleus test *in vivo* (2000 mg/kg) with relevant exposure to the drug and metabolites was negative. Tests of impurities or degradation products gave positive mutagenecity results in Ames test for Ro-1637, a 2-azo derivative of Ro 64-0976. The limit for this specific impurity is now 0.01%, which considered being safe.

- *Carcinogenicity*

Active oseltamivir was assayed in a 26-week TG: AC transgenic mouse model with dermal application. No significant evidence for the formation of skin papillomae was found. Skin reactions were comparable to those of controls. However according to the ILSI programme, this asay is not optimal to detect non-genotoxic carcinogens.

The applicant has recently completed a two-year rat carcinogenicity study. In addition, interim results of a standard mouse carcinogenicity study were submitted.

In the two years carcinogenicity study in the rat, a slightly increased mortality was observed in the male high dose group. There was a positive trend for dose dependent increase in blood vessel tumours (haemangiomas, haemangiosarcomas; $p< 0.01$, lymphoid tumours $p< 0.038$) in males and epithelial tumours ($p<0.034$) in females at the terminal kill. The positive trend in the carcinogenesis study was worrying considering the treatment of children and the prophylaxis in general.

The applicant presented several lines of evidence that help in rejecting the hypothesis that oseltamivir has a carcinogenic potential; *In vitro* and *in vivo* genotoxicity studies show no evidence of either mutagenic or clastogenic potential for either oseltamivir or the active metabolite. The TgAC mouse assay with the active metabolite was negative. Histological data from unscheduled deaths and scheduled sacrifices in the two-year rat carcinogenicity study show no evidence of an excess of pre-neoplastic lesions in drug-treated animals compared to controls.

The findings in the rat study cannot be regarded as a clear signal. Thus far, there is no reason to suspect that neuraminidase inhibitors would promote non-genotoxic carcinogenesis. The available data from the TgAC model and from the ongoing standard mouse carcinogenicity study support the concept that the findings in the rat are of minor significance. It is foreseen that prolonged exposure to oseltamivir through repetitive seasonal use will be very limited. Therefore, concerns regarding carcinogenicity are considered resolved and the applicant commits to provide CPMP with the final study report of the ongoing mouse carcinogenicity study as soon as it becomes available.

In the Syrian hamster embryo (SHE) cells assay, an increased number of morphologically transformed colonies were found in "a dose dependent manner" with Ro 64-0796/002 but not Ro 64-0802, the active compound. The concentrations shown to be negative in the assay were > 250 fold higher than oseltamivir concentrations likely to be achieved in both adults and children.

- *Reproductive toxicity*

In a fertility and early embryonic development study conducted in male and female rats with Ro 64-0796/002 at 0, 50, 250 and 1500 mg/kg/day no significant adverse effects on fertility, mating performance or early embryonic development were observed up to 1500 mg/kg/day dose level.

In pre- and post-natal studies in rat's prolongation of parturition and pup viability and impaired development were observed at high doses (1500 mg/kg/day). In rabbits, the dose of 500 mg/kg/day increased the number of abortions and 1500 mg/kg/day was markedly toxic for rabbits. No effect level of treatment was 50 mg/kg in rabbits.

In the teratology study in rats, the oral administration of Ro 64-0796/002 0, 50, 250 and 1500 mg/kg/day to female rats showed no teratogenic effects. In a teratology study in rabbits, with the oral administration of Ro 64-0796/002, no effect of treatment on the incidence of foetuses with minor skeletal abnormalities was observed. The incidence of variants (increased numbers of thoracic and caudal vertebral centra, extra 13th rib and vestigial 13th rib) was increased in a dose-related manner in the groups treated at 150 and 500 mg/kg/day. Treatment with Ro 64-0796/002 during the period of organogenesis at 500 mg/kg/day elicited significant maternal toxicity. In conclusion, there was evidence of embryotoxicity, in the 150 and 500 mg/kg/day dose regimen, which may indirectly be due to Ro 64-0796/002 maternal toxicity. However, this indirect relation was not proved.

- *Local Tolerance:*

In an oral tolerance study in rabbits, mortalities occurred in non-pregnant rabbits at 750 and l500 mg/kg/day of Ro 64-0796/002. Abnormalities of the stomach wall and intestinal contents e.g. erosion and reddening of the stomach mucosa were observed in dead animals.

In a seven days local gastrointestinal tolerance study in dogs, 2 males and 2 females received 75 mg capsules containing Ro 64-0796/002 at 12 hours intervals for seven days to study local gastrointestinal tolerance. There were no clinical and morphological indications of local or systemic intolerance.

- *Other toxicity*

The phototoxic potential of Ro 64-0796/002 was tested in an *in vitro* study in the presence of UVA radiation. There was no evidence of any potential toxicity.

A maximisation test in guinea pigs with Ro 64-0796/002 revealed that the test compound is a skin sensitiser.

The active form of oseltamivir inhibited the proliferation of an influenza-specific human T-cell line significantly *in vitro*. There is no clinical evidence that this *in vitro* observation of slight immuno-suppression is of relevance to the benefit/risk ratio for oseltamivir.

- *Ecotoxicity/Environmental Risk Assessment:*

In a carbon dioxide evolution test for determination of biodegradability, Ro 64-0796/002 was not readily biodegradable.

In an acute toxicity study in Daphnia magna, Ro 64-0796/002 was classified as harmful according to the EU Directive 67/548/EEC as amended.

Exposure estimations according to the worst case scenario for the environment has been carried out. According to the draft regulations a quotient of PEC and PNEC Predicted No-Effect Concentration equal or less than one is taken as indicative of environmental compatibility for a given active substance. (PECwater [Europe] /PNECwater = µg/l 33 ng/l 173 ˜0.005).

As the PEC/PNEC ratio is significantly smaller than 1, no long-term negative effect on the aquatic

environment is to be expected. Even using the lowest NOEC (NOEbC algae, 10 mg/l) for extrapolating the PNEC, the PEC/PNEC ratio is still below 0.02.

Considering ecotoxicological properties,use pattern, dosage and maximal estimated

Amounts of Oseltamivir to be placed on the market, no exposure levels of concern to the environment are to be expected.

- *Impurities:*

Toxicity tests of impurities or degradation products showed positive mutagenicity results for Ro-1637, a 2-azo derivative of oseltamivir, in Ames test (see Mutagenicity).

In a two weeks impurity toxicology study (active oseltamivir, 64-0951, 64-0952), a granulomatous focus in epididymis was found in 2/5 rats. Up to six weeks studies Ro 64-0952 did not produce any abnormal findings with the safety factor of 10-20 times the maximum human dose. Toxicity of impurities present on granules for oral suspension was tested in rats. No remarkable signs of toxicity were noticed.

Mutagenic potential of the contaminants Ro 64-0795/000, Ro 64-0792/000 and Ro 64-0789/000 performed by Ames test did not reveal cytotoxic or mutagenic activity.

Discussion on toxico-pharmacological aspects

Cortico-medullary mineralisation and a mild enhancement of chronic progressive nephropathy were observed in rats. The observed nodules consisted mainly of calcium phosphate and protein. It is concluded that this may be due to increased phosphate salt concentrations caused by oseltamivir phosphate at high dose levels, which results in a reduction in the calcium/phosphate ratio. This appears to be a species-specific phenomenon since no histopathological changes were found in marmoset kidneys after four or 39 weeks at 1000 mg/kg/day.

