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Product name: **TAMIFLU**
Procedure No: **EMEA/H/C/402/II/20**

SCIENTIFIC DISCUSSION

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel.(44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.eudra.org http://www.emea.eu.int

1. Introduction

Influenza is a respiratory viral infection caused by influenza type A, B, and C viruses. Influenza A and B viruses cause distinct annual epidemics that are associated with substantial morbidity and mortality. Excess mortality due to influenza is by far highest in the elderly population, and therefore influenza is often regarded as an illness of the elderly population. Ample evidence indicates, however, that the burden of influenza is substantial also in children. The attack rates of influenza during annual epidemics are consistently highest in children, in whom the rates of symptomatic influenza infection may exceed 30%, and rates of up to 50% have been observed in day-care children during regular influenza seasons. In parallel with the age-related incidence of influenza, the frequency of outpatient visits for acute respiratory disease during influenza outbreaks is also highest in children. Influenza often gives rise to bacterial complications such as acute otitis media, pneumonia, or sinusitis, and it is a frequent cause of acute exacerbation of asthma. Further, young children are hospitalised for influenza-attributable illnesses at rates similar to those for adults at high risk for influenza.

In addition to the high attack rates of influenza in children, the duration of viral shedding is more prolonged in children than in adults, and the titres of recovered viruses are also generally higher in children. All these features contribute to the current concept that children are the main disseminators of influenza both in the household and the entire community during local outbreaks.

There is general agreement that vaccination is the primary method of prevention of influenza. However, influenza vaccine is infrequently used even in children with high-risk conditions, and its use for healthy children in European countries is negligible.

Oseltamivir is an orally available selective inhibitor of influenza A and B neuraminidase. This medicinal product has been available in the EU since 2001 for treatment of influenza in subjects ≥1 year of age and for prevention of influenza in subjects ≥13 years of age. Thus oseltamivir has not been licensed for prevention of influenza in children younger than 13 years of age. However, on the basis of the substantial burden of influenza in children and the central role of children in the transmission of influenza in the community, it is obvious that if oseltamivir were shown to be safe and effective for prevention of influenza also in children, it would have the potential to greatly reduce the medical and socioeconomic burden of influenza during local influenza outbreaks.

This variation II/20 was submitted by the MAH in order to extend the therapeutic indication for the prevention of influenza to children between 1 and 12 years of age. The main efficacy data were from the clinical study **WV16193** "*A randomized, open-label, parallel group study of oseltamivir used for the management of influenza in households*".

2. Toxico-pharmacological aspects

- **Non-clinical pharmacology**

There have been no new non-clinical pharmacology/virology studies conducted by the MAH since the initial file was submitted for the approval of the use of Tamiflu in the treatment of influenza virus infection in children in February 2001.
However, with this type II variation, the MAH submitted published literature on non-clinical pharmacological data (with a cut-off date of December 31st 2004).

According to the article *Matrosovich M, et al. Neuraminidase is important for the initiation of influenza infection in human airway epithelium. J Virol. 2004;78(22):12665-12667*, new data have suggested that the inhibition of viral neuraminidase by oseltamivir carboxylate also inhibits the primary infection (receptor binding) stage of influenza virus infection of cells. This article describes the inhibition of infection of human tracheao-bronchial and nasal epithelial cells by various influenza strains in the presence of active oseltamivir. It is suggested that this mechanism contributes to the efficacy of oseltamivir, especially in the prophylaxis. However, the significance of these findings is difficult to estimate because of relatively high drug concentration used to demonstrate this *in vitro*

effect and because of the demonstration of anti-influenza immune responses in clinically symptomatic oseltamivir-treated individuals.

According to *Crain SM, et al. Neuraminidase inhibitor, oseltamivir blocks GM1 ganglioside-regulated excitatory opioid receptor-mediated hyperalgesia, enhances opioid analgesia and attenuates tolerance in mice. Brain Res. 2004;995:260-266*, inhibition of neuraminidase, the enzyme responsible for conversion of abundant polysialogangliosides to GM1 ganglioside, seemed to have dramatic effects on opioid analgesia and hyperalgesia in mice. Co-administration of oseltamivir with morphine markedly enhanced morphine-induced analgesia within the first hour of co-treatment. These results are intriguing from several points of view. The MAH stated that this is the only report of such findings, and it would be important to see replication of these data by other groups, and, in addition, in another species. The paper assessed only one behavioural parameter (tail flick latency) and there are other animal models that can be used for studying this interaction. In October 2005, the CHMP adopted a Request for Supplementary Information (RSI) addressed to the MAH and requested clarifications on this point.

In the answer to this RSI, the MAH provided preliminary results of a new study [*Prinssen EPM, Mortas P, Moreau J-L. Effect of Oseltamivir phosphate, alone and in combination with morphine, in the tail-flick test in rats.* Roche Study Report 1020287. In preparation].
This study was carried out to investigate whether the above-mentioned interactions could be replicated. Adult male Wistar rats (Harlan, the Netherlands) of around 200 grams were used in this study. The tail-flick latency was measured at 30, 60, 120, 180, 240, 300, and 360 min after injection. In the first experiment, an appropriate dose of morphine was determined which had moderate effects on its own, like the dose used in the Crain paper. From the dose-response data, the equivalent dose with respect to analgesic effects was 1 mg/kg, s.c., identical to that used in the Crain paper (Fig. 1a in Crain and Shen 2004). In the second experiment, the interaction between acute co-treatment with morphine (1 mg/kg, s.c.) and oseltamivir phosphate (1 and 10 mg/kg s.c.) was examined. Oseltamivir (1 or 10 mg/kg) did not increase the effects of morphine at any time-point. According to a new study, the finding of an abnormal tail-flick test in mice (Crain and Shen, 2004) upon co-administration of oseltamivir prodrug and morphine could not be repeated in rats. The negative finding in rats could not be explained by a decreased exposure to either oseltamivir prodrug or active oseltamivir. The effects of oseltamivir on the CNS in mice and rats have been investigated as part of the overall non-clinical program. Apart from the effect on very young animals (already reflected in section 5.3 of the SPC), no clear effect of oseltamivir alone has been demonstrated. Thus, the current hypothesis is that the abnormal tail-flick test upon co-administration with morphine is a mouse-specific phenomenon.

Further to the assessment of these data, the CHMP decided that the MAH should commit to provide the final study report of the rat oseltamivir-morphine interaction study as soon as available.

- **Resistance to oseltamivir**

Six publications cover the sensitivity of neuraminidases from clinical influenza virus isolates collected world-wide from untreated subjects over several influenza seasons. The publications provide data on 2972 isolates of which 713 are influenza B. All isolates were sensitive, except one in a series of 126 influenza B isolates as mentioned in the article *Hurt AC, et al. Identification of a human influenza type B strain with reduced sensitivity to neuraminidase inhibitor drugs. Virus Res. 2004;103:205-211*. The mechanism of the relative resistance remained unknown in spite of appropriate genetic testing. The authors emphasise that the resistance was not due to selection in an oseltamivir-treated individual and that the isolate was sensitive to zanamivir.

It is inevitable that resistance will emerge at some point of time if oseltamivir is used in a large scale. This case demonstrates that continuous monitoring of the sensitivity of virus isolates to oseltamivir is necessary. Such a monitoring is provided by the MAH as a commitment through PSURs.

