PUBLIC SUMMARY DOCUMENT
Product: Oseltamivir, capsules 30 mg, 45 mg and 75 mg, powder for oral suspension, 12 mg per mL, Tamiflu®
Sponsor: Roche Products Pty Ltd
Date of PBAC Consideration: November 2008

1. Purpose of Application
To seek a Restricted Benefit listing for the treatment of infections due to influenza A and B viruses in adults and children aged one year and older. The submission also requested PBS listing in the Emergency Drug (Doctor's Bag) Supplies.

2. Background
This was the first time oseltamivir had been considered by the PBAC.

3. Registration Status
Oseltamivir 75 mg capsules were registered by the TGA on 13 September 2000. Oseltamivir powder for oral suspension was registered by the TGA on 5 June 2003. Oseltamivir 30 mg and 45 mg capsules were registered by the TGA on 8 August 2008.

All strengths and dosage forms are indicated for:
- the treatment of infections due to influenza A and B viruses in adults and children aged 1 year and older. Treatment should commence as soon as possible, but no later than forty-eight hours after the onset of the initial symptoms of infection.
- the prevention of influenza in adults and children aged 1 year and older. Vaccination is the preferred method of routine prophylaxis against infection with influenza virus.

4. Listing Requested and PBAC's View
Restricted Benefit
Treatment of infections due to influenza A and B viruses in adults and children aged one year and older. Treatment should commence as soon as possible, but no later than 48 hours after the onset of the initial symptoms of infection.

The submission also requested PBS listing in the Emergency Drug (Doctor's Bag) Supplies. The PBAC considered listing in the Doctor's Bag was not appropriate.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy
Oseltamivir provides a treatment option for patients with influenza.

6. Comparator
The submission nominated placebo as the comparator. PBAC accepted this as appropriate.

7. Clinical Trials
The submission presented 11 randomised trials comparing oral oseltamivir phosphate 75 mg twice daily for 5 days (or weight adjusted dose in children) with placebo in patients with influenza-like illness. The submission presented individual trial results and a meta-analysis.

The key pivotal trials published at the time of the submission are presented in the table below.

Trial/First author	Protocol title/Publication title	Publication citation
WV15670 Nicholson KG, et al.	Efficacy and safety of oseltamivir in treatment of acute influenza: A randomised controlled trial.	*Lancet*, 2000; 355(9218): 1845-1850
WV15671 Treanor JJ, et al.	Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: A randomised controlled trial.	*Journal of the American Medical Association* 2000; 283(8): 1016-1024
Li, et al. (2003)	A double-blind, randomised, placebo controlled multicentre study of oseltamivir phosphate for treatment of influenza infection in China.	*Chinese Medical Journal* 2003; 116(1): 44-48
Kashiwagi et al (2000)	Clinical efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir in treating acute influenza – placebo-controlled double-blind multicentre phase III trial.	*Kansenshogaku Zasshi* 2000; 74(12): 1044-1061
Lin et al. (2006)	A multicentre, randomised, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population.	*Current Medical Research Opinion* 2006; 22(1): 75-82
WV15758 Whitley RJ, et al.	Oral oseltamivir treatment of influenza in children.	*Paediatric Infectious Diseases Journa*l 2001; 20(2): 127-133
WV15759/15871 Johnston SL, et al.	Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma.	*Paediatric Infectious Diseases Journal* 2005; 24(3): 225-232.

8. Results of Trials

The submission conducted a meta-analysis of the primary efficacy outcome (time to alleviation of symptoms (TTAS)) for both the ITT-I (intention-to-treat infected population) and the ITT (intention-to-treat) population, and presented time-to-event data as differences in medians.

The PBAC considered that the appropriate population for analysis was the ITT population, not the ITT-I population. The PBAC noted the results in the ITT population showed that oseltamivir treatment reduced symptoms on average by around 16.8 hours, and by slightly more in otherwise healthy adults, however with only otherwise healthy adults achieving statistical significance.

The results for the ITT-I population are summarised in the table below.