4. Clinical aspects

The efficacy of Tamiflu has been investigated in the treatment of influenza in the adults and in children. Furthermore, studies have been conducted in postexposure prophylaxis and in seasonal prophylaxis at the community level. In total, 11675 subjects participated in the clinical program, 7642 of which received oseltamivir and 4033 placebos. Most patients had influenza A. In the treatment studies, influenza B was diagnosed in 117 and 178 individuals in the placebo and Tamiflu groups, respectively. The product has not been investigated in critically ill or in immunocompromised patients.

The approved indication is, "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 of SPC).
Prevention of influenza

- 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 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 adolescents 13 years 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".

Clinical pharmacology

Pharmacodynamics

The applicant has performed three clinical challenge studies in healthy volunteers to investigate the dose response of oseltamivir in the treatment of "experimental" influenza A and B:

In the Phase II Clinical Study, Protocol GS 97-801, 80 healthy male and female volunteers were recruited. Sixty-nine individuals (86%) developed influenza after the challenge and were included in the final evaluation. The five-day treatment was started 28 h after the inoculation of virus, A/Texas/36/91 (H1N1), intranasally. The doses of oseltamivir were 20 mg twice, 100 mg twice, 200 mg twice, 200 mg once and placebo twice daily.

The primary efficacy parameter, AUC of virus titer, for the *post hoc* pooled active drug-treated group was found to be significantly lower than that of the placebo group (p=0.020). In the combined drug-treatment groups, there were also significant reductions in the duration of viral shedding (by half) and time to amelioration of symptoms as compared to placebo.

Nasal mucus weights from subjects in the drug-treated groups were found to be reduced by half compared to those in the placebo group.

In the Phase II Clinical Study Protocol NP15717**,** pharmacokinetics (PK), pharmacodynamics (PD) and antiviral efficacy of oral oseltamivir treatment were evaluated in healthy volunteers experimentally inoculated with human influenza B virus (Yamagata/16/88). Doses of 75 or 150 mg twice daily commenced at 24 h post-inoculation and continued for five days were compared with placebo in 60 randomised subjects of whom 46 showed evidence of infection (more than 4-fold increase in HAI titre). The mean AUC virus titre for the pooled active treatment groups (75 mg + 150 mg: 30 subjects) were reduced by 44% and median AUC by 81% compared to placebo. However, none of these differences was statistically significantly different from placebo. The higher dose did not appear to be better than 75 mg twice daily for any of the efficacy variables. There were no between-group differences in HAI antibody titres.

In the other Phase II Clinical Study, Protocol NP15827**,** in experimental influenza B infection**,** antiviral efficacy of 75 mg oseltamivir twice daily for 5 days was compared to placebo in 117 volunteers. The first dose was taken 24 h after the inoculation. Twenty- eight out of 117 individuals were excluded due to lack of infection. The primary efficacy parameter, area under the curve (AUC) of virus titers, was significantly smaller in the Tamiflu group compared to placebo. The duration of viral shedding was also significantly reduced in the active treatment group, 43 $\pm$ 6.3 (SE) h, compared to placebo, 93 $\pm$ 12, p=0.0005. Less than 30% of the subjects in the Tamiflu group exhibited virus shedding 36 h after start of treatment, that is, after the third dose.

The applicant has performed two clinical studies in healthy volunteers to investigate the dose response of oseltamivir in the prophylaxis of influenza A and B:

In the Phase II prohylaxis Study, Protocol GS 97-802, 37 healthy volunteers were nasally inoculated with human influenza virus A/Texas/36/91 (H1N1). The duration of the oseltamivir/placebo administration was 5 days. Dosages were 100 mg once or 100 mg twice daily of oseltamivir or placebo. Subjects were inoculated at 24 h after the first dose. Six out of 21 (29%) subjects in the two active groups had influenza as determined by HAI antibody titres only. The difference between the placebo group, 8 out of 12 (67%), was not statistically significant. None of the 21 subjects in the oseltamivir groups shed virus compared with 6/12 in the placebo group. The composite symptom score was significantly reduced and time to alleviation of symptoms was significantly shorter with both oseltamivir doses. The mean (SD) AUC of the sums of composite symptoms (7 symptoms) scales was 237 (185) for placebo, 91 (139) for oseltamivir 100 mg once daily and 123 (74) for 100 mg twice daily.

In the Phase II prophylaxis Study, Protocol NP 15757, 58 healthy volunteers were nasally inoculated with human influenza B virus. Treatment with either 75 mg of oseltamivir once or twice daily or with placebo was started 24 h before inoculation, and was continued for 7 days. There was no between-group difference in the proportion (80-89%) found to be infected. Fifty six per cent of the subjects in the combined oseltamivir group and 74% in the placebo group were found to shed virus (NS). The peak (1.2 vs. 2.3, p=0.040) and AUC of virus titres (58 vs. 161, p=0.033) were significantly lower, and the duration of shedding shorter (52 vs. 86 h, p=0.034) for the pooled treated groups. AUC of the composite symptom scores and time to alleviation of symptoms were in favour of the oseltamivir treatment groups. The mean $\pm$ SD of the composite symptom scores were 157 $\pm$ 135, 123 $\pm$ 105 and 116 $\pm$ 98 after placebo, 75 mg once daily and 75 mg twice daily, respectively.

Viral resistance to oseltamivir:

The applicant presents data on more than 2500 individuals who have been screened for oseltamivir-resistant viruses before treatment. Posttreatment samples from 1500 individuals were also assessed. The main method to show resistance was the neuraminidase phenotype assay. Genotype assays were not performed on routine basis.

Virus strains that are resistant (or less sensitive) to oseltamivir (carboxylate) can be generated in vitro by serial passages of the virus in the presence of the drug. The degree of reduced sensitivity varies from 2 fold to 30000 fold. NA mutations are virus sub-type specific. Mutations in the hemagglutinin causing a decreased sensitivity to oseltamivir have been described *in vitro*. Thus, resistance may be due to mutations in both NA and hemagglutinin. However there is no evidence for resistance arising via HA mutation *in vivo*. The screening for resistant strains will be based on the phenotype of the NA

only, as there is currently no HA phenotype assay available. Thus, should resistant virus arise via HA mutation, they will not be detected.

Resistance was observed in 2/55 cases in the treatment study of experimental A virus infection and in no case of 70 individuals with experimental B virus infection. Resistance was seen in 10/248 children with a natural influenza infection but only in 4/1009 adults. The longer virus shedding in children may explain the difference. The number of cases that were examined in the prophylaxis studies is too small for any conclusions.

The phenotypic and genotypic assays were compared in samples from 240 adults. Only one case of NA mutation that was not detected by the phenotypic assay was found by the genotypic assay. In children, nine cases of reduced sensitivity to oseltamivir were detected from which three cases may have been raised during the expansion of the original sample. Genotypic analysis revealed no cases of resistant influenza B viruses. The resistance developed after day 4 and the viruses were cleared in 2-4 days. The presence of a resistant virus seemed not to be associated with an atypical clinical presentation of the infection.

The genotypic analysis of the hemagglutinin revealed a similar frequence of mutations in the placebo and Tamiflu groups. In contrast to the in vitro studies, no concomitant hemagglutinin and NA mutations were found in clinical samples.

Cross-resistance with zanamavir does not occur in most types of mutations. However, the most common mutation in the clinical isolates, R292K, leads to a moderate resistance to zanamavir as well. No cross-resistance between oseltamivir and amantadine/rismantadine has been observed.

