1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
   Yes ☑ No
   The Application lists only randomized clinical trial data obtained from the manufacturer’s trials in mainly adults with influenza like illness and dismisses the observational studies and ecological data from the pandemic conditions.
   The Application rests on the assumption that the manufacturer’s failure to provide all relevant clinical data might be a sufficient reason to withhold the treatment from patients, whatever the circumstances.
   While such rigor is commendable under usual clinical care circumstances, efforts need to be undertaken to make the best use of all available data in decision-making in the situations like the recent pandemic to avoid harming patients due to the inability of the manufacturer to provide data with the usual seal of scientific quality. At the same time, possible and frequently seen bias in the use of the observational data in the efficacy evaluation has to be kept in mind.
   The reasons why the trial data has not been obtainable during the pandemic have been discussed in a more balanced editorial by Aoki FY and and Hayden FG (J Infect Dis. (2013) 207(4): 547-549; doi:10.1093/infdis/jis727), a systematic review and meta-analysis of the observational data collected during the 2009-10 influenza A(H1N1) pandemic has been published in the same journal (Muthuri SG, Myles PJ, Venkatesan S, Leonardi-Bee J, Nguyen-Van-Tam J. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009-10 influenza A (H1N1) pandemic: a systematic review and meta-analysis in hospitalised patients. J Infect Dis. (2012) doi: 10.1093/infdis/jis726).

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
   The Cochrane Review of RCT-s in influenza like illness (where the placebo group hospitalization rate was 0.84%) concludes that currently there is insufficient evidence that oseltamivir reduces the risk of serious complications from influenza.
   Other efforts to summarise the RCT data in these patients have reached different conclusion, notably a meta-analysis funded by the manufacturer (Keiser L et al, 2003) and an independent reanalysis of 11 randomized clinical trials by Hernan (Hernan MA, Lipsitch M. Oseltamivir and Risk of Lower Respiratory Tract Complications in Patients With Flu Symptoms: A Meta-analysis of Eleven Randomized Clinical Trials. Clin. Infect. Diseases; doi: 10.1093/cid/cir400) in which oseltamivir treatment was shown to reduce the risk of lower respiratory tract complications requiring antibiotic treatment by 28% overall (95% CI, 11%–42%) and by 37% among patients with confirmed influenza infections (95% CI, 18%–52%).

   c. Please provide any additional relevant information with reference

Deletion of Oseltamivir
A recent review and meta-analysis (Muthuri et al) of observational data from 90 studies (80 reported exclusively laboratory confirmed diagnoses) trying to assess the impact of neuraminidase inhibitor treatment on severe outcomes in hospitalized patients during the 2009–2010 Influenza A(H1N1) pandemic. There was a nonsignificant reduction in mortality associated with NAI treatment (at any time) versus none, OR, 0.72 (95% CI, 0.51 to 1.01), a significant reduction for early treatment (≤ 48 hours after symptom onset) versus late, OR, 0.38 (95% CI, 0.27 to 0.53) and for early treatment versus none, OR, 0.35 (95% CI, 0.18 to 0.71). NAI treatment (at any time) versus none was associated with an elevated risk of severe outcome (defined as receiving critical care or death), OR, 1.76 (95% CI, 1.22 to 2.54), but early versus late treatment reduced the likelihood, OR, 0.41 (95% CI, 0.30 to 0.56).

Most of the rest of the observational data were available during the latest EML discussion related to oseltamivir.

2. Assessment of safety
a. Have all relevant studies on safety been included
Yes ✓ No

In addition to the Cochrane review, a reference to a single safety study (Hama R et al. Oseltamivir and early deterioration leading to death: a proportional mortality study for 2009A/H1N1 influenza. Int J Risk Saf Med. 2011;23(4):201–215) is provided.

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
The finding brought to the Attention of the Committee by the Application reads:

Of 119 deaths after Tamiflu was prescribed, 38 deteriorated within 12 hours (28 within 6 hours), while of 15 deaths after Relenza, none deteriorated within 12 hours. Pooled OR for early deterioration and overall death were 5.88 (95% CI: 1.30 to 26.6, p = 0.014) and 1.91 (p = 0.031) respectively. Baseline characteristics including risk factors did not contribute to early deterioration after Tamiflu use. These data suggest Tamiflu use could induce sudden deterioration leading to death especially within 12 hours of prescription. These findings are consistent with sudden deaths observed in a series of animal toxicity studies, several reported case series and the results of prospective cohort studies.

c. Please provide any additional relevant information with reference

Good tolerability of oseltamivir has been reported overall. For example, the safety data from Hernan (above) provided the risk ratio of 1.46 (1.05–2.02) for nausea, 1.55 (1.14–2.12) for vomiting, .83 (.66–1.04) for diarrhea, 1.47 (1.05–2.04) for headache, and 1.02 (.72–1.44) for other neuropsychiatric disorders.

3. Assessment of cost and availability
a. Have all relevant data on safety provided
Not applicable for a proposal of deletion.

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

NA

Deletion of Oseltamivir
c. Please provide any additional relevant information with reference

NA

d. Is the product available in several low and middle income countries?

Yes

4. Assessment of public health need

a. Please provide the public health need for this product (1-2 sentences)

A product able to reduce the occurrence of severe negative clinical outcomes of influenza during an influenza pandemic is of utmost public health importance.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

Several international and national bodies (WHO, ECDC, US CDC, IDSA) recommend judicious use of the product within and outside of a pandemic (e.g. “empiric neuraminidase inhibitor treatment for all persons with suspected or confirmed 2009 H1N1 virus infection who are at increased risk for influenza complications or “all persons with laboratory-confirmed disease or highly suspected influenza virus infection who are at high risk for developing complications receive treatment, when treatment can begin within 48 hours after symptom onset”).


5. Are there special requirements for use or training needed for safe/effective use?

If yes, please provide details in 1-2 sentences

No.

6. Is the proposed product registered by a stringent regulatory authority?

Yes ✓ No

7. Any other comments

8. What is your recommendation to the committee (please provide the rationale)

Not to delete, keep the conditions for use in line with the WHO up to date guidance on the management of influenza. The totality of data provides a reasonable assurance of the efficacy of the timely administration of oseltamivir A in persons at high risk for developing complications. This conclusion is in line with the interpretation of the available data by several international and national bodies providing guidance on the treatment of infectious diseases.