



EUROPEAN MEDICINES AGENCY  
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Emergency Task Force

## Considerations on posology for the use of the vaccine Jynneos/Imvanex (MVA-BN) against monkeypox

### Introduction

On July 23<sup>rd</sup> 2022, the World Health Organisation (WHO) declared the monkeypox outbreak a Public Health Emergency of International Concern (PHEIC). The disease is caused by monkeypox virus, which is an orthopoxvirus closely related to smallpox virus.

Imvanex (Bavarian Nordic A/S) is the only vaccine authorised in the EU for the prevention of smallpox, monkeypox<sup>1</sup> and disease caused by vaccinia virus in adults. Imvanex is a non-replicating live attenuated third-generation vaccine based on the Modified Vaccinia Ankara – Bavarian Nordic vector (MVA-BN). It is given as two doses at least 28 days apart administered via subcutaneous injection.

The vaccine is authorised in the EU under exceptional circumstances. As smallpox virus is no longer circulating it is not possible to generate efficacy data and it is considered not feasible to estimate vaccine efficacy against monkeypox due to the epidemiology of the disease in humans prior to the ongoing emergency. The same vaccine is authorised in adults against infection and disease caused by both smallpox and monkeypox virus in the USA (Jynneos) and Canada (Imvamune) as well as other related orthopoxviruses (Canada only). There are minor differences in terms of manufacturing process and quality specifications between the various marketing authorisations in the different regions, which are due to differences in the datasets, but which do not affect the final quality of the vaccine.

Since the EU authorised vaccine Imvanex is not immediately available, in order to allow rapid containment of the outbreaks, the European Health Emergency preparedness and Response Authority (HERA) purchased the US made vaccine Jynneos for donation to EU MSs.

The EMA Emergency Task Force (ETF) together with the CHMP Biologics Working Party (BWP) and the European Directorate for the Quality of Medicines & HealthCare (EDQM) have evaluated the specificities of the FDA-approved Jynneos and prepared a public statement<sup>2</sup> including safety, efficacy and manufacturing considerations in case Jynneos is used as a replacement of Imvanex in the EU.

However, given the sudden global demand for this vaccine, vaccine supply is currently limited. In order to minimize current shortages in view of the increasing number of cases, the ETF has evaluated the available evidence in support of vaccination strategies for antigen sparing (intradermal delivery of a fractional dose) based on the approved liquid formulation (suspension for injection) for subcutaneous administration, which contains Modified Vaccinia Ankara – Bavarian Nordic Live virus no less than  $5 \times 10^7$  infectious units per 0.5 mL dose presented in a single-dose type I glass vial.

### Summary of the available evidence

Intradermal delivery of vaccines, allowing antigen sparing, is approved for several vaccines, notably BCG (tuberculosis vaccine), influenza and rabies vaccines.

Intradermal delivery of a reduced dose of MVA-BN has been investigated in a phase 2 clinical trial (NCT 00914732)<sup>3</sup>. Vaccinia-naïve healthy adults (18-38 years) with no prior history of smallpox vaccination were randomised to receive either 2 subcutaneous [SC] doses (0.5 mL,  $10^8$  TCID<sub>50</sub>/dose) in the deltoid area or 2 intradermal [ID] doses (0.1 mL,  $2 \times 10^7$  TCID<sub>50</sub>/dose) in the volar area of the forearm with a 4-week interval. The vaccine administered in the trial can be regarded as similar to the currently marketed product even though the description of the nominal strength is different. The lower ID dose of IMVANEX, one fifth of the SC dose, was immunologically non-inferior to the standard SC dose. After the second vaccination (day 42-208), the peak geometric mean neutralization titres (GMTs) against MVA-

<sup>1</sup> <https://www.ema.europa.eu/en/news/ema-recommends-approval-imvanex-prevention-monkeypox-disease>

<sup>2</sup> [https://www.ema.europa.eu/en/documents/public-statement/possible-use-vaccine-jynneos-against-infection-monkeypox-virus\\_en.pdf](https://www.ema.europa.eu/en/documents/public-statement/possible-use-vaccine-jynneos-against-infection-monkeypox-virus_en.pdf)

<sup>3</sup> Frey SE et al, Vaccine, 2015 <https://pubmed.ncbi.nlm.nih.gov/26143613/>



BN were 49.5 (95% CI: 40.0, 61.3) and 59.6 (95% CI: 48.1, 74.0) for the SC group [N=149] and ID group [N=146], respectively. The maximum number of responders (defined as the number and proportion of responders with titres  $\geq$  the assay cut-off PRNT value 15) in each group was 142/149 (95.3%) and 138/146 (94.5%), respectively. At 180 days after the second vaccination, GMTs declined to 10.2 (95% CI: 9.4, 11.0) and 10.4 (95% CI: 9.4, 11.5), with 39.2% and 35.2% of subjects remaining seropositive for the SC and ID groups, respectively. Nearly identical results were observed following SC and ID administration for humoral immune responses at individual timepoints measured using other serology assays. No data on cellular immunity have been reported.