Pharmacokinetics

Pharmacokinetics of oseltamivir oral preparations, capsules and oral suspension, were evaluated in adults and in children at the age of 1 or older. In addition, studies have been performed in patients with renal insufficiency, including patients in dialysis. 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). In healthy humans, at least 75% of an oral dose enters the systemic circulation as the active metabolite. Food does not significantly affect the rate or extent of absorption of oseltamivir. Plasma concentrations of both the prodrug and the active metabolite are proportional to dose and are unaffected by co-administration of food. Oseltamivir carboxylate is distributed widely to different tissues, including the respiratory tract. The mean volume of distribution at steady state of the active metabolite is approximately 24 litres in humans. The active metabolite is not metabolised further but is eliminated practically completely in urine. The renal elimination takes place through both glomerular filtration and tubular secretion. The apparent half-life of elimination of the active compound in plasma is 6 to 10 hours in healthy subjects and is similar in the elderly. Thus, no dose adjustment is needed.

The applicant has carried out two clinical studies of pharmacokinetics in children. In the Study NP 15826, single doses of 2 mg/kg of the prodrug, as an aqueous suspension of 30 mg in5 ml, were administered to 18 subjects of 5 -18 years of age. The subjects were divided in three age groups, each with 6 children. Clearances of both the prodrug and the active moiety were faster in younger children, resulting in 75% and 60% exposure to these molecules, respectively, in 5-8 years olds compared with the 13-18 years group. The average Cmax for the active metabolite was 183, 231 and 319 ng/ml, and AUC 2746, 3208 and 4534 ng*h/ml in the age groups 5 - 8, 9 - 13 and 13 - 18 years. The average T½elim ranged from 7.8 to 8.8 h, and no effect of age was seen. Exposure of 5 - 9 years olds to the active metabolite was similar to that of adults with a 75 mg dose, whereas 2 mg/kg in 13 - 18 year olds was about equivalent to a 150 mg dose in adults. The PK profile and T½elim suggested that steady-state trough levels in children dosed with 2 mg/kg twice daily would be within the range measured in adults with 75 or 150 mg twice daily dosing.

The applicant has also investigated the kinetic exposures of the doses proposed for the market in children of $\leq$5 years of age. Study PP16351 was not included in the MAA but was submitted as a response to the CPMP List of Questions. In this study, 12 healthy children aged 1-2 years old were given a single oral dose of 30mg and an additional 12 children aged 3-5 years were given a single dose of 45mg oseltamivir. The mean body weight normalised doses given were approximately 2.9mg/kg.

The findings in this study are consistent with the results of other studies in children (NP15826, WV15758), demonstrating that the hepatic conversion of oseltamivir to Ro 64-0802 is similar to the conversion rate in adults while the body weight normalised clearance of Ro 64-0802 is faster in younger children than in older children and adults. The revised clearance was slightly lower than that derived from the literature and extrapolation of data from older children. The revised values lie well within the steady-state exposures following 75mg bid and 150mg bid oseltamivir doses (mean 2713-5466 ng.h/mL; range 1600 to 7700 ng h/mL) that were previously shown to be both safe and efficacious in adults.
Oseltamivir pharmacokinetics were evaluated in patients with impaired renal function in study WP 15648 that compared 100 mg twice daily dosing for 4 days in four groups of five subjects with creatinine clearance (CrCl) in the range of < 30 ml/min, 31-60 ml/min, 61-90 ml/min and > 90 ml/min. With the prodrug, there was no accumulation in any group over 6 days. Both Cmax and AUC (0 - 12h) increased with decreasing CrCl. A linear relationship between CrCl and renal clearance of the prodrug was demonstrated by results on day 6. Cmax and AUC (0-12) of the active drug increased with decreasing CrCl on days 1 and 6. On day 6, AUC in the group with CrCl < 30 ml/min was > 10-fold compared to subjects with normal renal function, and there were 2.5-fold and 3.5-fold differences between the results of the group > 90 ml/min and the groups 60-90 and 30-60 ml/min, respectively.

Accumulation of active oseltamivir between days 1-6 was relatively greater as CrCl declined, with a three-fold increase in AUC in the < 30-ml/min group, two-fold in the 31-60 ml/min group, but less thantwo-fold for those with CrCl 60-90 ml/min. A linear relationship between CrCl and renal clearance of the active drug was demonstrated by day 6 results. Trough levels at 120 and 132 h suggested that there was some diurnal variation in clearance of these molecules, regardless of renal function. A dose reduction in patients with severe renal dysfunction is recommended: 75 mg once daily dosing in subjects with CrCl 10 - 30 ml/min in treatment of influenza as further detailed in the SPC.

No drug-drug interactions are expected via CYP P450 enzymes. No significant interaction was observed with either paracetamol or amoxycillin. Probenecid reduced renal clearance of the prodrug by one third, but had no significant impact on AUC. A 50% reduction in renal clearance of the active oseltamivir was also seen and AUC increased by 2.5-fold. A near complete inhibition of renal tubular secretion appeared to have occurred. This suggests that oseltamivir is itself a weak inhibitor of anionic renal tubular secretion, and may have a modest ability to compete with other drugs for this elimination pathway. This possibility is mentioned in the SmPC.

Clinical efficacy

Treatment

Four major studies have assessed the safety and efficacy of oseltamivir for the treatment of influenza in adults. The safety and efficacy of oseltamivir for the treatment of influenza in otherwise healthy adults aged between 18 and 65 years was investigated in two randomised, placebo-controlled trials (WV15670 and WV15671) that together enrolled a total of 1355 patients. The safety and efficacy of oseltamivir for the treatment of influenza in elderly patients (65 years of age or older) was investigated in another randomised, placebo-controlled study of 741 enrolled patients (WV15819/WV15876/WV15978). Further, one randomised, placebo-controlled trial (WV15812/WV15872) enrolled 404 subjects to evaluate the efficacy of oseltamivir for the treatment of influenza in adults and adolescents ≥ 13 years of age with chronic cardiac and/or respiratory conditions. Two other randomised placebo-controlled studies (M76001 and JV15823) provide supportive data on the efficacy of oseltamivir in adults and adolescents ≥ 13 years of age and in Japanese subjects aged ≥ 16 years, respectively. Two major randomised, placebo-controlled studies have assessed the efficacy of oseltamivir for the treatment of influenza in children. One of these (WV15758) included 698 otherwise healthy children between 1-12 years of age. Another trial (WV15759/WV15871) enrolled 335 children aged 6-12 years with chronic asthma.

Prophylaxis

Three major randomised placebo-controlled studies have investigated the efficacy of oseltamivir for the prevention of influenza. One seasonal prophylaxis study (WV15673/WV15697) included 1562 unvaccinated healthy individuals aged 18 to 65 years. Another seasonal prophylaxis study (WV15825)

enrolled 572 elderly subjects, most of whom had received influenza vaccine prior to the study influenza season. The efficacy of oseltamivir for the post exposure prevention of influenza within families included 962 contacts of patients with an influenza-like illness (WV15799). Supportive data on the seasonal prevention of influenza by oseltamivir are derived from a study of 385 elderly subjects (WV15708) and a study of 308 Japanese subjects > 16 years of age (JV15824)

Dose-response studies and Main Clinical Studies

Dose response studies

The proposed dose regimens (75 mg once or twice daily in adults and 2 mg/kg in children) were essentially based on non-clinical studies and pharmacokinetic exposure data as described in the previous sections.