Several other research groups have continued to try to assess the antiviral potency of oseltamivir carboxylate and other neuraminidase inhibitors against whole virus in MDCK cell-based assays. In the article *Matrosovich M, et al. Overexpression of the alpha-2,6-sialyltransferase in MDCK cells*

increases influenza virus sensitivity to neuraminidase inhibitors. J Virol. 2003;77(15):8418-8425, while the antiviral activity of oseltamivir carboxylate is generally confirmed by cell culture experiments involving MDCK, the assay system may give some anomalous results. The newly developed SIAT1 cell line overexpresses the enzyme alfa-2,6-sialyltransferase. This modified MDCK-line may be better for the cell culture assessment of the antiviral activity of neuraminidase inhibitors as a class. Oseltamivir carboxylate shows antiviral activity in the low nanomolar range in these cells.

The antiviral activity of oseltamivir against influenza A and B has been investigated in animal models (chicken and mouse) against certain significant influenza strains, such as 1918 pandemic H1N1 virus, avian influenza virus H5N2, and H7N7 virus similar to that causing the outbreak in the Netherlands as expressed in the article: *Tumpey T, et al. Existing antivirals are effective against influenza viruses with genes from the 1918 pandemic virus. PNAS 2002;99(21);13849-13854*. Oseltamivir carboxylate is shown here to be active against these strains *in vitro* and *in vivo*. These data have been recently discussed by the CHMP in the context of the report on the use of antivirals during an influenza pandemic. The summary report has been published on the EMEA website in October 2005 (http://www.emea.eu.int/pdfs/human/pandemicinfluenza/33997205.pdf).

- **Toxicological studies**

Finally, the MAH reviewed the toxicological studies that demonstrated an increase of mortality in juvenile rats (7 days old, but not 14 days old) at the dose level of 750-1000mg/kg. The exposure of the brain of 7-day old rats to oseltamivir pro-drug was extremely high when compared to that of adult rats. The entry of the pro-drug to brain is probably related to the poor development of the blood-brain barrier.

This issue has been discussed previously by the CHMP. Further to the assessment of these pre-clinical data in the Type II variation II/08 adopted in September 2003, section 5.3 of the SPC was updated by adding results of a toxicological and toxicokinetic study in 7-42 days old unweaned rat.
These findings, leading to the cancellation of a planned pharmacokinetic study in infants (age < 12 months) in January 2005, are already reflected in the sections 4.2 and 4.4 of the SPC as follow "*The safety and efficacy of Tamiflu in children less than one year of age have not been established* ".

- **Changes to the Product Information further to the assessment of non-clinical data**

- **Section 5.1 of the SPC**

Further to the assessment of the findings in *Matrosovich M, et al. Neuraminidase is important for the initiation of influenza infection in human airway epithelium. J Virol. 2004;78(22):12665-12667* (see 3.2 Toxico-pharmacological aspects, Non-clinical pharmacology above), the proposed changes to 5.1 are endorsed:

"Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and ~~essential~~ for the release of recently formed virus particles from infected cells and the further spread of infectious virus in the body.
Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily."

3. Clinical aspects

- **Introduction**

Previous studies have demonstrated the efficacy of oseltamivir in both post-contact and seasonal prophylaxis of influenza in adults and adolescents ≥13 years of age. However, the earlier prophylaxis study within families (WV15799), which was pivotal for the approval of the post-contact prophylaxis indication, excluded children younger than 13 years of age because the efficacy of oseltamivir in the treatment of influenza in that age group had not been demonstrated by that time. Furthermore, the index cases were not treated with oseltamivir in the previous study.

In the current submission, the applicant is proposing to extend the therapeutic indication for the prevention of influenza to children 1-12 years of age. This proposal is based on one clinical study that was designed to determine the preventive efficacy of oseltamivir within households in which the index cases were also treated with oseltamivir. This study was not a paediatric study but included both adults and children aged ≥1 year. However, because a substantial proportion of the study participants were children 1-12 years of age, the study allowed for a subanalysis of the efficacy and safety of oseltamivir in children.

- **Clinical efficacy**

- **Description of the main clinical studies submitted to support this type II variation**

Study WV15799 that was included in the original submission demonstrated the efficacy of oseltamivir in the post-exposure prophylaxis in the family setting. In that study, index cases were left untreated while contacts received once-daily oseltamivir prophylaxis. A high degree of protection from infection was observed. However, the issue remained unclear as whether it was the optimal strategy for controlling the spread of influenza within households.

Therefore, study **WV16193,** a randomised, open-label, parallel group study of oseltamivir used for the management of influenza in households, was conducted to re-examine the impact of oseltamivir in a family setting in which index cases received treatment with oseltamivir and family members received prophylaxis with oseltamivir. The objectives of the study WV16193 were to investigate:

- The spread and the overall burden of influenza in households in which all index and secondary cases of influenza like illness are treated with oseltamivir
- Investigate the spread and the overall burden of influenza in households in which the index case of influenza like illness receives treatment with oseltamivir and close contacts receive prophylaxis with oseltamivir simultaneously.

- **Design of study WV16193**

This was a prospective, open-label, multicentre trial to evaluate the impact of oseltamivir on the spread of influenza within households. The subjects were recruited from 48 centres in the United States, Canada, Estonia, Finland, Germany, United Kingdom, and Sweden.

Households consisting of 3-8 eligible members were offered entry into the study. **Children aged <1 year were excluded from participation.** The participating household members were classified as either **index cases** or **contacts**. An index case was defined as the family member in whom influenza-like illness was diagnosed. The remaining family members were classified as contacts.

In the RSI adopted in October 2005, the MAH was requested to clarify whether the studied households with contacts below 12 years were of the size to the overall population. According to the demographic data provided by the MAH in this answer to the RSI, the size of the households with contacts below 12 years of age were very similar to those of the entire study population. Both in the overall population and in households with contacts younger than 12 years, there was a tendency towards a greater number of contacts in households randomised to the PEP (post-exposure prophylaxis arm. Therefore, even in the case that the size of the family had an impact on the risk of infection, this risk cannot be

considered to be lower in the PEP arm, which implies that the results do not overestimate the efficacy of the intervention.

The **inclusion criteria for index cases** were: age ≥1 year; fever ≥37.8°C plus cough and/or coryza; and less than 48 hours´ duration of symptoms before the first dose of medication. All index cases were treated with oseltamivir once daily for 5 days. In the RSI adopted in October 2005, the MAH was requested to provide information on the interval between the first index case and the last index case, as the inclusion period in a household study is important for the number of index cases. According to the information provided in the answer to this RSI, only the first cases in a household were ever considered index cases, and any other members of the family who contracted influenza at any time after the household's entry into the study could not become new index cases but were consistently considered as contacts in the analyses. Therefore, the length of the inclusion period cannot be expected to bias the results.

The **dosing** of oseltamivir was based on the subject's age (single dose: 1-2 years, 30 mg: 3-5 years, 45 mg; 6-12 years, 60 mg; ≥13 years, 75 mg). However, the current recommended dose of Tamiflu oral suspension for the treatment of influenza is based on the actual weight (≤15 kg 30 mg twice daily, >15 kg to 23 kg 45 mg twice daily, >23 kg to 40 kg 60 mg twice daily, >40 kg 75 mg twice daily).

The table below summarises the difference between the doses in the study WV16193 as compared to the currently approved dosing:

	Less	Same	More
Contacts			
1-2 years	1	5	0
3-5 years	3	17	4
6-12 years	26	67	8
Total	30	89	12

In the study, the age-based algorithm was based on ideal body weights. Examination of PK data revealed that the algorithm gives similar exposure in the younger children (1-3 years of age) but a lower exposure in the age group of >6 years, the exposure was higher for the mg/kg dosing. With regard to the above table, the efficacy is not in question as the used dosages in the study were mainly the same as or less than the approved dosages. According to the present knowledge, the observed differences in dosages are not significant from a safety point of view.