Time to alleviation of symptoms (TTAS) (hours) in the ITT-I population (influenza confirmed)

Trial	Treatment	N	Median (95% CI)	P-value
Otherwise healthy adults				
WV15670	Placebo Oseltamivir	161 157	116.5 (101.5, 137.8) 87.4 (73.3, 104.7)	0.02
WV15671	Placebo Oseltamivir	128 121	103.3 (92.6, 118.7) 71.5 (60.0, 83.2)	<0.001
Li *et al.* (2003)	Placebo Oseltamivir	139 134	95.0 (84.5, 105.3) 91.6 (80.2, 101.3)	0.0466

Trial	Treatment	N	Median (95% CI)	P-value
Kashiwagi *et al.* (2000)	Placebo Oseltamivir	130 121	93.3 (73.2, 106.2) 70.0 (53.8, 85.9)	0.0216
At-risk adults and the elderly				
Lin *et al.* (2006)	Placebo Oseltamivir	29 27	174.4 110.4	NR
Children				
WV15758	Placebo Oseltamivir	225 209	137.0 (125, 150) 101.0 (89, 118)	<0.0001
WV15759/15871	Placebo Oseltamivir	95 83	134.3 123.9	0.542

Abbreviations: CI = confidence interval; ITT-I = intention-to-treat-infected; NR = not reported.

The results of the meta-analysis of the TTAS data for the ITT-I population (influenza confirmed cases) showed that across all 11 trials (i.e. otherwise healthy adults, 'at-risk' and elderly adults, and children trials combined), treatment with oseltamivir was associated with a statistically significant reduction in TTAS compared with placebo.

However, the PBAC noted the results of the meta-analysis for the ITT-I population showed that in all children and in at-risk adults and the elderly, the use of oseltamivir did not statistically significantly reduce the median TTAS compared to placebo. The results of the meta-analysis for the ITT-I population showed that the use of oseltamivir in otherwise healthy adults significantly reduced the median TTAS compared to placebo.

For the secondary efficacy outcomes, the analyses presented in the submission were only for the ITT-I population, which the PBAC considered less applicable to the population to be treated under the requested restriction. The results were mixed and generally inconsistent. In the case of 'antibiotic use for secondary illness' the results of the meta-analysis for the ITT-I population showed that oseltamivir statistically significantly reduced the risk of requiring antibiotics for secondary illnesses in 'all children' and 'at-risk adults and the elderly' but not in 'otherwise healthy adults'. In the case of 'bronchitis requiring antibiotics' the results of the meta-analysis for the ITT-I population showed that oseltamivir reduced the risk of requiring antibiotics in patients with bronchitis in 'otherwise healthy adults' but not in 'all children' or in 'at-risk adults and the elderly'. Similar mixed results were observed across all of the other secondary efficacy outcomes. The PBAC noted that there was no firm evidence that oseltamivir treatment reduced the risk of hospitalisation or the incidence of secondary illness.

The most frequently reported adverse events (AEs) in the key trials were gastrointestinal disorders including nausea, vomiting and diarrhoea. In general, nausea and vomiting occurred more frequently in subjects treated with oseltamivir, whereas diarrhoea occurred more frequently in subjects treated with placebo. The submission also presented an extended assessment of comparative harms, referring to long-term safety data obtained from the oseltamivir Periodic Safety Update Report (PSUR no. 1025973).

The PBAC was concerned at the adverse events associated with oseltamivir, particularly as a substantial number of patients with influenza-like illness are likely to be prescribed this drug.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that oseltamivir phosphate is superior in terms of comparative effectiveness and similar in terms of comparative safety over standard care (no antiviral treatment). The PBAC considered that based on the evidence presented in the submission, this claim was not reasonable.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A stepped economic evaluation was presented for three patient cohorts – healthy adults (aged 13-64 years), at-risk adults and the elderly, and children (aged 1-12) – and the three patient cohorts combined (weighted by the proportion of laboratory-confirmed notifications of influenza in Australia by age).

The model followed patients who present to their GP with influenza-like illness (ILI). Patients in the oseltamivir arm who consult their doctor within 48 hours of the onset of symptoms receive oseltamivir; those with ILI, but not influenza are assumed to receive no benefit from oseltamivir treatment. In both arms of the model, patients who are influenza positive may develop pneumonia, bronchitis, or otitis media or have no further complications. Patients with complications have a risk of hospitalisation. All influenza positive patients have a risk of influenza-related mortality. All patients have a risk of all-cause mortality. Oseltamivir-treated patients are assumed to have a lower risk of bronchitis, pneumonia, antibiotic use, otitis media (children only), hospitalisations and influenza-related mortality.

The weighted incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained for the combined patient cohorts estimated in the model was less than $15,000.