Main studies

Treatment

- Case definition

For enrollment of patients in the treatment trials, a standardised definition of influenza illness was used in an attempt to identify patients with influenza on clinical grounds. The clinical case definition of influenza illness in adults consisted of the presence of: (1) fever ≥ 37.8°C (or ≥ 37.5°C in the studies of elderly subjects); (2) at least one respiratory symptom (cough, nasal congestion, or sore throat); and (3) at least one systemic symptom (fatigue, chills/sweats, myalgia, or headache). The case definition of influenza in children consisted of the presence of: (1) fever ≥ 37.8°C; and (2) either cough or coryza. In the prophylaxis studies, the definition of clinical influenza was identical to the clinical case definition in the adult treatment studies, with the exception that the requirement for fever was ≥ 37.2°C (instead of ≥ 37.8°C). Influenza could be confirmed by laboratory tests in approximately 70% of the patients enrolled to the treatment studies by using the above-mentioned clinical criteria.

- Efficacy endpoints

In all adult treatment studies, the primary efficacy parameter was the median time to alleviation of all seven symptoms: feverish feeling, myalgia, headache, sore throat, cough, overall discomfort, and nasal stuffiness or runny nose. The patients scored each of these symptoms twice daily on a diary card using a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe). Alleviation of all symptoms was considered to occur at the start of the 24-hour period in which the scores for all symptoms were either 0 or 1, and remained either 0 or 1 for at least 21.5 hours (the latter allowing for a 10% time window for completing diaries on consecutive days). Although arbitrary, the primary outcome used in the studies is considered to provide a robust measure of the duration of illness that is also relevant from the individual patient's point of view. Further, time to alleviation of various symptoms has been widely used in clinical studies of this nature, including studies of zanamivir for the treatment of influenza. It is a conservative endpoint that may underestimate the treatment effect. Secondary efficacy parameters used in the treatment studies included AUC of total symptom score and duration or AUC of viral shedding. The primary efficacy parameter in the treatment studies of children was time to freedom from illness which was defined as the length of time from the start of the treatment to the point at which the child had (1) no or only minor cough and nasal symptoms, (2) temperature ≤ 37.2°C, and (3) been able to resume normal daily activities.

- Analysis

In the treatment studies, the Intent-to-Treat Infected (ITTI) population was the primary population used for efficacy analyses. The ITTI population included subjects with laboratory-confirmed influenza infection who had received at least one dose of the study medication.

- Efficacy results in otherwise healthy adults

The safety and efficacy of oseltamivir for the treatment of influenza in otherwise healthy adults aged between 18 and 65 years was investigated in two randomised, placebo-controlled trials (WV15670 and WV15671. The studies established the efficacy of oseltamivir in the treatment of influenza infection in this population, as shown in the following table.

Study	Time to become afebrile (h)	Time to alleviation of all symptoms (h)	AUC of total symptom score (h)	AUC of virus titer (log10TCID50.hours/mL)	Duration of virus shedding (h)
WV15670					
Placebo (N=161)	73.5	116.5	943.0	130.8	71.0
Oseltamivir 75 mg b.i.d. (N=158)	43.6	87.4	773.3	78.2	70.2
p-value	p=0.0018	0.0168	0.0073	0.0259	0.0917
% reduction/days of reduction	40.6%/1.2	25%/1.2			
WV15671					
Placebo (N=129)	64.6	103.3	962.6	126.7	70.2
Oseltamivir 75 mg b.i.d. (N=124)	41.5	71.5	597.1	111.4	66.8
p-value	p=0.0011	<0.0001	<0.0001	0.2951	0.0332
% of reduction/days of reduction	35.8%/0.96	30.8%/1.3			

PROPHYLAXIS

- Case definition

In the prophylaxis studies, the definition of clinical influenza was identical to the clinical case definition in the adult treatment studies, with the exception that the requirement for fever was ≥ 37.2°C (instead of ≥ 37.8°C). Laboratory-confirmed influenza infection was based on the detection of influenza virus in nasal or throat swab specimens, or a 4-fold or greater rise in anti-HA. The primary efficacy parameter used in the prevention studies was laboratory-confirmed clinical influenza. Secondary parameters in the prevention trials included laboratory-confirmed asymptomatic influenza, laboratory-confirmed nonsymptomatic influenza (=symptomatic, but not fulfilling the criteria for clinical influenza), clinical influenza-like illness, complications of influenza, and the incidence of viral shedding.

- Prevention studies in healthy adults

The two separate studies (WV15673D and WV15697D) had an identical a double-blind, randomised, placebo-controlled design, and the results had been preplanned to be pooled together. Healthy adults between 18 and 65 years of age meeting the eligibility criteria were identified before the influenza season. When influenza appeared in the community, the participants returned to the clinic. At this baseline visit, the subjects were randomised to receive on a 1:1:1 basis either oseltamivir 75 mg o.d., oseltamivir 75 mg b.i.d., or placebo for 6 weeks.

A total of 1562 subjects were randomised in the studies combined (520 in 75 mg o.d., 521 in 75 mg b.i.d., 521 in placebo). In the ITT population (n=1559), the proportion of subjects with laboratory-confirmed clinical influenza was 1.2% in the 75 mg o.d. group, 1.3% in the 75 mg b.i.d. group, and 4.8% in the placebo group. During the 2-week follow-up period after discontinuation of the prophylactic medication, 7 subjects developed laboratory-confirmed clinical influenza (1 in the o.d. group, 4 in the b.i.d. group, and 2 in the placebo group).

A total of 25 patients withdrew from the study because of adverse events (8 in the o.d. group, 7 in the b.i.d. group, and 10 in the placebo group).

- Post exposure prophylaxis in the families

Study WV15799 was a double-blind, randomised, placebo-controlled study to investigate the safety and efficacy of oseltamivir for the prevention of influenza in subjects aged ≥ 13 years after contact with a family member with an influenza-like illness.

Eligible families (3-8 individuals) were identified before the start of the expected influenza season. After influenza was known to circulate in the community, the families were requested to return to the clinic within 48 hours of any member of the household developing an influenza-like illness. This index case received relief medication but was not treated with any anti-influenza medication. All other family members were randomised to receive either oseltamivir 75 mg o.d. or placebo for 7 days. All members of a single household received the same study medication, and daily contact with the index case was to be maintained. The subjects were followed up for 21 days.

A total of 962 contacts were randomised to the study (498 oseltamivir, 464 placebo). A total of 163 of 377 index cases were confirmed to have influenza virus infection; the contacts of 84 index cases received oseltamivir and those of 79 index cases received placebo. The age of the contacts ranged between 12 and 85 years (mean, 33 years). Thirteen per cent of the contacts in both groups had been vaccinated against influenza during the study season.

In families with a confirmed index case, the proportion of contacts with laboratory-confirmed clinical influenza during the treatment period was 1% in the oseltamivir group, compared with 12% in the placebo group. Oseltamivir also reduced the number of clusters in which at least one contact developed laboratory-confirmed clinical influenza by 89% ($p<0.001$).

Eighteen subjects in the placebo group and none in the oseltamivir group had influenza A infection (treatment effect 100%, p=0.002). On the other hand, influenza B virus infection was confirmed in 6 placebo recipients and in 2 subjects on oseltamivir (treatment effect 67.5%, p=0.227). In the ITT population, laboratory-confirmed clinical influenza type B was documented in 13 contacts in the placebo group, compared with 3 contacts in the oseltamivir group (78.4% efficacy, p=0.015).