As shown with another MVA vaccine<sup>4</sup>, the ID route resulted in significantly higher local adverse reactions (i.e., erythema, induration) than the SC route. Around 30% more subjects for ID vs. SC administration reported symptoms of local reactogenicity after the first dose and around 20% more subjects after the second dose. Moderate/severe erythema and induration occurred after any vaccination in almost all subjects with the ID route, with higher rates of severe reactions after the second dose (80% vs. 40%). Following any vaccination, the proportion of subjects with erythema or induration at the local injection site graded as severe ( $>30$  mm) was 58.1% for the SC group and 94.8% for the ID group. In addition, the proportion of subjects who experienced local reactogenicity lasting at least 30 days, unexpected nodules and skin discolouration at the vaccination site was 25% and 67.0% for the SC group and ID group, respectively. However, SC and ID groups did not significantly differ in systemic reactogenicity. There was no significant difference in the proportion of subjects with moderate/severe systemic reactions among groups after vaccination. No vaccine-related serious adverse events were reported during the study.

### Conclusions

The results of the study in healthy adults demonstrated comparable humoral immunogenicity when MVA-BN was given as a standard SC dose or as 1/5<sup>th</sup> of a dose administered ID. The exact level of protection and duration of protection afforded by the vaccine regimens are unknown.

As the study was conducted in healthy subjects, questions remain whether the reduced ID dose will be immunologically non-inferior to the standard SC dose in specific groups such as immunocompromised individuals or in people with HIV.

No new safety signal was raised for ID administration of MVA-BN but the higher local reactogenicity following the ID administration of MVA-BN may raise concerns during the vaccination campaigns. In the ongoing emergency situation with continuous spread among individuals at high risk of infection and with significant shortage of vaccine, the safety profile of the vaccine following ID route can be considered acceptable. However, these data are limited, and more data may be generated in additional studies.

It is essential to recognise the importance of correct intradermal administration to ensure that immune responses will be comparable to those achieved with a standard SC dose. Therefore, it is recommended that ID delivery of reduced dose of IMVANEX is performed by professionals with ID vaccine administration experience.

It is also important to note that the available data on ID administration are based on 2 doses of vaccine, which are deemed critical to achieve vaccine response and to maintain protection in the longer term. This means that based on current evidence, the ID fractional dose would be suitable for pre-exposure prophylaxis following 2 doses regimen. There remains a possibility that the local reactogenicity associated with ID vaccination could increase the proportion of subjects who do not attend for the second dose, potentially leading to reduced protection.

A delay or omission of the second subcutaneous or intradermal dose, or the administration of a first dose by SC route followed by a second one by ID route, has not been investigated. Clinical trials exploring different vaccination strategies are warranted to ensure we make efficient use of currently limited vaccine supply.

### Additional notes on usage

Imvanex is a suspension for injection which contains Modified Vaccinia Ankara – Bavarian Nordic Live virus no less than  $5 \times 10^7$  infectious units per 0.5 mL dose presented in a single-dose type I glass vial for subcutaneous administration. In use storage of the unopened vial is 2-8 °C in the dark, for a maximum of 2 months post-thawing<sup>5</sup>.

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<sup>4</sup> Wilck MB, Seaman MS, Baden LR, Walsh SR, Grandpre LE, Devoy C et al. Safety and immunogenicity of modified vaccinia Ankara (ACAM3000): effect of dose and route of administration. *J Infect Dis* 2010;201:1361–70. doi:10.1086/651561 PMID:20350191

<sup>5</sup> <https://www.ema.europa.eu/en/medicines/human/EPAR/imvanex#product-information-section>

There is no intradermal presentation authorised in the EU. The EMA has neither information on the maximum number of 0.1 mL doses that can be effectively withdrawn from the authorised presentation nor information on vial stopper performance/integrity after repeated puncture since no feasibility study has been conducted on this. However, the use of low-dead volume syringes is recommended to maximise dose withdrawal.

There is no information on storage conditions (e.g. time out of refrigeration) between multiple uses to support physico-chemical stability or stability from a microbiological perspective.

From a microbiological point of view, once opened, the product should be used immediately.

It is important that pharmacovigilance and effectiveness monitoring are ensured, and that data are collected by Public Health Authorities or research Institutions to confirm the use of the vaccine.