Consolidated stakeholder feedback

Clinical Evidence Synthesis Report
Oseltamivir and baloxavir marboxil to treat or prevent influenza A and B

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

1 Bundesamt für Wirtschaftliche Landesversorgung, Fachbereich Heilmittel

SH	SH comment	Reply authors / BAG & implemented changes in the report
1	Overall comments: The report is fine and sound. However, there are the following caveats from our side: - A pandemic of influenza is relevant only if a new variant produces more damage (mortality, ICU hospitalisation, etc). A new variant will certainly also have new properties/characteristics - therefore it might be important to have the 2 drugs at hand since they do not block the virus in the same way. Indeed, one of the two might be less efficient than the other - not “no difference between the two” as suggested by the present analysis. Surprises come with new variants.	This evidence synthesis does not provide recommendations regarding the antiviral drug stockpiling system in Switzerland but instead presents evidence for decision-making. Whether it is regarded as appropriate to maintain the availability of two different drugs is beyond the scope of the current evidence synthesis. The included studies show no statistically significant differences between oseltamivir and baloxavir for all efficacy outcomes except for fever. The time to resolution of fever was only slightly shorter in the baloxavir group compared to the oseltamivir group. No studies were found comparing oseltamivir with baloxavir in terms of hospitalization duration, re-consultations with a doctor or onward transmissions. In terms of safety, baloxavir was associated with significantly fewer adverse events, while no statistically significant differences were observed for severe adverse events. No changes implemented.
1	- Are there no studies combining the 2 drugs?	Assessing the combination of the two drugs was not within the scope of this evidence synthesis. No changes implemented.
1	- If a new killer variant produces a pandemic, prophylaxis of the whole population might be relevant.	To determine under which circumstances it is appropriate to prophylactically treat the whole population is beyond the scope of the current evidence synthesis. The report presents results from available trials for different populations, including both healthy individuals and those with comorbidities or at-risk conditions (see Table 3 and Table 5). These results can be used to make recommendations under the specific conditions of a given pandemic situation. No changes implemented.
1	- The proposed and restrictive strategy of today might miss the point: these drugs will be efficient only if they are given at the start of the infection, when symptoms are still mild.	It is agreed that timing of drug administration is important for its efficacy. Therefore, this factor was incorporated into the evidence synthesis. The report includes results demonstrating that oseltamivir is more effective than placebo when administered within 48 hours since symptom onset (see Figure 13). All subsequent subgroup analyses were limited to

		studies in which the intervention was provided within this 48-hour window. No changes implemented..
1	- The global sample sizes analysed here are so small as compared to what might occur with a deadly new variant (see COVID, or the Spanish influenza of 2018), and evidently more rare side-effects might not have shown up. The use of the drugs available should be re-analysed from the start of a pandemic so as to define which strategy is the best. In other words: we recommend to not rely too much on past studies, which might not be relevant at the time of a new pandemic.	While the included trials had sufficiently large sample sizes to assess most outcomes, they were less powered to assess mortality. We acknowledge that during a pandemic, the effectiveness of antiviral drugs should be closely monitored, particularly to identify rare side effects. It is agreed that in case of a pandemic caused by new influenza variants, the efficacy of the drugs assessed in this report is not clear.