# Tamiflu

Procedural steps taken and scientific information after the authorisation

| Application number | Scope | Opinion/ Notification [1] issued on | Commission Decision Issued [2] / amended on | Product Information affected [3] | Summary |
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| PSUSA/2225/ 201809 | Periodic Safety Update EU Single assessment - oseltamivir | 16/05/2019 | n/a | | PRAC Recommendation - maintenance |
| II/0135 | B.II.f.1.b.4 - Stability of FP - Extension of the shelf life of the finished product - Based on extrapolation of stability data not in accordance with ICH/VICH guidelines | 21/02/2019 | | SmPC | The SmPC section 6.3 has been updated to change the shelf-life for TAMIFLU Capsules (30mg and 45mg) from 7 years to 10 years. |

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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| II/0136 | Update of sections 4.2, 4.8, 5.1 and 5.2 to guide prescribers on the use of Tamiflu for treatment in immunocompromised (IC) patients based on study NV20234, a Phase III, double-blind, randomized, stratified, multicenter study of conventional and double dose oseltamivir for the treatment of influenza in IC patients. The PL and RMP (v18.1) have been updated accordingly.<br>In addition, the MAH took the opportunity to correct some minor errors.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 15/11/2018 | 11/01/2019 | SmPC and PL | Based on results of the study NV20234, the product information is updated to guide prescribers on a longer treatment duration for immunocompromised adult patients with a recommended oral dose of 75 mg oseltamivir twice daily for 10 days. Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.<br>Study NV20234 was a randomized, double blind study, to evaluate safety and characterize the effects of oseltamivir on the development of resistant influenza virus (primary analysis) in influenza-infected adult immunocompromised patients, included 151 patients evaluable for efficacy of oseltamivir (secondary analysis, not powered). The study included solid organ transplant [SOT] patients, haematopoietic stem cell transplant [HSCT] patients, HIV positive patients with a CD4+ cell count <500 cells/mm3, patients on systemic immunosuppressive therapy, and those with haematological malignancy. These patients were randomized to be treated, within 96 hours of symptoms onset, with standard dose (73 patients) or double dose (78 patients) of oseltamivir, for a duration of 10 days. The median time to resolution of symptoms (TTRS) was similar between the standard dose group (103 hours [90% CI 75.4-110.0]) and double dose group (104 hours [90% CI 65.8-131.0]). The proportion of patients with secondary infections in the standard dose group and double dose group was comparable (8.2% vs 5.1%). The safety profile of Tamiflu observed in this study was consistent with that observed in previous clinical trials where Tamiflu was administered for treatment of influenza in non-immunocompromised patients (otherwise healthy patients or "at risk" patients [i.e., those with respiratory |

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| | | | | | and/or cardiac co-morbidities]). The percentage of patients reporting adverse events was lower in the standard dose group compared to the double dose group (49.0% vs 59.4 %, respectively) |
| IA/0140 | A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient | 20/11/2018 | n/a | | |
| IAIN/0138 | B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking | 28/09/2018 | n/a | | |
| N/0137 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 09/08/2018 | 11/01/2019 | PL | |
| IB/0132 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 08/08/2018 | n/a | | |
| II/0133 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 12/07/2018 | n/a | | |
| IG/0944/G | This was an application for a group of variations.<br><br>B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting | 14/06/2018 | n/a | | |

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| | material/reagent/intermediate/or excipient from a new or an already approved manufacturer<br>B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) | | | | |
| T/0131 | Transfer of Marketing Authorisation | 20/02/2018 | 06/04/2018 | SmPC, Labelling and PL | |
| II/0128 | Update of section 4.6 of the SmPC in order to reflect the final study results from non-interventional safety study BV29684, which assessed the safety of oseltamivir exposure in pregnant women, and was listed as a category 3 study in the RMP (MEA099). The RMP version 15.2 has also been updated to reflect the study results.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 22/02/2018 | 11/01/2019 | SmPC | Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations, including congenital heart defects. A large amount of data on oseltamivir exposure of pregnant women from post-marketing reports and observational studies (more than 1000 exposed outcomes during the first trimester) indicate no malformative nor feto/neonatal toxicity by oseltamivir.<br>However, in one observational study, while the overall malformation risk was not increased, the results for major congenital heart defects diagnosed within 12 months of birth were not conclusive. In this study, the rate of major congenital heart defects following oseltamivir exposure during the first trimester was 1.76% (7 infants out of 397 pregnancies) compared to 1.01% in unexposed pregnancies from the general population (Odds Ratio 1.75, 95% Confidence Interval 0.51 to 5.98). The clinical significance of this finding is not clear, as the study had limited power. Additionally, this study was too small to reliably assess individual types of major malformations; moreover women exposed to oseltamivir and women unexposed could not be |

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| | | | | | made fully comparable, in particular whether or not they had influenza.<br>Overall, the use of Tamiflu may be considered during pregnancy if necessary and after considering the available safety and benefit information and the pathogenicity of the circulating influenza virus strain. |
| IG/0887 | A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) | 29/01/2018 | n/a | | |
| IA/0129 | A.7 - Administrative change - Deletion of manufacturing sites | 20/11/2017 | n/a | | |
| IA/0126 | B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method | 27/04/2017 | n/a | | |
| IA/0127 | A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient | 24/04/2017 | n/a | | |
| IB/0125 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 21/03/2017 | n/a | | |
| IA/0124 | A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the | 19/12/2016 | n/a | | |

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| | finished product, including quality control sites (excluding manufacturer for batch release) | | | | |
| II/0122 | Update of section 5.1 of the SmPC and RMP (v 13.2) to reflect the results of study IRIS (NV20237), a prospective, multicentre, information-gathering study, comprising virological surveillance and assessment of clinical outcomes, which enrolled patients over a 7-year period.<br>In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version and combine the SPCs of Tamiflu 30, 45 and 75 mg capsules.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 15/12/2016 | 20/04/2017 | SmPC | Section 5.1 of the SmPC has been updated to reflect the results of Study NV20237, (Influenza Resistance Information Study (IRIS) a study that primarily aimed to elucidate clinical significance of new resistance information in immunocompetent patients. The data shows that developing oseltamivir-resistant virus during treatment was more frequent in children than adults, ranging from less than 1% in adults to 18% in infants aged below 1 year. Children who were found to carry oseltamivir-resistant virus in general shed the virus for a prolonged period compared with subjects with susceptible virus. However treatment-emergent resistance to oseltamivir did not affect treatment response and caused no prolongation of influenza symptoms. |
| IB/0123 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 14/09/2016 | n/a | | |
| II/0116/G | This was an application for a group of variations.<br><br>B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)<br>B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range<br>B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a | 09/06/2016 | 20/04/2017 | SmPC | |