11. Estimated PBS Usage and Financial Implications

The financial cost to the PBS was estimated to be less than $10 million per year. The PBAC considered the estimate was likely to be highly uncertain.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC noted that there were a number of issues with the requested listing and clinical place of oseltamivir. Although the wording requested is consistent with the TGA approved indication for treatment of influenza, oseltamivir is also TGA approved for prophylaxis. Also the diagnosis of influenza is usually made on clinical grounds and no diagnostic tests are usually performed to confirm the diagnosis, a view confirmed in the submission to the PBAC from the Influenza Specialist Group (ISG). There are likely to be a large number of presentations for influenza-like-illness that are not actually influenza. In addition, treatment is only effective if people commence treatment within 48 hours of onset of symptoms. The existence of all these factors means that there is a high potential for the drug to be used outside the restriction and thus in a manner for which there is no evidence of clinical or cost-effectiveness.

The PBAC noted that the sponsor proposed mitigating some of this risk by limiting reimbursement to months of May to October, but the Committee did not accept that such a restriction was workable or clinically appropriate. PBAC also considered that an authority

restriction was not suitable and agreed with RWG and DUSC Advices that listing in the Doctor's Bag was not appropriate.

PBAC agreed with the ESC that the analysis using the intention to treat (ITT) population was the most appropriate. The evidence presented showed oseltamivir was effective in shortening illness duration by 16.8 hours on average; however, benefits were principally seen in 'otherwise healthy' adults and children. The benefit of reducing symptoms of influenza was statistically significant in 'otherwise healthy' adults only, with reductions in symptoms for 'at risk' adults not achieving statistical significance. PBAC did however note that NICE in the UK had recommended subsidising oseltamivir in 'at risk' populations. A listing for patients at high-risk of influenza complications was also supported by the ISG.

The secondary outcomes were only presented for the intention-to-treat-proven influenza population which PBAC considered less applicable to the population likely to be treated under the requested restriction. The PBAC noted the intention-to-treat-proven influenza (ITT-I) analysis results were mixed and generally inconsistent, with benefits principally seen in 'otherwise healthy' adults with confirmed influenza, while efficacy in 'at risk' adults and children was not convincingly demonstrated. It was accepted that there was some reduction in use of antibiotics, but perhaps more importantly no change in hospitalisation rates, or in the incidence of secondary illnesses.

The PBAC was concerned at the adverse events associated with oseltamivir, particularly as a substantial number of patients with influenza-like-illness are likely to be prescribed this drug. It was noted that the adverse events reports are difficult to definitely associate with oseltamivir for example neuropsychiatric events have also been reported in patients with influenza who have not taken oseltamivir.

The extent to which resistance to oseltamivir is developing is uncertain. The sponsor's monitoring of resistance was noted. The uncertainty about developing resistance in various influenza virus subtypes (discussed by sponsor and ISG) was also considered. PBAC agreed with ESC that there is a potential public health issue associated with increasing environmental exposure and the implications for effective treatment in the event of a future pandemic remain uncertain.

The PBAC considered that there were significant uncertainties in the economic model and that these had been well captured in the ESC advice. For example, the model included non-significant results (such as reductions for complications and reduced hospitalisations). Therefore, the stepped economic evaluation should not have included certain steps, and a more reasonable base case might have been derived at an earlier step. However, the ICER is also highly uncertain because of the assumptions in the model that only patients with symptoms of less than 48 hours will be treated. The PBAC noted that previous research by O'Brien has demonstrated that the cost effectiveness of oseltamivir is highly sensitive to the percentage of patients who receive oseltamivir greater than 48 hours after onset of symptoms. The model did not adequately deal with patients who start taking oseltamivir more than 48 hours after onset of symptoms, or how prevalence in practice might differ from that in the trials.

The PBAC agreed with the DUSC that the financial estimates were highly uncertain and that the true number of presentations to general practitioners was influenced by health system

capacity and the fluctuations in influenza. In addition, there is a risk of prescribers providing prescriptions for prophylaxis, or 'just in-case' which adds additional uncertainty to the numbers of prescriptions dispensed.

Therefore, the PBAC rejected the submission on the grounds of uncertain cost-effectiveness, uncertainty about the clinical benefit in all groups, concern about the use in a way that is not intended in the restriction, potential for toxicity and the uncertain impact on resistance patterns in influenza viruses.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no further comment.