Consolidated stakeholder feedback

A clinical evidence synthesis protocol

«Oseltamivir, baloxavir marboxil and zanamivir to treat or prevent influenza A and B»

Stakeholders (SH; in alphabetical order) that have provided comments:

1	Wirtschaftliche Landesversorgung (WL); Fachbereich Heilmittel; Schifferli Jürg A.
2	F. Hoffmann-La Roche AG
3	GlaxoSmithKline AG

SH	SH comment	Reply authors / BAG & implemented changes
1	Allgemein: Die WL begrüsst die geplante Studie zur klinischen Evidenzsynthese basierend auf dem Kriterium der Wirtschaftlichkeit. Bei allen Überlegungen zum Thema "Lagerhaltung Tamiflu oder anderer Neuraminidase Hemmer" muss der Fokus auf der Wirtschaftlichkeit und Finanzierung liegen. Zum Studienprotokoll speziell: Excellent and very complete project. Translation: General: The WL welcomes the planned study on clinical evidence synthesis based on the criterion of cost-effectiveness. In all considerations regarding the topic of “stockpiling Tamiflu or other neuraminidase inhibitors”, the focus must be on cost-effectiveness and funding. Specifically on the study protocol: Excellent and very complete project.	The protocol was not changed based on this comment. This study will focus on clinical evidence synthesis and will not address economic aspects.
1	Minor comments: 1) It might not be possible to solve all inconsistencies. In such cases, they should be clearly stated in the conclusions.	This general comment will be considered, if applicable. The protocol was not changed based on this comment.

1	2) Some comments about futility could be helpful (e.g. treatments that are started too late).	The protocol was not changed based on this comment. This information will be considered in the subgroup analyses (please see Chapter 6.3.2).
1	3) I regret that there will be no comments about treatments that may include two different molecular targets.	The protocol was not changed based on this comment. Since combination therapy was not part of the policy question and does not seem to provide additional clinical benefits over monotherapy and clinical evidence on safety is limited it was not included in the research questions.
1	4) Sometimes, too many data (sophisticated statistical) analyses miss the central message.	The protocol was not changed based on this comment. The central findings will be highlighted.
2	We would like to thank you very much for the opportunity to contribute our input to the planned Health Technology Assessment (HTA) on "Oseltamivir, baloxavir marboxil and zanamivir to treat or prevent Influenza A and B". Below we present our comments on the policy question (see section I) and the research questions (see section II).	Introductory section. The protocol was not changed based on this comment.
2	Section I - Policy Question The policy question to be addressed by the report is framed as follows: "Should Switzerland replenish or maintain the current antiviral stockpile of oseltamivir (Tamiflu®)?": It goes on to state that Switzerland has established the stockpile of oseltamivir (Tamiflu®) to address foreseeable supply shortages during such volatile phases of a pandemic. Comment: A HTA involves the systematic evaluation of medical procedures and technologies. We agree that the planned HTA on "Oseltamivir, baloxavir marboxil and zanamivir to treat or prevent Influenza A and B" will provide a sound basis for the competent authorities to make the strategic decision on whether to maintain mandatory stockpiling of Tamiflu. However, the decision itself to replenish or maintain the current mandatory stockpile cannot be the subject of the HTA itself. Section 1 should therefore be reworded accordingly.	It is correct, that the decision on whether to maintain a stockpiling system for oseltamivir is not within the scope of the current evidence synthesis However, the policy question mentioned in section 1 will be addressed by the research questions outlined in section 5. The report will not include any recommendations or decisions but solely the necessary evidence to make such a decision. The protocol was not changed based on this comment.
2	Similarly, the statement on why the stockpile was established should be revised. The current system of compulsory pandemic stock is challenging in that the system is conceptually designed to ensure the availability of products with regular demand and interruptions in supply. However, products needed during a pandemic are usually characterized by low demand outside a pandemic with an increased demand in the pandemic. At the same time higher supply levels are not available immediately. This is particularly important when it comes to the management of the stockpile and maintaining readiness to accompany the distribution, usage, pharmacovigilance and possible retraction/replacement of the product.	The statement in the protocol is in line with the Swiss Influenza Pandemic Plan 316_519_eng.pdf (cloudinary.com). It is not within the scope of the current evidence synthesis to evaluate the current system of compulsory stockpiling. The protocol was not changed based on this comment.
2	Section II - Research Questions 1) What are the benefits and harms of the treatment with oseltamivir (Tamiflu®), baloxavir marboxil (Xofluza®) and zanamivir (Relenza®) compared to each other, placebo or no treatment in patients with influenza A or B or influenza A-, B-like symptoms? 2) What are the benefits and harms of a preventive use of oseltamivir (Tamiflu®), baloxavir marboxil (Xofluza®) and zanamivir (Relenza®) compared to each other, placebo or no treatment in persons receiving prophylactic treatment against influenza (e.g., healthcare personnel or persons at risk)? Comment related to research question 1), we would propose to include an additional part to the treatment	Thank you for this further consideration. The protocol was changed based on this comment. The outcomes in Chapter 4 were supplemented by "transmission to household contacts".

	question, which looks at the effect of antiviral treatment on reducing onward transmission to household contacts. There are a number of observation and real-world studies that are currently published addressing this element, plus a small number of randomized control trials, including one related to baloxavir vs placebo, that is due to be complete in September 2024.	
2	Comment related to Research question 2), we would propose splitting the prophylaxis question into two parts: a) Post-exposure prophylaxis and b) pre-exposure prophylaxis. Each of these types of prophylaxis require different types of studies and safety data and therefore warrant separate analysis and recommendations from each other.	The protocol was not changed based on this comment. The research question will not be spitted, as it remains uncertain whether a clear distinction between pre- and post-exposure can be observed in the studies. However, if such a distinction emerges, subgroup analyses will be conducted accordingly (see Chapter 6.3.2).
3	Relenza (Zanamivir) steht für ein allfälliges Pflichtlager nicht zur Verfügung, da die Produktion weltweit eingestellt wurde. Die Zulassungsinhaberin vertreibt derzeit noch die bestehenden Lagerbestände bis zum Verfalldatum. GSK empfiehlt daher, Relenza (Zanamivir) nicht mehr in der klinischen Evidenzsynthese zu berücksichtigen. Translation: Relenza (zanamivir) is not available for mandatory stockpiling, as production has been discontinued worldwide. The marketing authorization holder is currently still distributing the existing stocks until the expiry date. GSK therefore recommends that Relenza (zanamivir) is no longer included in the clinical evidence synthesis.	Thank you for this comment. The protocol was changed based on this comment. Zanamivir was excluded as an intervention.