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| | new specification parameter to the specification with its corresponding test method<br>B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range<br>B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product<br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | | | | |
| PSUSA/2225/ 201509 | Periodic Safety Update EU Single assessment - oseltamivir | 13/05/2016 | n/a | | PRAC Recommendation - maintenance |
| II/0118 | Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to include information regarding use in post-exposure prophylaxis of children below 1 year of age during a pandemic based on a population pharmacokinetic model using data from studies CASG114 and WP22849. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 28/04/2016 | 20/04/2017 | SmPC, Annex II and Labelling | Simulation of once daily dosing of 3mg/kg in infants <1 year shows an exposure in the same range or higher than for once daily dosing of 75 mg in adults. Exposure does not exceed that for treatment of infants < 1 year (3 mg/kg twice daily) and is anticipated to result in a comparable safety profile (see Section 4.8). No clinical studies of prophylaxis in infants aged <1 have been performed. |
| IG/0667/G | This was an application for a group of variations.<br><br>B.III.1.b.2 - Submission of a new/updated or deletion | 08/04/2016 | n/a | | |

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| | of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer<br>B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer<br>B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) | | | | |
| II/0114 | Proposal for a new and alternative study BV29684 'Assessing the safety of prenatal exposure to oseltamivir' (study protocol version 4) as a category 3 study (MEA 099) to replace the agreed 2-year extension of the Danish-Swedish registry study NV25577. An updated RMP version 11.1 was agreed during the procedure.<br><br>C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required | 17/12/2015 | n/a | | N/A |
| IA/0119 | B.II.d.1.i - Change in the specification parameters and/or limits of the finished product - Ph. Eur. 2.9.40 uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 or Ph. Eur. 2.9.6 | 08/12/2015 | n/a | | |

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| IG/0573 | C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location | 01/07/2015 | n/a | | |
| II/0110/G | This was an application for a group of variations.<br><br>Extension of Indication to include a new population for Tamiflu (infants below 1 year of age not limited to an pandemic outbreak with dosing regimen 3 mg/kg twice daily for 5 days). Consequentially, addition of a 3 ml plastic oral dispenser, within the Tamiflu 6 mg/ml powder for oral suspension outer carton only (in addition to the already included 10 ml plastic oral dispenser), to enable the accurate dosing in infants below 1 year of age. This 3 ml oral dispenser is proposed following CHMP request as part of the line extension for 6 mg/ml (EMEA/H/C/402/X/0085 - European Commission Decision: November 2011).<br>As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC were updated to reflect the new data. The Package Leaflet and Labelling are updated in accordance.<br>Furthermore, the PI is being brought in line with the latest QRD template.<br><br>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one<br>B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is | 26/03/2015 | 05/05/2015 | SmPC, Labelling and PL | Please refer to the assessment report : EMEA/H/C/0402/II/0110/G<br><br>The current variation to extend the use in infants less than 1 year of age in the treatment of influenza is based on PK/PD modelling from studies CASG114 and WP22849. The MAH has used pharmacokinetic data, modelling and simulation to support the dosage of oseltamivir in infants <1 year of age. The simulations indicate that a 3 mg/kg BID regimen in infants <1 year of age is predicted to provide OC exposures that exceed those observed with marketed doses in adults on 75 mg BID and children 1-5 years of age. The highest and most variable exposure is predicted for infants < 1 month of age. OC exposures are, however, not anticipated in any infant group to exceed those observed with dosage 150 mg BID in adults, which was the alternative, well tolerated dosage in pivotal phase 3 studies. It is predicted that with a lower dosage (e.g. 2.5 mg/kg BID) the target OC levels will not be achieved in all patients. Predicted oseltamivir exposures are anticipated to be similar to some of the exposures that have been shown to be tolerated across the oseltamivir clinical pharmacology program. As data on preterm infants is very limited, the newly granted indication does not cover preterm babies (i.e. post-conceptual age less than 36 weeks). Based on the data assessed, the safety profile of oseltamivir in infants below 1 year of age is |

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| | not an integrated part of the primary packaging - Device with CE marking | | | | acceptable. As a consequence of extension of indication, a 3 ml plastic oral dispenser was proposed to be added to the Tamiflu 6 mg/ml powder for oral suspension outer carton (in addition to the already included 10 ml plastic oral dispenser), to enable the accurate dosing in infants below 1 year of age. |
| II/0113 | Update of sections 4.6, 5.1 and 5.2 of the SmPC in order to update the safety information regarding oseltamivir exposures in pregnant women at standard dosing for treatment of influenza (75 mg twice daily) and prophylaxis (75 mg once daily).<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 23/04/2015 | 13/04/2016 | SmPC | A pooled population pharmacokinetic analysis indicates that the recommended Tamiflu dosage regimen results in lower exposure (30% on average across all trimesters) to the active metabolite in pregnant women compared to non-pregnant women. The lower predicted exposure however, remains above inhibitory concentrations (IC95 values) and at a therapeutic level for a range of influenza virus strains. In addition, there is evidence from observational studies showing benefit of the current dosing regimen in this patient population. Therefore, dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza. |
| IA/0115 | A.7 - Administrative change - Deletion of manufacturing sites | 20/04/2015 | n/a | | |
| IG/0497 | C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location | 18/11/2014 | n/a | | |
| II/0107 | C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required | 23/10/2014 | n/a | | |

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| IB/0111/G | This was an application for a group of variations.<br><br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold<br>B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue | 21/08/2014 | n/a | | |
| IA/0109 | B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place | 07/07/2014 | n/a | | |
| IA/0108 | B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place | 21/05/2014 | n/a | | |
| II/0106 | to extend the shelf-life of Tamiflu 75 mg capsules from 7 to 10 years.<br><br>B.II.f.1.b.4 - Stability of FP - Extension of the shelf life of the finished product - Based on extrapolation of stability data not in accordance with ICH/VICH | 25/04/2014 | 05/05/2015 | SmPC and PL | |