Whole households were offered entry into the study. All **index cases** (who presented with symptoms typical of influenza **were to be treated** with oseltamivir. All other household **contacts** were randomised to receive either:

- active treatment for 5 days at the time at which they become unwell with an influenza like illness (**group T**) or
- prophylaxis for 10 days following the development of a febrile influenza-like illness in the first index case (**group P**).

Because influenza-vaccinated subjects were not excluded from the study, the study design resembles the real-life situation in which part of the population has received the vaccine. As should be expected in a randomised study, the proportions of vaccinated persons were similar (7% and 8%) among the contacts in the ET (expectant treatment) and PEP (post-exposure prophylaxis) arms. The lower percentage (4.4%) of vaccinated subjects among the index cases is explained by the fact that almost half of all index cases were children who are not usually vaccinated against influenza. Because the percentages of vaccinated persons were similar in the two arms, the vaccination status cannot be regarded as a source of bias for the results.

All subjects recorded their temperature and symptoms twice-daily using diary cards.

- **Endpoints and definitions of analysis populations**

The **primary endpoint** was the percentage of households with at least one secondary case of febrile laboratory-confirmed influenza illness (fever ≥37.8°C plus cough and/or coryza) during the 10-day period following initiation of treatment of the index case. A laboratory-confirmed case of influenza was defined as a febrile illness (temperature ≥37.8°C plus cough and/or coryza) together with detection of viral shedding within 2 days before or after the time that the fever was reported, and/or a 4-fold or greater rise in influenza-specific antibody levels between the baseline and day 30 sample.

A **secondary endpoint** was the percentage of individual contacts experiencing clinical influenza as described above.

In this study, all members of the family received the same treatment (either post-exposure prophylaxis or expectant treatment). This looks like a common situation in real life: prophylaxis will be started either to all or none of the family members after an index case in the family. Because the primary route of influenza transmission is via small-particle aerosols that linger in the air for an extended time, it is most likely that after one member of a household develops symptomatic influenza, all family members are exposed to the virus more or less at the same time, instead of a chain reaction-type of transmission from one family member to another after a certain incubation period. However, regardless of the pattern of transmission and theoretical differences in the risk of infection, the selected study design demonstrates the efficacy of the intervention in a real-life situation. The decision to initiate oseltamivir treatment in the household members was the same in both study arms. Thus, there is no bias here.

The following analysis populations were defined for the efficacy analyses:

a) The **Intent-To-Treat Index Infected** (ITTII) population was the primary efficacy population. It consisted of all contacts who were randomised into the study, provided efficacy diary card data after baseline, and whose index case had a laboratory-confirmed influenza infection.

b) The **Intent-To-Treat** (ITT) population consisted of all contacts who were randomised into the study and provided efficacy diary card data after baseline.

c) The **ITTIINAB** population consisted of all contacts in the ITTII population who had a negative virology result at the baseline.

ITT, ITTII and ITTIINAB analyses were based on the treatment regimen to which the contact was randomised.

In the RSI adopted in October 2005, the MAH was requested to provide clarifications on the new cases reported up to day 22 and whether these were caused by the initial index case during the follow up period. Further to the assessment of the data provided in the answer, only 4 and 1 cases of influenza in the ET and PEP arms of the study, respectively, developed after Day 10 in the contacts. The vast majority of cases in the contacts occurred within the first three days after identification of the index case in the household. Further, because all influenza cases in the contacts occurring after Day 10 were excluded from the analyses, the duration of the follow-up does not form a source of bias for the results.

- **Discussion on the overall efficacy**

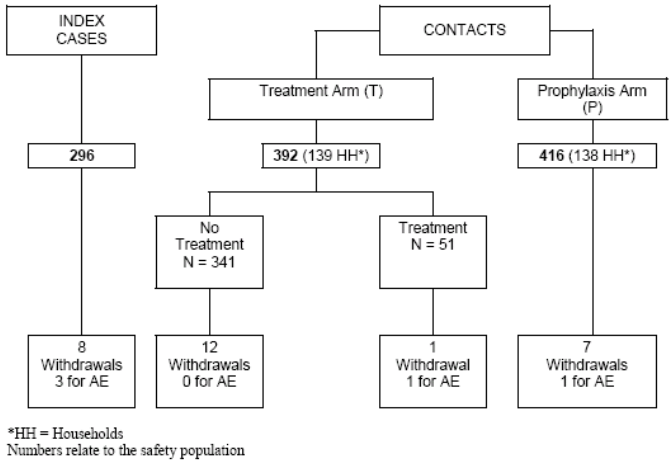
A total of 277 households were randomised into the study. There were no significant differences in the baseline characteristics between the prophylaxis and treatment groups. More than 60% of all index cases had a laboratory-confirmed influenza infection. The age profile of the study participants are shown in the table below:

Summary of Age for Contact Cases by Treatment Group (ITT Population)

Age	Group T (Treatment)		Group P (Prophylaxis)	
<= 5 yrs	18	(5%)	25	(6%)
6 to 12 yrs	94	(24%)	79	(19%)
13 to 17 yrs	53	(13%)	64	(16%)
18 to 64 yrs	221	(56%)	228	(56%)
>=65 yrs	9	(2%)	10	(2%)
All	395	(100%)	406	(100%)

The patient disposition is seen in the figure below:

Figure 1 Disposition of All Subjects



*HH = Households
Numbers relate to the safety population

The type of infection in the index cases is seen in the Table below:

Summary of Infection (All Index Cases)

INFECTION (a)	Group T (Treatment) N=148	Group P (Prophylaxis) N=150
Yes	94 (64%)	90 (60%)
Flu type A	65 (69%)	56 (62%)
Flu type B	29 (31%)	34 (38%)
No	54 (36%)	60 (40%)
NEG (by culture and serology)	51 (94%)	58 (97%)
No culture and no serology	1 (2%)	1 (2%)
NEG by culture and no serology	2 (4%)	1 (2%)
All	148 (100%)	150 (100%)

(a) Positive nasal/throat swab or 4-fold or greater rise in antibodies.
Illness-type determined from nasal/throat swab and/or antibody data

The proportion of households with at least one contact with a laboratory-confirmed influenza infection (the primary endpoint) was 11% in the prophylaxis group and 26% in the expectant treatment group, indicating a protective efficacy of 58.5% for oseltamivir in the ITTII population (95% CI 15.6-79.6%). Excluding the contacts who already had an asymptomatic influenza infection at the baseline (ITTIINAB population), the corresponding proportions of households in the groups were 5% and 22%, respectively, indicating a protective efficacy of 78.8% for oseltamivir in this population (95% CI 40.6-92.4%).

The table below features the outcome as measured by the primary efficacy variable:
Number of Households with Contact Cases of Febrile Laboratory-Confirmed Influenza Illness (ITTII Population)

	GroupT (Treatment) N=89	Group P (Prophylaxis) N=84
During 10 day period* All Households	89 (100%)	84 (100%)
No Infected Contact Cases	66 (74%)	75 (89%)
>=1 Infected Contact Case	23 (26%)	9 (11%)
Protective Efficacy:	58.5%	
95% C.I.:	[15.6, 79.6]%	
P value:	0.0114	

The ITT population analysis that involved all households, regardless of whether the index case had laboratory-confirmed influenza infection, further confirms the prophylactic efficacy of oseltamivir in a household setting (62.7% protection, p =0.0042).

With respect to the **secondary endpoint** (the percentage of individual contacts experiencing clinical influenza) the protective efficacy of oseltamivir was 68.0% in the ITTII population (95% CI 34.9-84.2%) and 84.5% in the ITTIINAB population (95% CI 59.1-94.1%).