Five subjects withdrew prematurely from the study because of adverse events (all in the oseltamivir group).

Clinical studies in special populations

TREATMENT

- Influenza B

The pooled analysis of the efficacy of Tamiflu against influenza B from all clinical studies includes 117 and 178 influenza B-infected individuals in the placebo and Tamiflu groups, respectively. In the Tamiflu groups, the duration of the illness in adults was shortened (from the median of 127.6 hours) by 15.8 hours (not significant) in the influenza B-infected individuals as compared to 23.8 hours in the influenza A-infected individuals. The largest proportion of influenza B-infected individuals was seen in the pediatric study WV15758 in otherwise healthy 1-12 years old children. In the whole population, Tamiflu reduced the time to freedom from illness by approximately one third by using various definitions/scales. In the influenza B-infected population, the only significant improvement in the Tamiflu group was seen in the median duration of all symptoms (difference of 40h, 41% reduction**).** Otherwise, the size of the effect was small in the influenza B-infected population as compared to the whole population (see table).

Parameter	All influenza patients			Influenza B patients		
	Placebo	Tamiflu	Difference1	Placebo	Tamiflu	Difference[1]
Time to freedom from illness (h)1	137.0	101.3	35.83	137.0	125.3	11.72
Time to return to normal health (h)1	111.7	67.1	44.63	111.7	90.1	21.52

1 Calculated for medians

The applicant has made an additional pooled analysis of adult and pediatric studies by using the complex fever, cough and coryza as the outcome measure. By using this approach, the size of the effect was similar in the whole (27%) and in the influenza B-infected population (22%). However, if the outcome was defined according to the primary outcome measure or by the alleviation of all influenza symptoms, the size of the effect was much smaller in the influenza B-infected population.

The efficacy of Tamiflu in prevention of influenza B can be evaluated by looking at the results of post-exposure prophylaxis study WV15799: Influenza B was diagnosed in 13/462 individuals in the placebo group and in 3/493 individuals of the Tamiflu group (p = 0.0101). The number of influenza cases in the other prevention studies was too small for any conclusions.

- The elderly

WV15819/WV15876/WV15978 (three identical substudies pooled) was a multicenter, double-blind, randomised, placebo-controlled study investigating the safety and efficacy of oseltamivir for the treatment of influenza in elderly patients aged 65 years or older. The mean age of the subjects was 73 years. A total of 43% of the patients had received influenza vaccine before the influenza season of the study, and 8% of the subjects had a chronic obstructive pulmonary disease. In the ITTI population, the observed difference (in favour of oseltamivir) in the median time to alleviation of all symptoms of 24.9 h (14%) was not statistically significant (p=0.43). Secondary illnesses requiring antibiotics were reported in 14% of oseltamivir recipients, compared with 19% in the placebo group (p=0.14). Eight patients in the placebo group and 3 in the oseltamivir group were hospitalised during the study (3 patients on placebo because of pneumonia).

- Patients with chronic disease

Study WV15812/15872 was a multicenter, double-blind, randomised, placebo-controlled study investigating the safety and efficacy of oseltamivir for the treatment of influenza in adults and adolescents ≥ 13 years of age who had chronic cardiac and/or respiratory disorders. In the ITTI population (n=251), the median time to alleviation of all symptoms was 151.5 h in the oseltamivir group, compared with 161.0 h in the placebo group. The observed median difference of 9.5 h (6%) was not statistically significant (p=0.77). In an exploratory analysis of the time to alleviation of the acute febrile illness (defined as fever, chills and myalgia), the duration of the febrile illness was significantly shorter in the oseltamivir group (median durations: oseltamivir 40.8 h, placebo 57.9 h; 30% difference; p=0.0005). Secondary illnesses requiring antibiotics were reported in 18% of oseltamivir recipients and in 20% in the placebo group (NS).

- Children

WV15758 was a multicenter, double-blind, randomised, placebo-controlled study investigating the safety and efficacy of oseltamivir for the treatment of influenza in children (aged 1-12 years). The mean age of the children was 5.3 years. Influenza infection was confirmed in 452 (65%) children. Influenza A was the predominant type of the virus, accounting for 303 (67%) of the positive cases, influenza B was diagnosed in 148 (33%) children, and one child had both influenza A and B.

In the ITTI population (n=434), the median time to freedom from illness was 101.3 h in the oseltamivir group, compared with 137.0 h in the placebo group. The observed median difference of 35.8 h (26%) was statistically significant (p<0.0001). In the ITT population, the difference in the median duration of illness was smaller (20.9 h) but still statistically significant (p=0.0002).

Any secondary illnesses (mainly otitis media) requiring antibiotics occurring on or after study day 3 were reported in 17% of oseltamivir recipients and in 28% of children in the placebo group (p=0.0048). During the first 10 days of the study, 12% of oseltamivir recipients without otitis media at baseline developed the complication, compared with 21% of the children on placebo (relative risk, 0.59, CI 0.36-0.95). For the primary outcome (time to freedom from illness) there was a clear benefit of 34% in favor of oseltamivir in children with influenza A (p<0.0001), but in children with influenza B the difference was only 8.5%, which was not statistically significant (p=0.27). However, in the analysis of the duration of all symptoms, the difference was statistically significant for both subtypes of influenza (influenza A, 35% reduction, p=0.0042; influenza B, 41% reduction, p=0.0081).

A total of 40 (6%) children were withdrawn prematurely from the study, 10 of whom because of adverse events (oseltamivir 6, placebo 4). Vomiting was reported in 14.3% of patients receiving oseltamivir, compared with 8.5% in the placebo group. For diarrhea, the corresponding figures were 8.8% and 10.5%, and for nausea, 3.8% and 4.0%, respectively. Most adverse events were considered mild or moderate. Three children on oseltamivir were prematurely withdrawn from the study because of adverse events possibly related to the drug (3 vomiting, 1 urticaria).

WV15759/WV15871 was a multicenter, double-blind, randomised, placebo-controlled study investigating the safety and efficacy of oseltamivir for the treatment of influenza in children aged 6-12 years with chronic asthma. Eligible children with influenza-like illness of less than 48 hours of duration were randomly assigned to receive either oseltamivir 2 mg/kg (maximum 100 mg/dose) b.i.d. or a matching placebo for 5 days. The children were followed-up until Day 28 after the start of the medication. Influenza infection was confirmed in 179 (54%) children in the ITT population of 334 subjects. Influenza A accounted for 104 (58%) of the positive cases and influenza B for 75 (42%) of the cases. In the ITTI population (n=178), the median time to freedom from illness was 123.9 h in the oseltamivir group, compared with 134.3 h in the placebo group. The observed median difference of 10.3 h (8%) was not statistically significant (p=0.54). By the end of treatment, median FEV1 had increased by 10.8 % in the Tamiflu group compared with a 4.7 % increase in the placebo group (p=0.0143). Six children were withdrawn from the study because of adverse events (2 oseltamivir, 4 placebo).

PROPHYLAXIS

- Elderly

Study WV 15825 was a double-blind, randomised, placebo-controlled multicenter study of the prevention of influenza in elderly subjects aged ≥ 65 years living in residential homes. The study was conducted at 31 different sites in the United States and Europe during the 1998-99 influenza seasons. The randomisation was stratified according to influenza vaccination status and presence of chronic obstructive airways disease.

Eligible subjects were identified within 4 months before the expected influenza season. When influenza appeared in the community, the subjects were randomly allocated on a 1:1 basis either oseltamivir 75 mg o.d. or placebo for 6 weeks.