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| | guidelines | | | | |
| II/0101/G | This was an application for a group of variations.<br><br>Update to the PL to reflect the findings of the PL User Test. In addition, section 6.3 was revised according approved microbial challenge tests and section 6.6 "Special precautions for disposal and other handling" has been aligned to reflect the PL changes made. The date of the last renewal was reflected.<br>Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0 and the list of local representatives was updated in the Package Leaflet.<br>The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.<br><br>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH<br>C.I.3.z - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation | 24/10/2013 | 04/12/2013 | SmPC, Annex II and PL | The current variation introduced changes to the package leaflets of Tamiflu is based on the assessment of a user consultation with target patient groups as requested by the CHMP. After the extension of oseltamivir use for the treatment and prevention of influenza in infants below 12 months of age during a pandemic influenza, issues on readability and appropriateness of the instructions for home preparation were encountered. Consequently, this variation has the objective to improve the instructions to prepare at home from Tamiflu capsules, the extemporaneous formulation for children. The CHMP endorsed the updates to the product information and considered that these updates do not alter the risk/benefit of Tamiflu which continues to be favourable. |
| IG/0311 | B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer | 28/06/2013 | n/a | | |

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| IB/0104 | B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products | 30/05/2013 | n/a | | |
| IB/0103/G | This was an application for a group of variations.<br><br>B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products<br>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place<br>B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation<br>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place | 18/03/2013 | n/a | | |
| IG/0228 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 23/11/2012 | n/a | | |
| II/0096 | Update of of section 4.9 of the SmPC to reflect available post-marketing safety data on overdose with Tamiflu. The Package Leaflet was proposed to be updated accordingly. | 15/11/2012 | 04/12/2013 | SmPC and PL | The MAH has performed a comprehensive analysis of all available data regarding overdose of Tamiflu. No unexpected tolerability issues were noted. The adverse events reported for patients having received an overdose were similar to |

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| | In addition, the MAH also took the opportunity to reflect the renewal date in the SmPC.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | adverse events reported with the normal dosage. There was no dose-response relationship between occurrence of ADRs and the amount of overdose. In addition, the analysis of the reported actions after overdose did not reveal any specific action that could be recommended to be followed after overdose to decrease or prevent ADRs.<br>The changes proposed by the MAH in the PI were endorsed.<br>The changes proposed by the MAH in the PI are endorsed. However the CHMP requested mentioning that overdose has been observed more frequently in children in order to alert Health Care Professionals and parents to exercise caution in administration of Tamiflu to children. The benefit/risk of Tamiflu remains positive. |
| A20/0093 | Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 15 December 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the manufacturing site Roche Carolina Inc. (RCI), Florence, in the United States of America (USA), to assess the impact thereof on the risk-benefit balance of Tamiflu and to give its opinion whether the marketing authorisation of this product should be maintained, varied, suspended or withdrawn. | 19/07/2012 | 01/10/2012 | | Please refer to the assessment report :<br>EMEA/H/C/402/A-20/0093 |
| IA/0099 | B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes | 17/09/2012 | n/a | | |

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| | place | | | | |
| II/0094 | Update of section 4.8 of the SmPC based on a review of all adverse events data in the pooled clinical trials with Tamiflu performed by the MAH and line with the SmPC guideline, as requested by CHMP. The package leaflet is updated in accordance.<br><br>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH | 19/07/2012 | 10/09/2012 | SmPC and PL | The MAH performed a review of all adverse event data reported in the pooled, worldwide clinical trials that investigated the recommended dosage regimens of oral oseltamivir phosphate. Based on the results of the safety analysis, the following adverse events have been deleted from the product information because there was no causal relationship confirmed or suspected between the events and Tamiflu based on the safety data available: Influenza, nasal congestion, arthralgia, back pain, myalgia, dysmenorrhea, influenza like illness and diarrhoea have been deleted from the list of adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in adults and adolescents; Bronchitis, nasopharyngitis, upper respiratory tract infections, sinusitis, lymphadenopathy, asthma (including aggravated), epistaxis, pyrexia, diarrhoea and pneumonia have been deleted from the list of adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in children. In addition the frequencies of cough and nasal congestion have been updated to 'very common' and the frequency of dermatitis has been revised to 'uncommon'. Description of the studies included in the new pooled datasets has also been updated in the SmPC. The PL has been revised in accordance. |
| IG/0176 | A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS | 25/06/2012 | n/a | | |
| IA/0097 | B.II.b.2.a - Change to batch release arrangements | 18/06/2012 | n/a | | |

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| | and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place | | | | |
| R/0089 | Renewal of the marketing authorisation. | 15/03/2012 | 22/05/2012 | SmPC, Annex II, Labelling and PL | Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers that the risk-benefit balance of Tamiflu remains favourable and therefore recommends the renewal of the marketing authorisation with unlimited validity, subject to the conditions and obligations as laid down in Annex II to the product information. The MAH is requested to submit yearly PSURs unless otherwise specified by the CHMP. |
| IG/0161 | C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH | 14/03/2012 | n/a | | |
| IA/0092 | A.7 - Administrative change - Deletion of manufacturing sites | 11/01/2012 | n/a | | |
| IG/0115/G | This was an application for a group of variations.<br><br>B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer<br>B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer | 16/12/2011 | n/a | | |
| IG/0125 | C.I.9.i - Changes to an existing pharmacovigilance | 06/12/2011 | n/a | | |