- **Discussion on the efficacy in children aged 1-12 years**

A substantial proportion of the participants in the clinical study WV16193 were children aged 1-12 years, which allowed a sub analysis of the efficacy of oseltamivir in this age group. Among the index cases, 134 of 296 (45.3%) subjects were 1-12 years of age, and 70% of them were confirmed as being infected with influenza. Among the family contacts, 106 of 416 (25.5%) subjects allocated to the prophylaxis group were children aged 1-12 years, and 113 of 392 (28.8%) subjects allocated to the expectant treatment group were children of this age. Among the paediatric contacts, the mean age of the children was 8 years, and there was an even distribution of boys and girls.

A total of 215 children 1-12 years of age were included in the ITT population. Among children who received oseltamivir prophylaxis, 7 of 104 (6.7%) were infected with influenza. In children allocated to expectant treatment, 21 of 111 (18.9%) developed influenza, which corresponds to a protective efficacy of 64.4% in the ITT population (95% CI 15.8-85.0%).

In the ITTII population, 6 of 55 (10.9%) children receiving oseltamivir prophylaxis and 18 of 74 (24.3%) children in the expectant treatment group had a laboratory-confirmed influenza, indicating a protective efficacy of 55.2% in the ITTII population (95% CI -13.0-82.2%).

Excluding paediatric contacts who were already shedding influenza viruses at the baseline (ITTIINAB population), 2 of 47 (4.3%) children receiving oseltamivir prophylaxis and 15 of 70 (21.4%) children in the expectant treatment group had a laboratory-confirmed influenza. These figures correspond to a protective efficacy of 80.1% in the ITTIINAB population (95% CI 22.0-94.9%).

A total of 88 children aged 1-12 years were contacts of index cases who were also aged 1-12 years. In the ITTIINAB population of these contacts (n=58), 1 of 22 (4.5%) children receiving oseltamivir prophylaxis and 9 of 36 (25.0%) children receiving expectant treatment had influenza, indicating a protective efficacy of 81.8% in this subgroup (95% CI -25.3-97.4%).

The proportion of contacts in different treatment groups who had a 4-fold or greater rise in antibody levels was also assessed in the trial. Among children aged 1-12 years in the ITTIINAB population, 28.3% of children receiving oseltamivir prophylaxis and 35.3% of those with expectant treatment had increased influenza antibody levels.

During the influenza season when the study was conducted, the predominant circulating strains of influenza virus in the regions where the study was conducted were influenza A (H1N1) (44 to 49 %) and influenza B (31 to 37 %). Influenza A (H3N2) was seen in 2 to 4 % of all index cases in the study. Concordance between infection in the index cases and in the contacts was high — 76 % for H1N1 and 64 % for influenza B. There were only 3 documented cases of influenza A (H3N2) among index cases in the study. Very few contacts were exposed to influenza A (H3N2) during that season, thus explaining the low sero-positivity to this influenza A subtype. Because H3N2 viruses were essentially not circulating during the study period, it is obvious that serological responses against H3 viruses could not observed.

In the data submitted, the serological responses against the circulating H1N1 and B viruses were similar among the contacts in the ET and PEP arms. Based on the well-demonstrated mechanism of action of oseltamivir, it could be expected that a proportion of subjects receiving the medicinal product for prophylaxis of influenza will develop antibodies against the virus that they are exposed to. The formation of antibodies against the infecting strain is desirable because the presence of sufficient levels of antibodies would prevent further infection by the same strain later during the epidemic, after cessation of the prophylaxis. However, it remains unclear which proportion of subjects receiving oseltamivir for prophylaxis develop truly protective titers of antibodies because the protective antibody levels in serum are not known.

- **Resistance to oseltamivir**

The incidence of resistance in children under 13 years of age in the MAH-sponsored trial NV16871 (asthmatic children) and in the published Japanese trial (*Kiso M et al Lancet 2004; 364:759*) was 7.7% (2/26) and 18% (9/50), respectively. Also in another MAH-sponsored paediatric study, JV16284, the incidence of resistance was high 19% (8/43). In the RSI adopted in October 2005, the MAH was requested to comment on these results in order to properly update the section 5.1 of the SPC.
In Study NV16871 [*Roberts NA. Assay for phenotypic and genotypic resistance to Ro 64-0802 (oseltamivir carboxylate) in influenza virus neuraminidase samples from clinical study NV16871 for Tamiflu (oseltamivir phosphate). Research Report No. 1018554, June 2005.]* both children in whom resistant virus emerged were taking oral corticosteroids for their asthma and for one of these the dose was at the high end of normal. Thus both patients were potentially subject to a degree of immunosupression and therefore potentially more likely to select resistant virus.
Study JV16284 was the last study to be conducted in children by the MAH using a 2 mg/kg dosing regimen for all children. It was the high incidence of resistance in this study [*Covington E, Roberts NA. Assay for phenotypic resistance to Ro 64-0802 in influenza neuraminidase samples from clinical study JV16284. Research Report 1005366. 6 August 2001.*], particularly among the children under 5 years, which alerted the MAH to the possibility that these children were not adequately exposed to oseltamivir carboxylate and that an improved dosing regimen may be needed for the very young.
The approved dosing regimen for children is now based on their weight and is adjusted upwards from 2 mg/kg oseltamivir phosphate for younger children to ensure adequate exposure to oseltamivir carboxylate irrespective of age. The incidence of resistance in children using this improved dosing regimen appears much lower with a current estimate of 1.2% [*Roberts N. Resistance Summary, (Update to RR1015254, May 2004), Research Report 1018181, May 2005*].

The MAH proposes to support a study similar to the one reported by Kiso et al. but to be conducted in the UK and using the EU-approved unit-based dosing regimen. This study would likely be supervised by Dr. Stephenson and Prof. Zambon and be conducted in the 2006-2007 influenza season. The CHMP decided that the MAH should commit to providing a report of this study by January 2007 as well as any relevant interim data when appropriate.

The proposed section 5.1 of the SPC has been updated to specifically highlight the risk of emergence of resistance for young children.

In an article published in the Weekly Epidemiological Record (*Neuraminidase Inhibitor Susceptibility Network. Use of influenza antivirals during 2003-2004 and monitoring of neuraminidase inhibitor resistance. Weekly Epidemiological Record, World Health Organization, Geneva. 2005:17:156*), new

surveillance data on resistance during widespread use of oseltamivir in the season 2003-4 have been published from Japan (6 million treatment courses equivalent to treatment of 5% of the population). Influenza isolates were collected in the society throughout the season. None of the isolates were from people known to have been taking oseltamivir. Among 1180 influenza A (H3N2) isolates, 4 (0.4%) were oseltamivir resistant. In the RSI adopted in October 2005, the MAH was requested to discuss whether these findings could represent low-level transmission of resistant strains to contacts or spontaneous emergence of resistance. According to the MAH, 4 of 1180 (ca. 0.4%) H3N2 isolates were resistant to oseltamivir carboxylate, two carrying the E119V mutation and one the R292K mutation. The fourth was known to be an erroneous result (personal communication, NISN), which would give an overall incidence of resistance in this study of less than 0.3%. The positive incidence values in this study although small may well be significant and the possibility of some low level transmission of resistant virus cannot be ruled out. However, it is not known whether these strains were transmitted from oseltamir-treated individuals or whether the resistant strains resulted from spontaneous mutations.

- **Clinical safety**

- **Discussion on the duration of the prophylaxis treatment**

Almost all subjects received their planned course of medication (75 mg (or corresponding unit dose in children) b.i.d. for 5 days for index cases and for those in the T arm requiring treatment, and 75 mg (or corresponding unit dose in children) once per day for 10 days for those in the P arm). A small number of index cases (N = 4) received a second course of treatment, and 17 contacts received b.i.d. treatment after receiving once daily prophylaxis.

In the RSI adopted in October 20005, the MAH was requested to justify the change of the duration of prophylaxis to 10 days for all contacts for children and adults.