A total of 548 subjects received the prophylactic treatment (276 oseltamivir, 272 placebo). The demographic characteristics of the groups were comparable at baseline. The mean age of the subjects was 81 years (range, 64-96 years). 80% of the subjects had been vaccinated against influenza during the study season, and 14% of them had chronic obstructive lung disease.

In the ITT population (n=548), the proportion of subjects with laboratory-confirmed clinical influenza was 0.4% in the oseltamivir group, compared with 4.4% in the placebo group. Further, the incidence of laboratory-confirmed clinical influenza in the subgroup of subjects who had received influenza vaccine (80% of all subjects) was decreased by 91% in the oseltamivir recipients (p=0.0028). Apart from one subject in the placebo group, all subjects with laboratory-confirmed clinical influenza had received influenza vaccine in the study season. The incidence of influenza complications (otitis media, sinusitis, lower respiratory tract infection, bronchitis, or pneumonia) was significantly lower in the oseltamivir group than in the placebo group (0.4% versus 2.6%, p=0.037).

A total of 29 patients withdrew prematurely from the study because of adverse events (18 oseltamivir, 11 placebo).

Discussion on clinical efficacy

- Influenza B

The concentrations of oseltamivir that are obtained in plasma with the recommended dose of Oseltamivir are sufficient to inhibit the B neuraminidase of the less sensitive strains by 99% (treatment) or 95% (prophylaxis). The concentrations in plasma and extracellular fluids are similar. In general, the IC50 is somewhat higher for B strains as compared to A strains. The number of B strains that have been tested is still small. Oseltamivir was also effective against influenza B virus in pharmacodynamic studies in rodents as well as in healthy volunteers (AUC of viral titers and duration of virus shedding) as described above.

In the additional analysis (performed in response to the CPMP concerns over the magnitude of the effect) that covers 308 adult/adolescent influenza B-infected subjects who were enrolled into the clinical treatment trials, the median time to alleviation of all symptoms was 16.8 h shorter in the oseltamivir group vs placebo group (p=0.4926). A previous analysis of influenza B-infected children in study WV15758 showed a shortening of the disease but the difference was neither statistically nor clinically significant. When children and adults are pooled, the difference becomes statistically significant while the magnitude of the difference remains the same. As described above, the efficacy of Tamiflu in prevention of influenza B can also be evaluated by looking at the results of post-exposure prophylaxis study WV15799. Thus, oseltamivir is active against influenza B but a clinically significant treatment effect remains to be demonstrated. Nevertheless, influenza is a clinical diagnosis in the clinical praxis and oseltamir was effective in populations containing both influenza A- and B-infected individuals. The lower treatment effect of oseltamivir in the treatment of influenza B virus infections as compared to influenza A is mentioned in the SPC (section 5.1).

- Efficacy in the elderly and in the risk groups

It can be argued that the studies in the elderly and high risk patients were not adequately powered due to an unexpectedly high variation in the primary efficacy variables consisting of non-specific symptoms. The selected symptom complex was not optimal in risk groups due to the underlying diseases (e.g. cough in chronic bronchitis and asthma) and that the epidemics were mild (rapid spontaneous improvement). Looking at the more specific secondary endpoints, significant differences in favour of oseltamir with regard to viral shedding, viral AUC, and duration fever and febrile disease were found. The prophylactic use of oseltamivir was associated with very few failures.

In an additional pooled analysis of elderly patients in five double-blind, randomised and placebocontrolled studies, a reduction in the bacterial complications requiring antibiotic treatment was noted; 29 /250 patients and 52 /268 patients in the oseltamivir and placebo group, respectively (p=0.0156, 95% CI 1.6% - 14.0%). Taken together the data are compatible with a clinically meaningful effect of oseltamivir in the elderly. However, the results are not striking which is addressed in the SPC (section 5.1). The efficacy of oseltamivir has not been established in other high risk patients (chronic cardicac and/or respiratory disease (SPC sections 4.4. and 5.1). This point was discussed in an expert meeting.

- Children

The efficacy of oseltamivir treatment in otherwise healthy children has been demonstrated. In influenza-infected children, the time to freedom of illness was shortened by 35.8h and the time to return to normal health by 44.5h. Furthermore, the use of antibiotics for secondary illnesses, mainly otitis media, as significantly reduced. The treatment effect is usually not dramatic for an individual child but oseltamivir may significantly reduce the burden of influenza epidemics to the health care system. The benefit in asthmatic children has not been convincingly demonstrated but the trends are similar to those in otherwise healthy children. It is possible that there is a benefit for asthmatic children who are treated within 24 h. The observed improvement of FEV1 may not be of major clinical significance as such. However, the lack of any adverse effect in asthma is important considering the treatment alternatives. The clinical significance of the oseltamivir treatment of children was discussed in an expert meeting. The applicant committed to perform a new study in asthmatic children in order to further clarify the potential clinical benefits.

- Secondary illnesses

The applicant shows that in children, adults and adolescents, oseltamivir treatment significantly reduced episodes of secondary illnesses that required antibiotic treatment. In a pooled analysis of adults and adolescents, oseltamivir reduced the number of episodes requiring antibiotic therapy from 13% to 9% (p= 0.0012) by ITTI (influenza-infected individuals) and from 12% to 9% (p= 0.0050) in the ITT analysis. The reduction was due to a decrease in the episodes of acute bronchitis. In children (=< 12 years), the incidence of episodes that required antibiotic treatment was higher in placebo-groups both by the ITTI (23 vs 15%, p= 0.0086) and ITT analyses (22 vs 18%, p= 0.0992). The most common secondary illness in children was otitis media.

- Viral resistance

The frequency of resistance to oseltamivir seems to be relatively low as compared to amantadine/rimantadine resistance. Studies have suggested that cross-resistance with zanamavir does not occur in most types of observed mutations**.** The database is still relatively small and further studies are warranted e.g. on the resistance in strains with different combinations of hemagglutinins and neuraminidases as well as on the possible circulation of a drug-resistant strain e.g. in children who are shedding the virus for a longer period than adults.

There are data suggesting that mutations of NA are associated with a reduced infectivity in experimental models. Thus, there appears to be little concern over the simultanous use of Tamiflu for both treatment and prophylaxis, e.g. in a family or in an institution.

There are models to predict the emergence of resistance in a population. Using such models in the current database, the applicant finds that the emergence of viral resistance to oseltamivir is not very likely. Finally, the oseltamivir-resistant mutant strains are still immunogenic.

The current clinical data concern predominantly influenza A H3N2 subtype. It is not known whether the mutations that decrease the sensitivity to oseltamivir will persist from one influenza season to another.

- Prophylaxis of influenza

Oseltamivir treatment is effective in preventing influenza infection both after exposure and at the population level in the seasonal prophylaxis. It was shown that oseltamivir can add to the protection provided by influenza vaccination, which is an important finding. For time being, a limited number of influenza A epidemics have been studied ant the data of influenza B are scarce. The main issue discussed in an expert meeting was the magnitude of the clinical effect on population/community level. The net benefit is highly dependent on the nature of the epidemics (incidence of infections in the general population) and the timing of administration in relation to the influenza epidemic in a given region. These difficulties are highlighted by the results of the major population prophylaxis studies (see the following table)

Table: Prevalence of influenza in the seasonal prophylaxis studies

Clinical study	No. Of subjects	Per cent of infections
WV15673D/WV15697D(adults)		
Oseltamivir 75mg x 1	520	1.2%
Oseltamivir 75mg x 2	521	1.3%
Placebo	521	4.8%
WV15825 (elderly)		
Oseltamivir 75mg x 1	276	0.4%
Placebo	272	4.4%
JV15824 (adults)		
Oseltamivir 75mg x 1	155	1.3%
Placebo	153	8.5%
WV15708 (elderly)		
Oseltamivir 75mg x 1	194	0.0%
Placebo	191	0.5%

The results suggest that, during a mild epidemic, the timing of oseltamivir treatment becomes a crucial issue. The prophylactic use of oseltamivir without reliable epidemiological information is not feasible. This point was discussed in an expert meeting.