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| | system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH | | | | |
| X/0085 | Addition of 6 mg/ml powder for oral suspension.<br><br>Annex I_2.(c) Change or addition of a new strength/potency | 22/09/2011 | 28/11/2011 | SmPC, Labelling and PL | |
| II/0088/G | This was an application for a group of variations.<br><br>Update of section 4.5 of the SmPC to include information on warfarin and rimantadine. The MAH also took the opportunity to update the details of the French local representative in the PL.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data<br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | 22/09/2011 | 03/11/2011 | SmPC and PL | The MAH provided the results of two clinical studies. Study WP21272 was an open-label, randomised 2-period crossover study to investigate the pharmacodynamics, pharmacokinetics, safety and tolerability of warfarin in combination with oseltamivir in 20 volunteers (18–45 years of age) stabilised on warfarin therapy. Study NP22770 was an open-label, multiple dose, randomised, three-period crossover study in 21 healthy subjects to evaluate the effect of co-administration of oseltamivir 75 mg twice daily and rimantadine 100 mg twice daily on the pharmacokinetic properties of oseltamivir and rimantadine. Based on the results from these two clinical studies performed by the MAH, the SmPC is updated to reflect that no pharmacokinetic interactions between oseltamivir have been observed when co-administering oseltamivir with rimantadine, or warfarin (in subjects stable on warfarin and without influenza). |
| II/0087 | Update of section 4.8 of the SmPC and section 4 of the PL to include new adverse reactions (influenza, sinusitis, herpes simplex, pyrexia, back pain, arthralgia, myalgia, and dysmenorrhoea) as per CHMP request following the assessment of PSUR 10. The MAH also takes the opportunity to make some changes | 22/09/2011 | 03/11/2011 | SmPC and PL | Following the CHMP request from the previous PSUR assessment, 8 new adverse drug reactions (ADRs) are included in the SmPC with the frequency 'common': arthralgia, influenza, back pain, myalgia, dysmenorrhea, pyrexia, herpes simplex, and sinusitis. In addition, the MAH provided an analysis of four larger pooled datasets including |

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| | in accordance with the SmPC guideline.<br><br>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH | | | | data from controlled clinical studies investigating Tamiflu for treatment and prophylaxis. The overall safety profile of Tamiflu is now based on data from 4624 adult/adolescent and 1480 paediatric patients treated with Tamiflu or placebo for influenza, and on data from 3533 adult/adolescent and 148 paediatric patients receiving Tamiflu or placebo for the prophylaxis of influenza in clinical trials. In these pooled datasets 6 ADRs have been identified and are also added with the frequency 'common': earache, nasopharyngitis, influenza like illness, pain in limb, nasal congestion, and sore throat. |
| IG/0092/G | This was an application for a group of variations.<br><br>C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV<br>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system | 08/08/2011 | n/a | | |
| II/0086 | Update of section 4.2 of the SPC with new dosing recommendations for Tamiflu as per CHMP request a) in renally impaired patients on dialysis treatment; b) in renally impaired patients with a creatinine clearance 10-30 ml/min and not on dialysis treatment and c) in renally impaired patients with a creatinine clearance 30-60 ml/min.<br><br>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article | 19/05/2011 | 23/06/2011 | SmPC | Based on clinical data from pharmacokinetics studies and modelling and simulation analysis on pharmacokinetics of oseltamivir in patients with varying degrees of renal function performed by the Marketing Authorisation Holder (MAH), section 4.2 of the SmPC is updated to include new dosing recommendations for the treatment and prevention of influenza for adults with moderate and severe renal impairment.<br>The recommended dose for hemodialysis patients is 30 mg after each hemodialysis session in the treatment of influenza and 30 mg after every alternate hemodialysis session in the |

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| | 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH | | | | prevention of influenza. For peritoneal dialysis patients, a 30 mg single dose is recommended in the treatment of influenza and a dosing regimen of 30 mg once weekly is considered appropriate in the prevention of influenza.<br>In addition, the data supported a lower dose of 30 mg once daily and 30 mg every second day for treatment and prophylaxis of influenza respectively, in patients with a creatinine clearance of 10-30 mL/min. With regards to patients with moderate renal impairment (creatinine clearance of 30-60 mL/min), the dose of 30 mg twice daily for treated patients and 30 mg once daily in prophylaxis of influenza are considered appropriate. |
| II/0084 | Update of section 4.8 of the SmPC to add "thrombocytopenia" as adverse reactions further to the assessment of a Clinical follow-up measure. Section 4 of the PL has been updated accordingly. The DDPS version number has also been removed from the Annex II.B as per recommendation from the EMA.<br><br>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH | 20/01/2011 | 21/02/2011 | SmPC, Annex II and PL | Following the assessment of the MAH response to PSUR 9 (PSU047) covering from 21 September 2008 to 20 September 2009 and the monthly PSR 13 covering January 2010, the CHMP requested the update of section 4.8 of the SmPC to include "thrombocytopenia".<br>A check of the Advent Global Safety Database on "thrombocytopenia" performed by the MAH during the evaluation did not show a report of "thrombocytopenia" in children less than 6 months of age. Therefore and in view of the data available for the time being, "thrombocytopenia" has been added in the PL only to 3 of the 4 age groups, namely: "Adults and adolescents (children aged 13 years and older)", "Children (aged 1 to 12 years)" and "Infants (aged 6 to 12 months)". |
| II/0081 | Update of section 3 and of Tamiflu capsules PL to provide improved instructions for the home preparation of Tamiflu extemporaneous mixture for paediatric patients, following assessment of a follow-up measure (FUM 061). Section for health care | 18/11/2010 | 20/12/2010 | SmPC, Annex II and PL | In the September 2009 CHMP meeting, the use of oseltamivir for the treatment and prevention of influenza was extended to include infants below 12 months of age during a pandemic influenza and issues on readability and appropriateness of the instructions for home preparation were raised. |

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| | professionals at the end of the PL has consequently been updated. The MAH took the opportunity of this variation to bring the annexes in line with QRD v7.3.1 template for all pharmaceutical presentations<br><br>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH | | | | Consequently, the type II variation II/81 was submitted in order to improve the instructions to prepare at home from Tamiflu capsules, the extemporaneous formulation for children.<br>A number of changes were proposed to the instructions and some additional procedures introduced in all Tamiflu capsules strengths. The improved instructions apply when dosing below and above 1 year old children. The section 3 of the PL now specifies this and also informs that more steps are needed in the preparation of doses to children below 12 months of age. . For children above 1 year but below 40 kg receiving 30 mg, 45 mg or 60 mg doses prepared from 75 mg capsules, preparation also requires more steps compared to dosing of full capsules of appropriate strength. |
| II/0082 | Update of the SmPC of the 12mg/ml oral suspension to warn that the formulation is not suitable for infants less than 1 yr of age, following assessment of FUM 66. The PL is being updated accordingly.<br><br>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH | 21/10/2010 | 26/11/2010 | SmPC and PL | During September 2009 CHMP meeting, the use of oseltamivir for the treatment and prevention of influenza was extended to include infants below 12 months of age during a pandemic influenza. At that time, accurate dosing of Tamiflu 12 mg/ml oral suspension could not be achieved based on volume and label strength.<br>The MAH committed then to provide the correct concentration of the powder for oral suspension and the correct dosing scheme as soon as possible. In December 2009 the MAH also committed to:<br>- provide a correct dosing table in section 4.2 of Tamiflu paediatric suspension SPC for children less than 1 year of age,<br>- investigate the use of an appropriate device to fit the small volume administered to children less than 1 year of age.<br>The update concerns section 4.2 of the SmPC to warn that Tamiflu 12mg/ml oral suspension formulation is not suitable |