In the answer to the RSI the MAH explained that the proposed change for the duration of prophylaxis to 10 days for all contacts was based upon information obtained from treatment studies looking at duration of viral shedding in influenza infected children, adults and the elderly. Viral shedding data derived from the phase III treatment trials across patients aged 1- 97 years provide evidence that duration of shedding differs by age. Children and the elderly shed virus for longer periods than do adults and adolescents and are therefore infectious for longer periods. Increasing the duration of prophylaxis to 10 days would provide protection in those situations where either the sick index case does not receive treatment and continues to shed virus or in situations where the index case is a child or the elderly and likely to shed virus beyond day 6.

The data presented to support this answer to the RSI were from Pooled Studies and are listed below:

1- In adults and adolescents aged 13-65 years, by day 6 of the study viral shedding had ceased in the vast majority of patients. In elderly patients aged > 65 years, viral shedding continued beyond day 5 of treatment in some cases. In a subset of patients (n= 149, overall), nose and throat swabs were collected at baseline, days 3, 5 and 10 of the study. On day 5 of the study, 37% of placebo patients and 23% of treated patients were still shedding virus (Table below).

Summary of Virus Shedding (ITTI Population(a)– Pool of Studies in the Elderly)

Studies with Viral Swabs on Days 3 and 5

Summary of Viral Shedding -Restricted
Subjects (a) (ITT Infected Population)

Protocols included: WV15707, WV15819, WV15876, WV15978

VIRAL SHEDDING	Placebo N=260	Ro 64-0796 75mg bid N=229
Baseline Yes	76 (100%)	73 (100%)
All	76 (100%)	73 (100%)
Day 3 No	23 (30%)	33 (45%)
Yes	53 (70%)	40 (55%)
All	76 (100%)	73 (100%)
Day 5 No	48 (63%)	56 (77%)
Yes	28 (37%)	17 (23%)
All	76 (100%)	73 (100%)
Day 10 No	71 (96%)	71 (99%)
Yes	3 (4%)	1 (1%)
All	74 (100%)	72 (100%)

(a) Subjects with baseline influenza positive samples plus 2 or 3 additional titres (protocol dependent).

2- In a study conducted in children aged 1-12 years, nose and throat swabs were collected more frequently (at baseline and days 2, 4, 6 and 10) in a subset of patients (n=198, overall). In this subset, approximately one-third of children were shedding virus on day 6 of the study (Table below). In a smaller study conducted in children with chronic asthma aged 6-12 years, 19% of patients on placebo and 5% of patients receiving oseltamivir treatment were shedding virus on day 6 of the study.

Summary of Viral Shedding in Children in the Intensive Subgroup — ITTI Population

VIRAL SHEDDING	Placebo bid N=235	Ro 64-0796 2.0mg/kg bid N=217
Baseline		
Yes	105 (100%)	93 (100%)
All	105 (100%)	93 (100%)
Day 2		
No	17 (16%)	21 (23%)
Yes	88 (84%)	72 (77%)
All	105 (100%)	93 (100%)
Day 4		
No	33 (31%)	42 (45%)
Yes	72 (69%)	51 (55%)
All	105 (100%)	93 (100%)
Day 6		
No	70 (67%)	63 (68%)
Yes	35 (33%)	30 (32%)
All	105 (100%)	93 (100%)
Day 10		
No	98 (98%)	86 (98%)
Yes	2 (2%)	2 (2%)
All	100 (100%)	88 (100%)
Any Visit		
Yes	105 (100%)	93 (100%)
All	105 (100%)	93 (100%)

All = Number of subjects who consented for more intensive viral swabs.
Note: Subset is defined by positive culture at baseline and swab samples available at day 2, day 4 and day 6.

In both children and the elderly, by day 10 of the studies, viral shedding was observed in a very small proportion of patients. These viral shedding data support the need to extend the duration of prophylaxis to 10 days in adults and to indicate the period of prophylaxis for 10 days in children (see Table above, Day 10 data).

Data derived from the studies indicate that, especially in children, viral shedding often persists for longer than 7 days and may continue even after the resolution of clinical symptoms. Children are generally considered as the main transmitters of influenza in the community, as demonstrated also by the present study in which almost half of all index cases in the households were children. In another study, one third of children were still excreting the virus on day 6 despite having been treated with oseltamivir. Since the protective effect of oseltamivir discontinues rapidly after cessation of the prophylaxis, extending the duration of prophylaxis to 10 days could be expected to decrease the risk of infection especially in households where the index case is a child.

Further to the assessment of these data, the CHMP decided that the section 4.2 of the SPC should be updated by replacing *at least 7 days* by *10 days*.

- **Discussion on the overall safety from study WV16139**

The overall incidence of adverse events from study WV16139 is shown in the table below:

Overview of Adverse Events by Body System Contacts

Body System/ Adverse Event	**Ro 64-0796 BID** N = 51 No. (%)	**Ro 64-0796 OD** N = 399 No. (%)	**Ro 64-0796 OD+ BID** N = 17 No. (%)
ALL BODY SYSTEMS	16 (31.4)	181 (45.4)	2 (11.8)
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS	2 (3.9)	75 (18.8)	1 (5.9)
GASTROINTESTINAL DISORDERS	8 (15.7)	65 (16.3)	1 (5.9)
GENERAL DISORDERS	1 (2.0)	42 (10.5)	-
INFECTIONS & INFESTATIONS	5 (9.8)	32 (8.0)	1 (5.9)
NEUROLOGICAL DISORDERS	-	36 (9.0)	-
MUSCULOSKELETAL, CONNECTIVE TISSUE & BONE DISORDERS	-	5 (1.3)	-
DISORDERS OF METABOLISM & NUTRITION	-	3 (0.8)	-
INJURY & POISONING	-	3 (0.8)	-
DISORDERS OF THE EAR & LABYRINTH	-	1 (0.3)	1 (5.9)
PSYCHIATRIC DISORDERS	-	2 (0.5)	-
SKIN & SUBCUTANEOUS TISSUE DISORDERS	1 (2.0)	1 (0.3)	-
RENAL & URINARY DISORDERS	-	1 (0.3)	-
DISORDERS OF BLOOD & THE LYMPHATIC SYSTEM	1 (2.0)	-	-
DISORDERS OF THE EYE	-	1 (0.3)	-
DISORDERS OF THE IMMUNE SYSTEM	1 (2.0)	-	-
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST	-	1 (0.3)	-

Amongst contacts, respiratory, gastrointestinal (nausea, vomiting) and general disorders were the most commonly reported. Only a small number of individual adverse events were reported by > 2% of contacts in either the prophylaxis group or amongst those receiving treatment in the T group; the most frequently-reported of these were nasal congestion and nausea. The incidence of vomiting was greater amongst those receiving treatment than those receiving prophylaxis.

There were no deaths. Five subjects participating in this study experienced serious adverse events, three of which were on treatment. Two of these subjects were index cases who had pneumonia, and a nervous breakdown, respectively. One contact receiving once-daily prophylaxis experienced aggravated asthma. Two further subjects experienced serious adverse events off-treatment (both were index cases): one experienced cardiac failure, and the other developed tuberculosis.

- **Discussion on the safety in children aged 1-12 years from study WV16139**

As shown with other clinical oseltamivir trials, gastrointestinal symptoms were the most frequently observed adverse events (see table below). Vomiting occurred in 10.1% and nausea in 4.0% of children receiving oseltamivir prophylaxis. No deaths or any other serious adverse events were observed in children receiving either oseltamivir prophylaxis or treatment in this study.