Clinical safety

Exposure

The cumulative experience of the use of oseltamivir in more than 7000 patients enrolled in the clinical trials suggests that the treatment is not associated with major safety concerns.

Adverse events

Across virtually all studies, gastrointestinal complaints, especially nausea and vomiting, have been more frequently reported in the oseltamivir group than in the placebo group (see the table beneath). However, the vast majority of these events have been rated as mild or moderate in intensity, and only few subjects were withdrawn prematurely from the studies because of adverse events.

Table: Summary of adverse events in the pooled adult population of the treatment studies (WV15760, WV15671, WV15730, WV15707, WV15812, WV15872, WV15819, WV15876, WV15978)

	Placebo N=1050	Ro 64-0796 75 mg b.i.d. N=1057	Ro 64-0796 150 mg b.i.d. N=447
Vomiting	32 (3.0%)	85 (8.0%)	53 (11.9%)
Nausea	71 (6.8%)	113 (10.7%)	68 (15.2%)
Vertigo	6 (0.6%)	9 (0.9%)	5 (1.1%)
Abdominal pain	21 (2.0%)	23 (2.2%)	9 (2.0%)
Fatigue	7 (0.7%)	8 (0.8%)	7 (1.6%)
Pneumonia	8 (0.8%)	9 (0.9%)	2 (0.4%)
Insomnia	10 (1.0%)	11 (1.0%)	8 (1.8%)
Headache	16 (1.5%)	17 (1.6%)	13 (2.9%)
Dyspepsia	6 (0.6%)	6 (0.6%)	6 (1.3%)
Sore throat	8 (0.8%)	6 (0.6%)	5 (1.1%)
Cough	12 (1.1%)	10 (0.9%)	9 (2.0%)
Herpes simplex	12 (1.1%)	9 (0.9%)	5 (1.1%)
Nasal congestion	10 (1.10)	6 (0.6%)	6 (1.3%)
Dizziness	31 (3.0%)	20 (1.9%)	10 (2.2%)
Bronchitis	52 (5.0%)	39 (3.7%)	0 (0.0%)
Diarrhoea	84 (8.0%)	58 (5.5%)	26 (5.8%)

Table: Summary of adverse events in pooled prophylaxis studies in naturally acquired influenza by event and by dose (WV15763, WV15697, WV15708)

	Placebo N=701	Ro 64-0796 75 mg b.i.d. N=520	Ro 64-0796 75 mg o.d. N=710
Vomiting	5 (0.7%)	14 (2.7%)	22 (3.1%)
Nausea	39 (5.6%)	76 (14.6%)	80 (11.3%)
Insomnia Headache	11 (1.6%)	10 (1.9%)	16 (2.3%)
Abdominal pain Sore	228 (32.5%)	242 (46.5%)	263 (37.0%)
throat	17 (2.4%)	21 (4.0%)	23 (3.2%)
Fatigue	67 (9.6%)	57 (11.0%)	74 (10.4%)
Herpes simplex	84 (12.0%)	60 (11.5%)	92 (13.0%)
Cough	6 (0.9%)	4 (0.8%)	10 (1.4%)
Nasal congestion	64 (9.1%)	27 (5.2%)	68 (9.6%)
Diarrhoea Dizziness	92 (13.1%)	53 (10.2%)	85 (12.0%)
	27 (3.9%)	23 (4.4%)	38 (5.4%)
	12 (1.7%)	7 (1.3%)	11 (1.5%)

Serious adverse events

There were no important differences in the reporting of serious adverse events in any of the active groups compared with placebo.

The incidence of serious adverse events during the on-treatment period was low and similar in the treatment groups: 13/1050 subjects on placebo and 14/1057 on oseltamivir 75 mg b.i.d. Very few SAEs were considered to be treatment-related. No deaths have been associated with oseltamivir treatment in any of the clinical studies.

The serious adverse event profile in elderly subjects was similar in subjects receiving oseltamivir or placebo. In the pediatric treatment studies, 13 serious adverse events were reported during the on-treatment period (4 on placebo, 9 on oseltamivir). None of these events were considered to be related to study treatment, by the investigator or the sponsor.

A total of 47 subjects had at least one serious adverse event during the on-treatment period, in prophylaxis studies: 23 on placebo, 21 on oseltamivir 75 mg o.d and 3 on oseltamivir 75 mg b.i.d. The serious adverse events reported for oseltamivir were considered by the investigator to be unrelated to study medication, except for two cases: angina pectoris and exacerbation of COPD, which were considered to be remotely related.

The overall rate of premature withdrawal from clinical studies, in treatment of influenza in adults, was low and lower in subjects receiving oseltamivir than placebo.
Further, the incidence of laboratory abnormalities has been similar in the oseltamivir and placebo groups both in the treatment and prophylaxis studies.

Postmarketing safety data are available from some countries where oseltamivir is used for the treatment of influenza. Rare cases of hypersensitivity, mainly rashes, and liver disorders, such liver enzyme elevations, have been reported. However, the experience of the large-scale prophylaxis with a longer exposure to oseltamivir is very limited. Therefore, continued follow-up of adverse events is necessary to discover any infrequent but serious adverse effects of oseltamivir. Subjects with serious underlying diseases (e.g. renal, liver, cardiac, malignancies) have been excluded from most major clinical trials. However, it is often just these subjects who are considered to be at an increased risk of developing complications of influenza and, therefore, may be offered oseltamivir treatment or prophylaxis

Discussion on clinical safety

Oseltamivir is well tolerated by most individuals both in short and in long-term administration. Nausea and vomiting are not uncommon but will rarely lead to the discontinuation of the treatment. The applicant has performed several preclinical studies of potential cardiotoxic effects of oseltamivir. These studies as well as the clinical trial data base, analysis of the observed ECG abnormalities, and the current post-marketing experience do not raise cardiac safety concerns. Likewise, no obvious pattern of central nervous system effects has emerged.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

In general, the quality of the product has been well presented. The dossier indicates that the active substance and the finished products are manufactured and controlled in a relevant way, in compliance with current EU and ICH guidelines. Satisfactory information has been provided to demonstrate that these manufacture and control processes routinely and consistently generate a product of uniform quality when used in accordance with the conditions defined in the Summary of Product Characteristics. However, at the time of the opinion, the CPMP identified a few minor unresolved quality issues. These issues were considered to have no impact on the benefit/risk balance of the product when used according to the SPC and it was agreed that they will be resolved as follow-up measures post-authorisation.

Efficacy

- Treatment

Studies in otherwise healthy adults when predominantly influenza A was circulating in the community have demonstrated that oseltamivir reduces the duration of naturally acquired influenza infection by approximately 30 hours (representing a 25-30% reduction in the time to alleviation of all symptoms) when the treatment is started within 36 hours of the onset of symptoms.

