23rd Expert Committee on the Selection and Use of Essential Medicines

Application for the deletion of Tamiflu® (oseltamivir) 12 mg/mL Powder for Oral Suspension from the WHO Model Lists of Essential Medicines

Submitted by
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1. **Summary statement of the proposal for inclusion, change or deletion.**

   F. Hoffmann-La Roche Ltd. (Hereafter referred to as Roche) proposes the deletion of Tamiflu (oseltamivir) 12 mg/mL Oral Powder from the WHO Model complementary List of Essential Medicines (EML) and Model complementary List of Essential Medicines for Children (EMLc) under the category of 6.4.3 Other Antivirals.

   Roche ceased manufacture and supply of the Tamiflu (oseltamivir) 12 mg/mL powder for oral suspension as of August 2016, the last commercial supply was in February 2017 (batch expired in August 2018) and is no longer marketed anywhere in the world. De-registration of Tamiflu (oseltamivir) 12 mg/mL powder for oral suspension in the European Union (EU) under European Medicines Agency (EMA) procedure EMEA/H/C/000402/IB/0143 was approved on 8 October 2019. Global de-registration is ongoing for Tamiflu (oseltamivir) 12 mg/mL powder for oral suspension. Generic versions of Tamiflu (oseltamivir) 12 mg/mL powder for oral suspension are no longer manufactured and marketed worldwide.

   Tamiflu (oseltamivir), in capsule (30, 45, 75 mg) and powder for oral suspension (12 mg/mL) formulations, was moved from the WHO "core" to the "complementary" list in 2019, and its use restricted to severe illness due to confirmed or suspected influenza virus infection in critically ill-hospitalised patients. Tamiflu (oseltamivir) capsules 30 mg; 45 mg and 75 mg will remain listed on the "complementary" EMLs.

   Labeling for Tamiflu (oseltamivir) capsules includes instructions for the preparation of an oral suspension using the content of 30, 45 or 75 mg capsules. Generic versions of the capsule formulations are available in many countries worldwide and can be used to make an oral suspension, if required.

2. **Name of the WHO technical department and focal point supporting the application (where relevant).**

   Not applicable

3. **Name of organization(s) consulted and/or supporting the application.**

   F. Hoffmann-La Roche Ltd.

4. **International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.**

   INN: oseltamivir phosphate
   ATC: J05AH02

5. **Formulation(s) and strength(s) proposed for inclusion; including adult and paediatric (if appropriate).**

   Roche proposes the deletion of Tamiflu (oseltamivir) 12 mg/mL powder for oral suspension from the WHO complementary EML and EMLc.

   Roche ceased manufacture and supply of the Tamiflu (oseltamivir) 12mg/mL powder for

oral suspension as of August 2016, the last commercial supply was in February 2017 (batch expired in August 2018) and it is no longer being marketed anywhere in the world.

6. **Whether listing is requested as an individual medicine or as representative of a pharmacological class.**

Oseltamivir, in capsule (30, 45 and 75 mg) and powder for oral suspension (12 mg/mL) formulations was moved from the "core" to the "complementary" list in 2019, and its use restricted to severe illness due to confirmed or suspected influenza virus infection in critically ill-hospitalised patients.

Oseltamivir capsules 30, 45 and 75 mg, not included in this application will remain on the WHO complementary EML and EMLc, and can be used to make an oral suspension, if required. Generic oseltamivir capsules, 30, 45 and 75 mg are also widely available in many countries worldwide.

7. **Treatment details (requirements for diagnosis, treatment and monitoring).**

Not applicable.

8. **Information supporting the public health relevance.**

Influenza is an acute respiratory infection caused by viruses of the orthomyxoviridae family. Influenza serotypes A and B infect humans and are responsible for an acute febrile infection of the respiratory tract characterized by the sudden onset of fever, malaise, headache, myalgia, and cough. Influenza is a seasonal illness, with epidemic infections occurring annually during cooler months. Influenza causes numerous deaths each year (Murphy and Webster 1996). Although difficult to assess, annual influenza epidemics are thought to result in between 3 and 5 million cases of severe illness and between 250,000 and 500,000 deaths every year around the world (WHO 2018, Iuliano et al. 2018).

Influenza infection in otherwise healthy (OwH) adults and adolescents is usually a self-limiting condition that is not associated with a high risk of secondary complications. However, in children, elderly, pregnant, chronically ill, and immunocompromised populations, influenza infection can be associated with substantial morbidity and mortality (Murphy and Webster 1996).

Tamiflu (oseltamivir phosphate), a neuraminidase inhibitor (NAI) is approved for the treatment of influenza in adults and children including full-term neonates, and the prevention of influenza in adults and children one year of age and older in many countries globally.

Since its first approval (in September 1999 in Switzerland), oseltamivir has been widely used throughout the world for the treatment of influenza infections. In a pooled analysis of all influenza-positive adults and adolescents (N = 2413) enrolled into treatment studies, use of oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately 1 day, from 5.2 days (95 % confidence interval [CI] 4.9,

5.5 days) in the placebo group to 4.2 days (95 % CI 4.0, 4.4 days; p ≤0.0001) in the oseltamivir group (Nicholson et al. 2000, Treanor et al. 2000). In a meta-analysis that included only patients with laboratory confirmed infection, the reduction in time to resolution of symptoms was more pronounced (97.5 hours for oseltamivir versus 122.7 hours for placebo, reduction of 25.2 hours, 95% CI: 36.2, 16·0 hours) (Dobson et al. 2015). In addition, a random effects meta-analysis of observational studies of oseltamivir treatment based on studies that provided adjusted effect measures found that oseltamivir may reduce mortality (odds ratio [OR]=0.23, 95% CI: 0.13, 0.43), hospitalization (OR=0.75, 95% CI: 0.66, 0.89), and duration of symptoms (33 hours [95% CI: 21, 45 hours]) compared with no treatment (Hsu et al. 2012).