Summary by Age Category of those Adverse Events Occurring More than Once in any Age and Dose Category

	1-2 yrs				3-5 yrs				6-12 yrs .					
	BID Ro 64-0796 N= 12		OD Ro 64-0796 N= 3		BID Ro 64-0796 N = 28		OD Ro 64-0796 N =21		BID Ro 64-0796 N =118		OD Ro 64-0796 N = 75		OD+BID Ro 64-0796 N = 6	
VOMITING NOS	3	(25.0%)	0	(0.0)	7	(25.0%)	3	(14.3%)	21	(17.8%)	7	(9.3%)	1	(16.7%)
NAUSEA	0	(0.0)	0	(0.0)	4	(14.3%)	1	(4.8%)	6	(5.1%)	3	(4.0%)	0	(0.0)
DIARRHOEA NOS	0	(0.0)	0	(0.0)	2	(7.1%)	0	(0.0)	3	(2.5%)	1	(1.3%)	0	(0.0)
COUGH	0	(0.0)	0	(0.0)	1	(3.6%)	5	(23.8%)	3	(2.5%)	13	(17.3%)	1	(16.7%)
ABDOMINAL PAIN UPPER	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(2.5%)	1	(1.3%)	0	(0.0)
BRONCHITIS NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(2.5%)	0	(0.0)	0	(0.0)
NASAL CONGESTION	0	(0.0)	0	(0.0)	0	(0.0)	5	(23.8%)	3	(2.5%)	11	(14.7%)	1	(16.7%)
OTITIS MEDIA NOS	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.5%)	2	(1.7%)	0	(0.0)	0	(0.0)
UPPER RESPIRATORY TRACT INFECTION NOS	0	(0.0)	1	(33.3%)	0	(0.0)	0	(0.0)	2	(1.7%)	0	(0.0)	0	(0.0)
DYSPEPSIA	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8%)	1	(0.8%)	2	(2.7%)	0	(0.0)
RHINORRHOEA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8%)	2	(2.7%)	0	(0.0)
ABDOMINAL PAIN NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.7%)	0	(0.0)
HEADACHE NOS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(6.7%)	0	(0.0)
PYREXIA	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.8%)	0	(0.0)	2	(2.7%)	0	(0.0)

Two children withdrew prematurely from this study as a consequence of adverse events. The first one was a 8-year old boy receiving once-daily oseltamivir prophylaxis who developed mild vomiting on days 7 and 8 and withdrew from the study on day 8. The second child to withdraw was a 6-year old male index case who suffered severe nausea and moderate vomiting, commencing on day 1. The subject withdrew on day 5 after seven doses of study drug. Both events were considered to be probably related to treatment.

- **Discussion on the safety in children aged 1-12 years from database study and literature**

1- Nordstrom B, et al. Skin reactions and other adverse events in children treated with Tamiflu. April 4, 2005.

The MAH has prepared a summary of adverse events in oseltamivir-treated children between the ages of 1 and 12 years on the basis of health insurance claims and pharmacy data from a HMO in U.S.A. The database comprised of health insurance claims data for over 20 million individuals across the U.S. and it includes data both from patients insured by UnitedHealthcare and from large national employer groups with administrative services provided by UnitedHealthcare.

Children from 1 – 12 years old with a diagnosis of influenza were identified in the database. The children were grouped into two cohorts: those with a pharmacy dispensing of Tamiflu on the day of influenza diagnosis, and those with no antiviral treatment during the influenza season. The present study was designed to identify potential adverse effects of Tamiflu, with particular focus on skin reactions and on any CNS related adverse events that may be identified through claims data.
It should be noted that in EU serious skin reactions are already labelled in section 4.8 of the SPC and that psychiatric disorders are under close surveillance. In a fax dated 17 November 2005, the MAH was requested to provide by 28 November 2005 a cumulative safety review of all available data on serious psychiatric disorders including all case reports with a fatal outcome

where Tamiflu is involved. The submission should include data on children. The assessment of the provided answer was discussed and endorsed during December 2005 CHMP plenary meeting and is not presented in this assessment report. However, it can be noted that the CHMP concluded that this review did not raise any new safety concerns.

In each of these two cohorts, the 30-day risk of several skin reactions, adverse drug reactions, anaphylactic shock, loss of consciousness, convulsions, dizziness, depression, and psychotic conditions were investigated. Logistic regression was used to compare the risk between cohorts. All diagnoses given to children during the month following influenza diagnosis were identified as well, classifying the diagnoses by system organ class.

All analyses were performed separately in six age groupings: one year, two years, one or two years, three to five years, six to 12 years, and the full cohorts (one to 12 years). Baseline characteristics were summarized within each age group. For each outcome, we counted the number of patients having an event during the 30 days following the index date, and performed logistic regression to estimate the 30th day odds ratios and 95% confidence intervals between groups.

The table below displays the demographics of the two cohorts of children with influenza in four age categories:

Demographic Characteristics of Study Cohorts by age

Ages 1 - 2

	Influenza with Tamiflu (n = 1566) N %	Influenza without Tamiflu (n = 12070) N %
Mean age, years (SD)	1.6 (0.5)	1.5 (0.5)
Gender		
Male	849 / 54.2%	6344 / 52.6%
Female	717/ 45.8%	5726 / 47.4%

Age 2

	Influenza with Tamiflu (n = 888) N %	Influenza without Tamiflu (n = 6400) N %
Mean age, years (SD)	2 (0)	2 (0)
Gender		
Male	471 / 53.0%	3334 / 52.1%
Female	417 / 47.0%	3066 / 47.9%

Ages 3 - 5

	Influenza with Tamiflu (n = 2151) N %	Influenza without Tamiflu (n = 16377) N %
Mean age, years (SD)	3.9 (0.8)	3.9 (0.8)
Gender		
Male	1129 / 52.5%	8355 / 51.0%
Female	1022 / 47.5%	8022 / 49.0%

Ages 6 - 12

	Influenza with Tamiflu (n = 5158) N %	Influenza without Tamiflu (n = 25939) N %
Mean age, years (SD)	9.4 (2.0)	8.9 (2.0)
Gender		
Male	2640 / 51.2%	13173 / 50.8%
Female	2518 / 48.8%	12766 / 49.2%

Thus, data from 8875 children who were exposed and from 54386 children who were not exposed to oseltamivir were included in the analysis.

The table below displays the incidence and odds ratios for the selected adverse events in the whole cohorts.

Adverse Events in 30 Days Following Index Date for Full Cohorts, Ages 1 - 12

	Number of Outcomes		
	Influenza with Tamiflu (n = 8875) N %	Influenza without (n = 54386) N %	Crude odds ratio (95% CI)
Rash	18/0.2%	182/0.3%	0.61 (0.36, 0.95)
Urticaria	14/0.2%	136/0.3%	0.63 (0.35, 1.05)
Pruritis	0/0.0%	11/0.0%	NA
Contact dermatitis	33/0.4%	278/0.5%	0.73 (0.50, 1.03)
Atopic dermatitis	16/0.2%	114/0.2%	0.86 (0.49, 1.41)
Dermatitis due to substance taken internally	7/0.1%	29/0.1%	1.48 (0.60, 3.19)
Erythematous conditions	0/0.0%	2/0.0%	NA
Erythema multiforme	1/0.0%	24/0.0%	0.26 (0.01, 1.21)
Bullous dermatoses	0/0.0%	0/0.0%	NA
Angioneurotic edema	1/0.0%	3/0.0%	NA
Adverse drug reaction	7/0.1%	35/0.1%	1.23 (0.50, 2.60)
Anaphylactic shock	0/0.0%	2/0.0%	NA
Loss of consciousness	3/0.0%	32/0.1%	0.57 (0.14, 1.60)
Convulsions	12/0.1%	149/0.3%	0.49 (0.26, 0.85)
Dizziness	2/0.0%	13/0.0%	NA
Depression	4/0.0%	7/0.0%	NA
Psychotic conditions	1/0.0%	4/0.0%	NA

According to the data in the 2 tables above, there were no significant differences between the cohorts in any of the four age categories.