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| | | | | | for infants less than 1 year of age since the syringe provided in the pack does not allow for appropriate dose adjustments and commercially available syringes (with ml markings) may lead to unacceptable dosing inaccuracies. In the absence of a suitable formulation for infants less than 1 year of age, a pharmacy compounded preparation based on Tamiflu capsules should preferentially be used.<br>This variation II/82 was then submitted to add warnings on the use of Tamiflu 12mg/ml oral suspension in children below 1 year of age. Additionnally, the PI has been updated to include a warning on the mild laxative effect of sorbitol, which dose have now been reflected in section 2 of the SmPC for Tamiflu 12mg/ml oral suspension. |
| II/0080 | Update of section 4.4 of the SmPC to add information on neuropsychiatry events following CHMP assessment of FU2 046.2. Section 4 of the PL is being updated accordingly.<br><br>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH | 21/10/2010 | 26/11/2010 | SmPC and PL | Following assessment of the Pandemic Safety Updates 10 and 11, and with reference to the documentation concerning the commitment from November 2009 to amend the SmPC in section 4.4 regarding neuropsychiatric events, the CHMP asked the MAH to update section 4.4 of the SmPC to highlight that neuropsychiatric events have been reported during administration of Tamiflu in patients with influenza, especially in children and adolescents, and therefore align this section with section 4.8 of the SmPC. Section 4 of the Package Leaflet have been updated accordingly. |
| IB/0083/G | This was an application for a group of variations.<br><br>B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary | 09/09/2010 | n/a | | |

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| | packaging, for non-sterile medicinal products<br>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place<br>B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions<br>B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits<br>B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits | | | | |
| II/0079 | Update of sections 4.1, 4.4 and 5.1 of the SmPC with new data concerning viral resistance to Oseltamivir. The MAH took this opportunity to correct a mistake in section 3 of the PL 45 mg.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | 20/05/2010 | 02/07/2010 | SmPC and PL | Following review of PSUR 8, the CHMP requested that the SmPC be updated with new information on the development of oseltamivir resistance. This type II variation application was submitted to include the requested information and concluded with the revision of sections 4.1, 4.4 and 5.1 of the SmPC. In addition the MAH took this opportunity to correct a mistake in section 3 of the PL 45 mg. |
| II/0077 | Update of the detailed description of the pharmacovigilance system (version 4.1). Annex II has been updated accordingly. In addition Annex II has been updated in line with the latest QRD template.<br><br>Update of DDPS (Pharmacovigilance) | 18/03/2010 | 27/04/2010 | Annex II | With this variation the MAH submitted a new version of the DDPS (core version 4.1) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. Consequently, Annex II has been updated with the new version number of the agreed core DDPS. In addition Annex II has been updated in |

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| | | | | | line with the latest QRD template. |
| II/0069 | Update of sections 4.2, 4.4, 4.8, 5.1 and 5.3 of the SPC with information on the prophylaxis of immunocompromised patients and safety information for the seasonal prophylaxis of children from 1 to 12 years of age. The PL has been updated accordingly. Additionally the MAH took the opportunity to change the instructions in the 45mg capsules PL to ensure more precise dosing when using a 3ml oral syringe compare to a 5ml oral syringe as stated previously.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 21/01/2010 | 15/03/2010 | SmPC and PL | In the context of a clinical follow-up measure, the MAH submitted this type II variation to add information on the prophylaxis of immunocompromised patients in Tamiflu product Information.<br>To support this variation, 2 clinical studies were submitted:<br>A prospective, randomised, double-blind, stratified (by transplant type, vaccination status, and age), multicenter trial of oseltamivir versus placebo for seasonal influenza prophylaxis for 12 weeks in immunocompromised adults and children of one year of age and older.<br>A prospective, non-randomised, open-label multicenter study to evaluate the safety of oseltamivir for seasonal influenza prophylaxis for 6 weeks in 52 children (1 to 12 years of age) considered at risk for infection or having susceptible individuals in their household.<br>The CHMP agreed that the data on the prophylactic use of oseltamivir in immunocompromised could be reflected in Tamiflu Product Information, but it should be clearly pointed out that no significant difference could be obtained between the Tamiflu and the placebo groups in this patient population. Consequently, the efficacy of Tamiflu in this population remains uncertain. |
| IB/0078 | C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH | 11/03/2010 | n/a | PL | |
| II/0076 | Update of section 4.4 of the SPC to add information on the treatment of premature infants. | 17/12/2009 | 20/01/2010 | SmPC | In September 2009 CHMP meeting, the use of oseltamivir for the treatment and prevention of influenza was extended to |

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| | Update of Summary of Product Characteristics | | | | include infants below 12 months of age during a pandemic influenza. The question of the use of Tamiflu in preterm infants was raised during the discussions concerning newborns. In order to address the issue of this very specific population, the MAH submitted in November 2009 a type II variation to add information on the use of Tamiflu in premature infants in the SPC. The MAH has shown that there are too few data which a meaningful dosing recommendation for the preterm infants could be based on. In view of the lack of data concerning the use of Tamiflu in preterm infants, there is a need to add in the product information a warning for this very specific population until more data are made available by the MAH and evaluated by the CHMP. |
| IB/0074 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 26/11/2009 | n/a | | |
| IB/0072 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 03/11/2009 | n/a | | |
| II/0071 | Update of section 4.2 of the SPC to provide instructions to prepare home and pharmacy extemporaneous formulations from Tamiflu capsules. Dosing recommendations from the extemporaneous formulations for children under 1 year of age have also been included. The PL has been updated accordingly.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 24/09/2009 | 23/10/2009 | SmPC and PL | The MAH submitted some preliminary data from a study being conducted in Europe to test mixing and dosing instructions from an extemporaneous solution prepared from Tamiflu 30, 45 and 75mg capsules. This mixing and dosing study has been performed in the UK (United Kingdom) and is being conducted in Germany. This variation has been submitted to give instructions to prepare extemporaneous solutions at home and in a pharmacy from Tamiflu capsules. Additionally, dosing recommendations from the extemporaneous solution have been included for children under 1 year of age. |