In elderly and chronically ill patients, oseltamivir treatment did not provide a statistically significant benefit over placebo, although the median duration of illness was shortened by approximately 10-25 hours. When the duration of febrile illness was studied, a significant difference favouring the oseltamivir group was demonstrated. In addition, a significant reduction of specified lower respiratory infections (mainly brochitis) in the elderly patients was also noted in an exploratory analysis. However, the expert group concluded that the warning section of the SPC should include a statement on the lack of demonstrated efficacy in high-risk patients with chronic cadicac and/or respiratory disease.

The secondary complications of influenza were infrequent in adults in this clinical program, which may partly explain why no significant differences could be demonstrated in the individual studies. The pooled analysis of the studies showed that oseltamivir was able to reduce the incidence of secondary illnesses requiring antibiotics, mainly bronchitis, by approximately 30%. Moreover, oseltamivir treatment resulted in approximately 40% reduction in the incidence of acute otitis media, the most common complication of influenza in children. The impact of these results on the burden of influenza for health care system was discussed in the expert meeting.

The efficacy in the treatment of influenza in children was largely comparable to the results obtained in adults (reduction of illness by approximately 1.5 days). The expert group concluded that influenza is a significant disease in particularly young children and that the efficacy of oseltamivir had been demonstrated. In children with asthma, the effect of oseltamivir needed further substantiation and the Applicant committed to perform an additional clinical trial in children with bronchial asthma.

The efficacy of oseltamivir against current influenza A strains cannot be disputed. However, the efficacy of oseltamivir against influenza B infections has been difficult to demonstrate. Across all treatment studies in adults, influenza B viruses accounted for only 11% of all cases of confirmed influenza. After combining all adult studies, the median duration of illness in oseltamivir recipients was shortened by 16 hours (12% reduction), which did not reach statistical significance. In one study in children, 33% of the influenza cases were caused by the B virus. In this study, the median time to freedom from illness was not significantly different between the groups, although the median time to alleviation of all symptoms was reduced by 41%. Thus, the efficacy of oseltamivir against influenza B looks very modest at best even if one accepts the impact of certain methodological difficulties. It should be remembered that influenza A and B infections can not be distinguished on clinical grounds. Thus, the physicians will rarely have the knowledge of the type of the virus by the time treatment decision.

The specificity of the clinical diagnosis in clinical trials was 60-70%. This is obviously the best case scenario that can be obtained only in a research program. In other published studies, the corresponding rate has ranged between 30% and 80%. In routine praxis, where the support of an organisation (e.g. in the timing of the epidemics, systematic evaluation of symptoms) is not available, the specificity of the clinical criteria may be significantly lower, especially during the early and late phases of influenza epidemics.

The effect of oseltamivir on influensa A and B has been described in section 5.1. of the SPC.

- Prophylaxis

Oseltamir treatment is effective in preventing influenza infection both after exposure and at the population level in the seasonal prophylaxis. It was shown that oseltamivir can add to the protection provided by influenza vaccination, which is an important finding.

The number needed to treat was high in some studies. This may be due to the nature of the influenza epidemics during oseltamivir development and/or to the difficulty of performing large clinical trials in a flexible way. The clinical effect on population/community level was discussed in the expert meeting. The net benefit is highly dependent on the nature of the epidemics (incidence of infections in the general population) and the timing of administration in relation to the influenza epidemic in a given region. The need for accurate epidemiological data in the clinical decision making was emphasized in the expert meeting.

The duration and timing of the influenza epidemics vary. Oseltamivir administration should overlap the peak of the epidemic that may not occur at the same time in all communities. Furthermore, epidemics caused by other viruses may cause problems in the clinical diagnosis of influenza. For these reasons, there must be a surveillance system in place to guiding the prophylaxis with a neuraminidase inhibitor.

- Emergence of resistance

Oseltamir-resistant influenza virus strains are rare. Resistant strains are relatively more common in children. The longer virus shedding in children as compared to adults probably explains this finding. The development of oseltamivir resistance is possible only in the presence of the virus. Thus, the prophylactic use of oseltamivir as such does not carry a higher risk of resistance. The applicant is co-sponsoring an independent program for the monitoring of viral resistance to neuraminidase inhibitors by using samples provided by WHO and CDC. The applicant will also continue to monitor the sensitivy of influenza virus strains to oseltamivir in future clinical trials. The monitoring system is based on the in vitro NA inhibition test. Positive cases are further analysed by genotyping and by the ferret model. This system may not be able to detect all strains with decreased sensitivity, such as those that are caused by mutations in the haemagglutinin. However, such mutants may not have a major clinical significance due to their apparently lower infectivity.

Safety

The cumulative experience of the use of oseltamivir in more than 7000 patients enrolled in the clinical trials suggests that the treatment is not associated with major safety concerns. Across virtually all studies, gastrointestinal complaints, especially nausea and vomiting, have been more frequently reported in the oseltamivir group than in the placebo group. However, the vast majority of these events have been rated as mild or moderate in intensity, and only a few subjects were withdrawn prematurely from the studies because of adverse events. The incidence of serious adverse events has been largely similar in the oseltamivir and placebo groups. No deaths have been associated with oseltamivir treatment in any of the clinical studies. Further, the incidence of laboratory abnormalities has been similar in the oseltamivir and placebo groups both in the treatment and prophylaxis studies.

Postmarketing safety data are available from some countries where oseltamivir is used for the treatment of influenza. However, the experience of the large-scale prophylaxis with a longer exposure to oseltamivir is very limited. Therefore, continued follow-up of adverse events is necessary to discover any infrequent but serious adverse effects of oseltamivir.

Benefit/risk assessment

As discussed above, oseltamivir treatment in children and other risk groups of influenza as well as its role in prophylaxis was discussed during a CPMP expert meeting on the 18 February 2002.

Following the CPMP review of the Applicant's data and the recommendation from the expert group, the CPMP concluded the efficacy and safety of oseltamivir had been established. However, the efficacy was not demonstrated in certain risk groups. The CPMP further agreed that there was a need for additional methods for treatment and prevention of influenza infections. On the basis of the current knowledge, neuraminidase inhibitors will not play a major role during typical influenza seasons. However, they might have a significant role in case of a pandemic or a drift in circulating influenza strains after the selection of the vaccine strains.

The Applicant also agreed to a perform an additional trial in asthmatic children, to submit new clinical data on the effect in influenza B as they become available, and to regularly report on the emergence of resistance to oseltamivir.

The applicant recognises the importance of vaccination and local guidelines for the treatment and prophylaxis of influenza as conveyed in the proposed SPC. The applicant also commits to highlight the importance of vaccination in the promotional material and to endorse an appropriate use of oseltamivir that is based on influenza-surveillance data. Introduction of neuraminidase inhibitors in the U.S.A. has not decreased the rate of vaccination. The data demonstrate that oseltamivir treatment has an effect also in a vaccinated population. Thus, vaccination and chemoprophylaxis are complementary measures. Oseltamivir may have an important role in situations, where the vaccination is insufficient to prevent the severe consequences of an influenza epidemic, such as the mis-match between the vaccine and circulating influenza strains as well as the pandemic situation.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by concensus the benefit/risk profile of Tamiflu in the treatment and prophylaxis of influenza was favourable and therefore recommended the granting of the marketing authorisation in the following indication:

> "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 of SPC).

Prevention of influenza

- 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 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 adolescents 13 years 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".