This large population of children in the United States, health care claims diagnoses given during the month following an influenza diagnosis did not raise any new safety signals in the areas under study. This kind of study may have several limitations because of its narrow scope and because of the uncertain relationship between events and claim-associated diagnoses. In addition, **the sample size is still too small for capturing very rare signals. Nevertheless, this study consolidates the current understanding of the safety profile of Tamiflu: severe and serious adverse effects are rare**.

2- KW Chik et al: Oseltamivir prophylaxis during the influenza season in a paediatric cancer centre: prospective observational study Hong Kong Med 10: 103-106, 2004

This publication documents the only clinical study investigating the use of oseltamivir for long-term prophylaxis of influenza in children. This was an uncontrolled pilot study, involving 32 patients immunocompromised by chemotherapy or bone marrow transplantation during the 2001 influenza season. The efficacy claim is based on a comparison of the study results to findings from a retrospective review of laboratory-confirmed influenza infection between 1998 and 2000 in the same centre.

Before the influenza season, patients older than 5 years who had received chemotherapy or bone marrow transplant in the past 1 year were recruited into the study. All patients received the same 75 mg daily dose of oseltamivir, with the result that in the youngest child this equated to a 4 mg/kg dose. The patients ranged in age from 6 – 23 years (median 14.3 years). Eight of the patients were aged 5 – 9 years, and a further eleven between 10 and 14 years.

Patients who experienced an episode of influenza-like illness in the 2 weeks before the study were excluded as were those who had previously received an influenza vaccination and those with significant renal impairment (creatinine clearance of <10 ml/min). In the study period, 32 participants were recruited into study: 17 females and 15 males. Sixty percent of the patients had leukaemia and approximately one third had a solid tumour. Twenty-nine patients belonged to the chemotherapy group and the remainder to the bone marrow transplant group.

Patient monitoring included weekly telephone interviews, a patient diary, and attendance of out-patient visits from the start of the study until 1 month after stopping oseltamivir treatment—12 weeks in total.

Six patients withdrew from the study because of various reasons: one patient developed fever and upper respiratory tract infection without a defined infective source on the first day of the study; one had a sore throat with no defined infective organism, as well as vomiting, and stopped taking prophylaxis voluntarily by week 3; one stopped because of sickness from concurrent chemotherapy; one stopped because of epigastric discomfort due to prophylaxis; one withdrew because of admission to the bone marrow transplant unit after 1 month's prophylaxis; and one withdrew voluntarily after recruitment. In total, 16% (5/32) of the recruited subjects had gastro-intestinal adverse effects.

This study is a pilot study that provides some safety data of long-term prophylaxis in children >6 years. The efficacy data, although encouraging, are very difficult to interpret because there was no systematic laboratory surveillance of influenza and no control group, comparison of different influenza seasons is difficult. The MAH wanted to describe these results in section 5.1 of the SPC for long-term use in immunocompromised children, but the CHMP decided that the data are not sufficient to be reflected in the SPC.

- **Other concerns on the safety in children**

During the Paediatric Working Party (PEG) meeting held in November 2005, the reporting of adverse events with respect to pandemic influenza was discussed. The PEG expressed its concern on the lack of available efficacy and safety data in infants below the age of 1, specifically in the context of need and potential misuse during a pandemic influenza, as there are current reports of off label use in this population. Therefore, the CHMP decided to consider the assessment of all available data on the use of Tamiflu in children younger than 1 year of age in order to introduce clear recommendations in the product information to guide healthcare professionals in the event of pandemic flu. The MAH has been requested to commit to providing all available data in children less than 1 year of age by March 2006.

- **Conclusions on clinical aspects**

The pivotal clinical trial WV16193 demonstrated that once-daily administration of oseltamivir for 10 days provides effective prevention against influenza infection also for children aged 1-12 years in the family setting when the prophylaxis is started within 48 h after the onset of symptomatic influenza in the first infected member of the family. The protective efficacy was 80.1% among children 1-12 years of age who were not shedding influenza viruses themselves at the baseline. This observed efficacy was similar to that observed for contacts ≥13 years of age (84.9%) in this study. The number of children at the age of 1-6 years was relatively small. On the basis of current knowledge, there are no reasons to suspect that the efficacy or safety would be different from older children.

Because the present study (WV16193) was not a double-blind, placebo-controlled study, the open-label nature of the trial might give rise to criticism about potential bias in the results. However, this problem was effectively avoided by the use of objective endpoints that required laboratory confirmation of influenza illnesses. Because all index cases were treated with oseltamivir and the same treatment was available to any participant presenting with an influenza-like illness, it seems very unlikely that the non-blinded design would have biased the results of the trial.

The study was not initially designed as a paediatric trial but it included subjects from all age groups. However, the proportion of children among the participants was sufficient for meaningful (preplanned) analysis of the efficacy of the prophylaxis in the subgroup of children 1-12 years of age.

In this study, the dosage of the medicinal product in children was based on the age of the child instead of the weight of the child. This decision was made prior to approval of the weight-based unit dosing that is currently approved for the use of oseltamivir in the treatment of children. The age-based dosing was based on calculated ideal weights and most children received the same dosage that they would have received even if the current weight-based dosing had been used. Thus, the results can be extrapolated to the current approved dosing.

- **Changes to the Product Information further to the assessment of clinical data**

- **Section 4.1 of the SPC**

Prevention of influenza
- Post exposure prevention in adults and children one year of age or older ~~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 children one year of age ~~adolescents 13 years of age~~ or older.

- **Section 4.2 of the SPC**

The section 4.2 has been updated as follows:

Tamiflu capsules and Tamiflu suspension are bioequivalent formulations, 75 mg doses can be administered as either one 75 mg capsule or by administering one 30 mg dose plus one 45 mg dose of suspension. Adults, adolescents or children (>40 kg) who are unable to swallow capsules may receive appropriate doses of Tamiflu suspension.
The safety and efficacy of Tamiflu in children less than one year of age have not been established (see Section 5.3).

Treatment of influenza

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.
For adults and adolescents 13 years or older the recommended oral dose is 75 mg oseltamivir twice daily, for 5 days.
For children one year or older, Tamiflu oral suspension is available. For children with body weight above 40 kg, capsules may be prescribed at the adult dosage of 75 mg twice daily for 5 days.
~~The safety and efficacy of Tamiflu in children less than one year of age have not been established (Please see also Section 5.3 Preclinical Safety Data).~~

Prevention of influenza
Post exposure prevention
For ~~in a~~adults and adolescents 13 years or older,~~: T~~ the recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for ~~at least 7~~10 days. Therapy should begin as soon as possible within two days of exposure to an infected individual.
Children weighing > 40 kg, who are able to swallow capsules, may also receive prevention with a 75 mg capsule once daily for 10 days as an alternative to the recommended dose of Tamiflu suspension.

Prevention during an influenza epidemic in the community: The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to six weeks.
~~The safety and efficacy of Tamiflu for the prevention of influenza in children 12 years or younger have not been established.~~

For Tamiflu 12 mg/ml powder for oral suspension, the following paragraphs have been adding to give information on the dosage to be used based on the weight.

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

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

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

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

- **Section 4.4 of the SPC**

The section 4.4 has been updated to reflect that Tamiflu has not been studied in children less than one year for prevention of influenza as indeed this type II variation does not bring any new data for this specific population.