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| II/0070 | Extension of the therapeutic indication to include treatment of children between 0 and 6 months of age and prophylaxis for children less than 1 year of age in case of pandemic influenza following the assessment of data falling under the frame of the Article 45 of the Paediatric Regulation (No 1901/2006) and further to the Article 5(3) procedure dated May 2009. The PL has been updated accordingly.<br><br>Extension of Indication | 24/09/2009 | 23/10/2009 | SmPC and PL | Please refer to the Scientific Discussion: Tamiflu-H-C-402-II-70 |
| IA/0073 | IA_28_Change in any part of primary packaging material not in contact with finished product | 19/10/2009 | n/a | | |
| II/0065 | To extend the shelf-life of Tamiflu 75 mg, 45 mg and 30 mg hard capsules from 5 to 7 years and to change the storage conditions from "This medicinal product does not require any special storage condition" to "Do not store above 25 °C". As a result of the above changes the hard capsules specifications with regard to the degradation products, assay and dissolution have been revised.<br><br>Quality changes | 29/05/2009 | 14/09/2009 | SmPC, Labelling and PL | |
| II/0068 | Extension of the therapeutic indication to include treatment of children between 6 and 12 months of age in case of pandemic influenza following the assessment of data falling under the frame of the Article 45 of the Paediatric Regulation (No 1901/2006) and further to the Article 5(3) procedure dated May 2009. The PL has been updated accordingly. | 23/07/2009 | 09/09/2009 | SmPC and PL | Please refer to the Scientific Discussion: Tamiflu-H-C-402-II-68. |

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| | Update of Summary of Product Characteristics and Package Leaflet | | | | |
| II/0067 | Update of section 4.6 and 5.3 of the SPC to include information concerning pregnancy and lactation following Article 5(3) procedure of Regulation (EC) No 726/2004. Section 2 of the PL has been updated accordingly. The MAH took this opportunity to amend editorial mistakes in the Labelling and PL.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet | 23/07/2009 | 09/09/2009 | SmPC, Labelling and PL | In the framework of this Article 5(3) procedure finalised on 7 May 2009, the MAH submitted an overview of 232 cases with maternal exposure to oseltamivir, including 12 cases with a foetal outcome of birth defect/other disorder. The overall data assessed at that time suggested that the benefit of using Tamiflu in pregnant or breastfeeding women outweighs the risk in the context of a novel influenza (H1N1) in a pandemic situation. Assessment of the data can be found in the assessment report published at the following address: http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/28766209en.pdf.<br>During its plenary meeting held in June 2009, the CHMP was of the opinion that the Tamiflu Product Information must be updated to include information concerning pregnancy and lactation and that according to the data available Tamiflu could be used in pregnant and breastfeeding women for circulating influenza virus and not only in the context of a novel influenza (H1N1) in a pandemic situation.<br>Consequently sections 4.6 and 5.3 of the SPC, as well as section 2 of the PL have been updated. |
| IB/0066 | IB_17_a_Change in re-test period of the active substance | 22/07/2009 | n/a | | |
| II/0062 | Update of section 5.3 of the SPC in order to amend the data related to brain penetration in juvenile rats.<br><br>Update of Summary of Product Characteristics | 18/12/2008 | 26/01/2009 | SmPC | The MAH submitted the final report of an oral toxicity study of Tamiflu in juvenile rats assessing behavior, histopathology, and brain penetration after oral administration of oseltamivir prodrug. The main goal of the new study was to examine |

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| | | | | | whether behavioral biomarkers could be identified for toxicity/lethality that was observed in previous juvenile rat toxicity studies; in addition, histopathological examinations of brains were made and brain levels of oseltamivir were measured. The results of this study together with the recalculation of brain concentrations of oseltamivir phosphate (prodrug) and oseltamivir carboxylate (active metabolite) from a pharmacokinetics and toxicity study after a single oral administration of the prodrug to juvenile rats showed lower brain penetration than previously reported and lead to the update of the data related to brain penetration in juvenile rats in section 5.3 of the SPC. This update to section 5.3 of the SPC does not change the overall risk benefit assessment for the use of oseltamivir in the treatment and prophylaxis of influenza and does not change the indication of Tamiflu and children under age of 12 months remain not included in the currently approved indication. |
| II/0061 | Update of section 4.2 of the SPC to provide instructions on the extemporaneous preparation of liquid formulations of Tamiflu using the contents of the 30mg, 45mg and 75mg capsules. Minor changes have also been made to section 5.1 of the SPC to provide clarification to the wording regarding resistance. Section 3 of the PL has been updated accordingly.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 18/12/2008 | 26/01/2009 | SmPC and PL | Tamiflu powder for oral suspension was developed and is approved and commercialised in the EU for children above 1 year of age and adults who cannot swallow capsules. This formulation has a shelf life of 24 months and it is anticipated that limited availability of this formulation may occur specifically in emergency situations such as an influenza pandemic or more simply when supplies of the oral suspension are not available. Development activities were undertaken to explore the feasibility of preparing extemporaneous formulations at home by the patient, parent or guardian using readily available sweetened food products to mask the bitter taste of the capsule content.<br>This type II variation (II/61) was submitted to provide instructions in the SPC and the PL on how this liquid |