Oseltamivir-associated benefit was also seen in a meta-analysis of data for 29,234 patients from 78 studies of patients admitted to hospital between 2009 and 2011, where 92% of patients received oseltamivir and 38% had at least 1 comorbid condition (Muthuri et al. 2014). Compared with no treatment, neuraminidase inhibitor treatment was associated with a 19% reduction in mortality risk (adjusted OR=0.81, 95% CI: 0.70–0.93). An even larger reduction in mortality risk (52%) was seen when treatment was initiated within 48 hours of symptom onset (adjusted OR=0.48 [95% CI: 0.41, 0.56]). A systematic review and meta-analysis by the same group failed to show a statistically significant association between neuraminidase treatment and no treatment, but a statistically significant association between early treatment (48 hours after symptom onset) and no treatment (OR=0.35 [95% CI: 0.18, 0.71]) as well as early treatment and treatment initiated > 48 hours after symptom onset (OR, 0.38 [95% CI: 0.27, 0.53]) was seen. (Muthuri et al. 2013).

In the case of patients with chronic illness complicating influenza infection, several observational studies have reported benefit associated with oseltamivir treatment. A retrospective cohort study in patients with diabetes (Orzeck et al. 2007) reported an OR of 0.83 (95% CI: 0.73, 0.93) for the risk of respiratory illness and an OR of 0.70 (95% CI: 0.52-0.94) for the risk of hospitalization for any reason in the 14 days after onset of influenza. In another study of patients with pre-existing cardiovascular disease the incidence of recurrent cardiac events within 30 days after influenza diagnosis was significantly reduced in treated patients (OR, 0.42 [95% CI: 0.35, 0.50]) (Casscells et al. 2009). Furthermore, treatment with oseltamivir was associated with a 51% reduction in the risk of stroke or transient ischemic attack within 30 days after influenza in adults older than 65 years (Madjid et al. 2009).

Since its first approval, Tamiflu has been extensively used in both clinical trial and clinical practice settings. As of 20 September 2020, an estimated 10,036 patients had received oseltamivir via clinical trial participation while post-marketing exposure to oseltamivir was approximately 220 million patients. Oseltamivir has therefore been very widely used and its safety profile is well established.

Generic versions of Tamiflu capsules 30, 45 and 75 mg are widely available in many countries worldwide and can be used to make an oral suspension, if required. Tamiflu capsules, 30, 45 and 75 mg are not included in this application and will remain on the WHO complementary EML and EMLc. Other antiviral NAIs zanamivir and peramivir approved worldwide for the treatment of influenza. Baloxavir marboxil, an antiviral polymerase acidic endonuclease inhibitor, is also approved for the treatment of influenza.

Roche has a long heritage in developing medicines that contribute to public health and are committed to bringing innovation to the field of infectious diseases including influenza. We will strive to address unmet needs in influenza to help people live better lives and continue to support WHO and governments pandemic preparedness efforts by contributing to WHO's Pandemic Influenza Preparedness (PIP) Framework.

9. Review of benefits: summary of comparative effectiveness.

The key benefits of oseltamivir are reduced mortality, reduced illness duration and complications, reduced length of hospitalization when used to treat influenza. In addition there is reduced probability of developing influenza illness when used in influenza prevention, typically with a protective efficacy of 70 - 90%. Tamiflu (oseltamivir) capsules 30, 45 and 75 mg will remain on the WHO "complementary" EMLs, and can be used to make an oral suspension, if required.

Tamiflu (oseltamivir), in capsule and powder for oral suspension formulations was moved from the "core" to the "complementary" list in 2019, and its use restricted to severe illness due to confirmed or suspected influenza virus infection in critically ill-hospitalised patients.

10. Review of harms and toxicity: summary of evidence on safety.

Since its first approval (in September 1999 in Switzerland), Tamiflu has been extensively used in both clinical trial and clinical practice settings across the globe. As of 20 September 2020 an estimated 10,036 patients had received oseltamivir via clinical trial participation while post-marketing exposure to oseltamivir was approximately 220 million patients. Oseltamivir has therefore been very widely used and its safety profile is well established.

Based on clinical and post-marketing experience, Tamiflu has proven to be well tolerated at the recommended dosages. The most common side effects experienced with oseltamivir are nausea and vomiting. The gastrointestinal side effects tend to be restricted to the first one or two doses and can be minimized by administration with food.

11. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group.

Not applicable.

12. Summary of regulatory status of the medicine.

Global de-registration is ongoing for Tamiflu (oseltamivir) 12 mg/mL powder for oral suspension. Tamiflu (oseltamivir) 12mg/mL powder for oral suspension was de-registered in the European Union (EU) under European Medicines Agency (EMA) procedure EMEA/H/C/000402/IB/0143, approved on 8 October 2019.

Generic versions of the capsule formulations are available in many countries worldwide and can be used to make an oral suspension, if required.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

Not applicable.

14. Reference list.

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