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

- **Section 4.8 of the SPC**

The table reflecting the most frequent adverse events occurring in children Aged 1 to 12 years in studies in naturally acquired influenza [Adverse events occurring on treatment in >1% of paediatric patients enrolled in phase III trials of Tamiflu treatment of naturally acquired influenza] has been updated to reflect the results of the studies submitted through this Type II variation.

A specific paragraph on prevention of influenza in children has been added:

Paediatric patients aged 1 to 12 years participated in a post exposure prevention study in households, both as index cases (n=134) and as contacts (n=222). Gastrointestinal events were the most frequent, particularly vomiting. Tamiflu was well tolerated in this study, the adverse events noted being consistent with those previously observed (see table above).

In the paragraph *Observed during clinical practice*, ~~*hepatic functions*~~ has been replaced by *hepatico-biliary system*.

It should be noted that *toxic epidermal necrolysis* and *angioneurotic oedema* have been added to this section 4.8 through the Type II variation II/21, which opinion is adopted in parallel during this December 2005 CHMP.

- **Section 5.1 of the SPC**

The proposed paragraph on *Reduced sensitivity of viral neuraminidase* has been updated to reflect the findings in children from 1 to 12 years of age and to highlight the risk of emergence of resistance in younger children.

There has been no evidence for emergence of drug resistance associated with the use of Tamiflu in clinical studies conducted to date in post exposure (7 days), post exposure within household groups (10 days) and seasonal (42 days) prevention of influenza.
The risk of emergence of drug resistance in clinical use in the treatment of influenza has been extensively examined. In all clinical studies in naturally acquired infection, 0.32% (4/1245) of adults and adolescents and 4.1% (19/464, range 0-19% in individual studies~~19/464~~) of children aged 1-12 were found to transiently carry influenza virus with decreased neuraminidase susceptibility to oseltamivir carboxylate. The emergence of resistance may be higher in young children and in children who had immunosuppression or who were under-exposed to oseltamivir. Patients carrying resistant virus cleared it normally and showed no clinical deterioration. Rare cases of oseltamivir-resistant virus strains in patients who were not exposed to oseltamivir have been reported. ~~All resistant genotypes are disadvantaged compared to the corresponding wild-type isolate and are likely to be less contagious in man.~~ Thus far, there is no evidence for resistance in influenza B *in vitro* or in clinical trials.
~~In clinical studies in naturally acquired infection, 0.34 % (4/1177) of adults and adolescents and 4.5 % (17/374) of children aged one to 12 years were found to transiently carry influenza A virus with decreased neuraminidase susceptibility to oseltamivir carboxylate. Neuraminidase from influenza B with reduced sensitivity has not been observed either in cell culture or in clinical studies.~~

~~Cross resistance between zanamivir-resistant influenza mutants and oseltamivir-resistant influenza mutants has been observed in vitro. Insufficient information is available to fully characterise the risk of emergence of oseltamivir resistance and cross-resistance in clinical use.~~

The findings of WV16193 have been reported as a paragraph on post-exposure prevention in adults, adolescents and children between 1 and 12 as this study is not specifically a paediatric study. It can therefore not be considered only for children between 1 and 12 years of age despite the scope of this variation. The proposed paragraph has been updated as follows:

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and children aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the households. The oseltamivir prophylaxis lasted for 10 days.
In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20% (27/136) in the group not receiving prevention to 7% (10/135) in the group receiving prevention (62.7% reduction, [95% CI 26.0-81.2]; p= 0.0042). In households of influenza infected index cases, there was a significant reduction in the incidence of influenza from 26% (23/89) in the group not receiving prevention to 11% (9/84) in the group receiving prevention .
According to subgroup analysis in children at 1-12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21/111) in the group not receiving prevention to 7 % (7/104) in the group receiving it. Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15/70) in the group not receiving prevention to 4 % (2/47) in the group receiving prevention(p=0.0206). The NNT for the total paediatric population was 9 (95 % CI 7-24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTII) respectively.

4. Overall Benefit-Risk conclusion

Ample evidence from several trials conducted during recent years in different countries demonstrates that influenza is an important infection not only among the elderly population but also among children. The accumulating data on the substantial burden of influenza in children have initiated an increasing discussion about more widespread vaccination of children against influenza. In the United States and Canada, influenza vaccine recommendations already include healthy children 6-23 months of age, but no similar recommendations have so far been made in European countries. Despite increasing discussions about routine influenza vaccination of at least the youngest children in Europe, several reasons make it unlikely that influenza vaccination programmes would be expanded to include healthy children in European countries any time soon.

Considering the burden of influenza in children, including its frequent bacterial complications and high rates of influenza-associated hospitalisations, it is obvious that prevention of influenza in children is an important goal. Prevention of influenza in children would not only be beneficial for children themselves. Children are known to be the main transmitters of influenza in the community during annual epidemics, and several clinical studies indicate that influenza vaccination of children could bring about substantial reductions in influenza-associated morbidity among other age groups, especially the elderly population. In the absence of widespread vaccination of children, the only alternative for prevention of influenza is the use of influenza-specific antiviral medicinal products.

The risk of acquiring influenza is greatest in the family setting after one member of the family has contracted the illness. This is because of the extent of sustained exposure to the virus among the other members of the household. The possibility to interfere with the chain of transmission of the virus is very important from both the medical and socioeconomic point of view. With the currently available evidence that oseltamivir prophylaxis is effective in preventing influenza also in children within households, it could be even seen as unethical not to make the prophylaxis available also to children above 1 year of age, provided that the prophylaxis is safe for them.

The study WV16193 indicates that once-daily administration of oseltamivir provides 55-80% efficacy in post-exposure prophylaxis against influenza in children 1-12 years of age in the family setting. This benefit clearly outweighs the risks of the prophylaxis, which mainly include mild and short-lived gastrointestinal symptoms. The positive benefit/risk ratio is further augmented by the findings that oseltamivir prophylaxis has not been shown to substantially prevent the development of immune response against the influenza viruses that the subject has been exposed to.

Because there have not been clinical trials of the use of oseltamivir for the seasonal prophylaxis of influenza in children, there are no convincing data on either the efficacy or safety of such an intervention in children younger than 13 years of age. The current literature evidence, albeit scarce, suggests that even long-term use of oseltamivir is safe in children, but no data on the efficacy of seasonal prevention in children are available.

The use of oseltamivir for seasonal prophylaxis during epidemics has been insignificant in EU. Therefore, it is very unlikely that oseltamivir would be used frequently for seasonal prophylaxis of influenza in healthy children. However, it is important from individual and public health point of view that the use of oseltamivir is possible in the exceptional circumstances mentioned in the proposed indication.

With potential increasing use of oseltamivir for prophylaxis and treatment of influenza, it is possible that oseltamivir resistance among influenza viruses could increase. So far, however, the resistance rates have remained low, and currently there are no ecological or medical reasons to withhold the use of oseltamivir either for the prophylaxis or treatment of influenza. In fact, the risk of oseltamivir resistance is mainly associated with treatment rather than with the prophylactic use.

The original submission of Tamiflu demonstrated that oseltamivir has a modest efficacy in the treatment of influenza. In contrast, it seems to be very effective for prophylaxis. The new data clearly indicate that the benefits of using oseltamivir for post-exposure prevention of influenza in children are

much greater than the potential risks. With respect to seasonal prophylaxis in children, no formal studies have been conducted on the efficacy and safety of such an intervention. However, some literature evidence and the extensive surveillance data on the adverse events associated with oseltamivir use for treatment in children indicate that even its long-term use, according to the proposed indication, would have a positive benefit/risk. Further, the similarity of the efficacy of post-exposure prophylaxis between children and adults suggests that also seasonal prophylaxis with oseltamivir would be as effective in children as in adults. Therefore, the CHMP concludes that the extension of the current prophylaxis indication to include children 1-12 years of age is approved.