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| | | | | | extemporaneous preparation should be made using the 30 mg, 45 mg and 75 mg capsules of Tamiflu.<br>As part of the dossier submitted to support this type II variation, the MAH also submitted an updated Risk Management Plan including new information on the extemporaneous use of capsules. |
| IB/0063 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 14/11/2008 | n/a | | |
| IA/0064 | IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer | 10/11/2008 | n/a | | |
| II/0060 | Update of section 4.8 of the SPC, with safety information concerning neuropsychiatric events, following the CHMP assessment of a pharmacovigilance follow-up measure. Section 4 of the PL was updated accordingly.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 25/09/2008 | 31/10/2008 | SmPC and PL | An analysis of neuropsychiatric adverse events reported in patients with influenza receiving oseltamivir showed that events like convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares) have been reported and in a very few cases resulted in accidental injury (such as falls), in some instances with fatal outcome. The neuropsychiatric events were reported more frequently in children and adolescents and often had a rapid start and rapid resolution. Although neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir, presently the contribution of oseltamivir to these events is not known. The product information was therefore updated with these data. |
| II/0059 | Update of section 4.8 of the SPC to include information on visual disturbance and cardiac arrhythmia following the assessment of a follow-up measure on the review of the Marketing Authorisation Holder (MAH)'s safety database. The PL has been amended accordingly. The | 24/07/2008 | 03/08/2008 | SmPC and PL | Based on the submission of information on eye and cardiac disorder as part of Periodic Safety Update Reports and follow-up measures, the SPC and the PL have been updated to include visual disturbances and cardiac arrhythmia (heart rhythm abnormalities) as undesirable effects of Tamiflu for |

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| | MAH took the opportunity to correct the Portuguese annexes.<br><br>Update of Summary of Product Characteristics and Package Leaflet | | | | adults, adolescents and children. |
| II/0056 | Update of section 4.8 of the SPC with all adverse drug reactions form clinical trials, post-marketing studies and spontaneous reports in line with the SPC guideline, as requested by the CHMP at the time of the renewal. The PL is updated accordingly.<br><br>Update of Summary of Product Characteristics | 30/05/2008 | 07/07/2008 | SmPC | Further to the renewal of the marketing authorization of Tamiflu, the MAH was requested to submit a type II variation to update the SPC section 4.8 and, as relevant the PL to be in line with the SPC guideline. In particular, all adverse reactions from clinical trials, post-marketing studies and spontaneous reports attributed to Tamiflu should be presented in a single table according to the MedDRA system organ class (SOC) and within each SOC by frequency categories.<br>A single table for adults/adolescents and a separate for children 1-12 years of age displaying data derived across clinical studies and per therapeutic indication are included in the SPC. Additional adverse reactions observed during post marketing surveillance and for which no frequency could be determine based on the available studies are included in a separate heading section. Section 4 of the PL is updated accordingly. |
| II/0057 | Update of section 5.1of the SPC with new data concerning viral resistance to oseltamivir. The PL has been updated accordingly. The details of the local representatives in Estonia and Finland have been also updated.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 24/04/2008 | 18/06/2008 | SmPC and PL | Section 5.1 of the SPC has been updated with data on reduced sensitivity of viral neuraminidase to describe both the rate of phenotypic and genotypic resistance in adults and in children aged 1-12 years as well as with data on resistance to oseltamivir in H5N1 viruses. It has been emphasized in the same section of the SPC that the emergence of resistance may be higher in young children and in children who had immunosuppression. |

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| | | | | | During the assessment of this variation application, agencies within Europe were made aware that new emergence evidence of resistance to oseltamivir in H1N1 viruses has occurred within Europe during the flu season 2007/2008 in patients not treated with the drug. This new information has now been reflected in sections 5.1 of the SPC, not in precise numbers or as details of resistance mechanisms, since this information can vary with time. Consequently section 4.1 of the SPC has also been updated with general statements that consideration on the appropriate use of antiviral agents according the official guidance should be given. |
| IA/0058 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 20/12/2007 | n/a | | |
| IA/0055 | IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer | 26/11/2007 | n/a | | |
| II/0050 | Update of section 4.8 of the SPC with information post-marketing information on gastro-intestinal bleedings. The PL has been updated accordingly.<br><br>Update of Summary of Product Characteristics | 20/09/2007 | 24/10/2007 | SmPC | Further to the assessment of post-marketing data during the period covering 1 April 2005 to 30 September 2006, the MAH was requested to submit a type II variation to include gastrointestinal (GI) bleeding in the SPC section 4.8 and, as relevant, the PL. In July 2007, the MAH submitted it with analyses from its safety database with a cut-off date 23 March 2007. The review of post-marketing cases showed that a causal relationship cannot be completely excluded due to the absence of alternative explanations for a portion of the cases. The most reported ADRs were melaena (35%), haematochezia (18.9%). Therefore bleeding in the gastrointestinal tract has been included in section 4 of the PL. |
| X/0045 | Annex I_2.(c) Change or addition of a new strength/potency | 19/07/2007 | 19/09/2007 | SmPC, Labelling and | |

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| X/0044 | Annex I_2.(c) Change or addition of a new strength/potency | 19/07/2007 | 19/09/2007 | SmPC, Annex II, Labelling and PL | |
| II/0049 | Update of section 4.8 of the SPC to add information on fulminant hepatitis and hepatic failure following the assessment of a safety review of hepatic reactions submitted as a pharmacovigilance follow-up measure as requested by the CHMP on 2 May 2007. Section 4 of the PL has been updated accordingly.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 19/07/2007 | 13/09/2007 | SmPC and PL | At the end of 2006, 7 cases of fulminant hepatic failure had been received in total at the EMEA, 3 of which were fatal. The MAH was requested to provide a cumulative safety review of all available data on serious hepatic disorders including all cases reports with a fatal outcome where Tamiflu was involved in order to complete the assessment. The data were received in February 2007 and assessed within the frame of the Tamiflu first five years renewal procedure. The CHMP concluded that a causal relationship between oseltamivir and severe hepatic disorder including fatal fulminant hepatitis/hepatic failure could not be excluded, especially in patients with a pre-existing liver disease. The MAH submitted this type II variation to update the SPC and the PL accordingly. |
| IB/0048 | IB_42_b_Change in storage conditions of the finished/diluted/reconstituted product | 10/07/2007 | n/a | SmPC, Labelling and PL | |
| R/0040 | Renewal of the marketing authorisation. | 26/04/2007 | 29/06/2007 | SmPC, Annex II, Labelling and PL | |
| IB/0047 | IB_33_Minor change in the manufacture of the finished product | 24/05/2007 | n/a | | |
| IB/0046 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 24/05/2007 | n/a | | |

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| II/0043 | Update of section 4.8 of the Summary of Product Characteristic to include Neuropsychiatric disorders, cough and vertigo as requested by the CHMP on 21 September 2006 further to the assesment of PSUR 5 (covering period 1 April 2005 - 31 March 2006). The Package Leaflet has been updated accordingly. The local representatives for Bulgaria and Romania were also added in the Package Leaflet.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 22/02/2007 | 28/03/2007 | SmPC and PL | Following the request of the CHMP after assessment of the PSUR 5, the MAH submitted a safety report of all the neuropsychiatric disorders since the introduction worldwide of the product. The appropriate wording is now included in the relevant section 4.8 of the SPC. Further more the adverse events of "cough" and "vertigo" are added in the section 4.8 to aligning the SPC to the Core Data Sheet. |
| IB/0042 | IB_10_Minor change in the manufacturing process of the active substance | 08/01/2007 | n/a | | |
| IB/0041 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 08/01/2007 | n/a | | |
| IA/0039 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 31/10/2006 | n/a | Annex II and PL | |
| IA/0038 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site<br>IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms | 09/10/2006 | n/a | | |
| IB/0037 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 06/10/2006 | n/a | | |
| IB/0036 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 06/10/2006 | n/a | | |

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| IB/0035 | IB_10_Minor change in the manufacturing process of the active substance | 06/10/2006 | n/a | | |
| IB/0034 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 13/09/2006 | n/a | | |
| IB/0033 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 13/09/2006 | n/a | | |
| IB/0032 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 25/08/2006 | n/a | | |
| IB/0030 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 25/08/2006 | n/a | | |
| IA/0031 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site | 01/08/2006 | n/a | | |
| IB/0028 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 30/06/2006 | n/a | | |
| IB/0027 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 30/06/2006 | n/a | | |
| IA/0029 | IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer | 29/06/2006 | n/a | | |
| IB/0026 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 23/06/2006 | n/a | | |

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| IB/0025 | IB_10_Minor change in the manufacturing process of the active substance | 10/03/2006 | n/a | | |
| IB/0023 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 10/03/2006 | n/a | | |
| IA/0024 | IA_01_Change in the name and/or address of the marketing authorisation holder | 15/02/2006 | n/a | SmPC, Labelling and PL | |
| II/0020 | Update of SPC in its Sections 4.1, 4.2, 4.4, 4.8 and 5.1 to include data to further extend the therapeutic indication for the prevention of influenza to children of 1-12 years. The Package Leaflet has been updated accordingly.<br><br>Extension of Indication | 14/12/2005 | 25/01/2006 | SmPC and PL | Please refer to the Scientific discussion: Tamiflu-H-402-II-20 |
| II/0021 | Update of section 4.8 of the SPC to include the adverse reactions "angioneurotic oedema" and "toxic epidermal necrolysis" following the CHMP assessment of PSUR covering the period from 01/04/2004 to 31/03/2005.<br><br>Update of Summary of Product Characteristics | 14/12/2005 | 20/01/2006 | SmPC | Further to a request from the CHMP, a cumulative assessment of severe skin reactions has been submitted within the PSUR covering the period from 01/04/2004 to 31/03/2005. The cumulative analysis showed 10 cases of angioneurotic oedema and 9 cases of toxic epidermal necrolysis . Therefore, the MAH proposal to add "angioneurotic oedema" and "toxic epidermal necrolysis" in the section 4.8 is in compliance with the CHMP request. |
| IA/0022 | IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer | 06/01/2006 | n/a | | |
| N/0019 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 13/09/2005 | n/a | Labelling and PL | |

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| IA/0018 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 26/05/2005 | n/a | | |
| IB/0017 | IB_37_a_Change in the specification of the finished product - tightening of specification limits | 25/05/2005 | n/a | | |
| IB/0016 | IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site | 01/04/2005 | n/a | | |
| II/0013 | Further to post-marketing surveillance.<br><br>Update of Summary of Product Characteristics | 20/01/2005 | 23/02/2005 | SmPC | Update of SPC Sections 4.2 "Posology and method of administration" and 4.4 "Special warnings and precautions for use" further to the assessment of the PSUR covering the period 01.04.2003 - 30.09.2003.<br><br>Sections 4.2 and 4.4 of the SPC was updated after the sentence "The safety and efficacy of Tamiflu in children less than one year of age have not been established " to include a cross reference to section 5.3 where information relating to the results of a toxicological and toxicokinetic study in 7-42 days old rats are mentioned.<br><br>These findings led to the cancellation of a planned pharmacokinetic study in infants (age < 12 months), which is already reflected in the sections 4.2 and 4.4 of the SPC. |
| IA/0015 | IA_13_a_Change in test proc. for active substance - minor change | 28/01/2005 | n/a | | |
| IB/0014 | IB_42_a_01_Change in shelf-life of finished product - as packaged for sale | 03/12/2004 | n/a | SmPC | |
| N/0012 | Minor change in labelling or package leaflet not | 27/09/2004 | n/a | PL | |

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| | connected with the SPC (Art. 61.3 Notification) | | | | |
| IB/0011 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 29/04/2004 | n/a | | |
| IB/0010 | IB_42_a_01_Change in shelf-life of finished product - as packaged for sale | 22/03/2004 | n/a | SmPC | |
| IB/0009 | IB_17_a_Change in re-test period of the active substance | 22/03/2004 | n/a | | |
| II/0008 | Further to the assessment of data from a pre-clinical study.<br><br>Update of Summary of Product Characteristics | 25/09/2003 | 27/01/2004 | SmPC | The SPC was updated in its section 5.3 " Preclinical safety data" including results of a two-week study in unweaned rats. |
| II/0005 | Further to new pre-clinical and clinical safety data.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 24/07/2003 | 07/11/2003 | SmPC, Labelling and PL | The SPC has been updated in its section 4.8 "Undesirable effects" by adding:<br>- "dermatitis, rash, eczema, urticaria, hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, as well as very rare reports of severe skin reactions, including Steven-Johnson Syndrome and erythema multiforme"<br>- and "hepatic function disorders" further to new clinical safety data.<br>and in its section 5.3 "Preclinical safety data" by adding results from a two-year mouse carcinogenicity study .<br>The Package Leaflet was updated accordingly. The list of local representatives in the Package Leaflet was also updated. |
| I/0007 | 15_Minor changes in manufacture of the medicinal product | 12/06/2003 | 19/06/2003 | | |

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| I/0004 | 20a_Extension of shelf-life or retest period of the active substance | 18/12/2002 | 13/01/2003 | | |
| I/0001 | 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process | 13/09/2002 | 24/09/2002 | | |