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ETF statement on the use of Imvanex for the prevention of mpox in children below 12 years of age

On August 14, 2024, the World Health Organisation (WHO) declared the mpox outbreak ongoing in several African countries a Public Health Emergency of International Concern (PHEIC). A global mpox outbreak, affecting also several countries in the European union (EU), occurred in 2022-23.

Mpox is a disease caused by the monkeypox virus, an orthopoxvirus closely related to the smallpox virus. Over 24,000 confirmed or suspected mpox cases have been reported since the beginning of 2024 in the African continent, including more than 5,000 confirmed cases and 600 deaths[1]. Children are more at risk of developing severe mpox than adults and are disproportionately affected in the current emergency, representing approximately 50% of all cases[2].

Imvanex (Bavarian Nordic A/S), known as Jynneos in the US, is the only vaccine authorised in the EU for the prevention of smallpox, mpox, and of disease caused by vaccinia virus in adults and in adolescents from 12 years of age. Imvanex is a replication-deficient live attenuated third-generation vaccine based on the Modified Vaccinia Ankara – Bavarian Nordic vector (MVA-BN). It is given in two doses of no less than $5x10^7$Inf.U at least 28 days apart, via subcutaneous injection[3].
There is no vaccine authorized in the EU for children below 12 years of age. No data from clinical trials are yet available in this age group; two clinical trials of immunogenicity and safety are planned and soon to start in children from 2 to 12 years and below 2 years of age, respectively.

Of note, in September 2024 the WHO Strategic Advisory Group of Experts on Immunization stated that Imvanex may be used "off-label" in infants and children in outbreak settings, as well as in pregnant women, where the benefits of vaccination outweigh the potential risks[4]. Imvanex is the only vaccine that can also be used in immunocompromised persons.

The EMA Emergency Task Force (ETF) has considered the available evidence supporting the potential use of Imvanex in children younger than 12 years of age, in view of the need for mpox vaccines that can be used to protect children in the current public health emergency.

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Summary of the available evidence

Imvanex data, and use in paediatric populations

The safety of Imvanex was assessed in clinical trials in more than 5,000 Vaccinia-naïve adults who received two vaccine doses of no less than 5 x 10^7 Inf.U four weeks apart. The most common adverse events were injection site and systemic reactions typical for vaccines, mild to moderate in intensity, and resolving without intervention[3], showing a favorable safety profile.

The marketing authorization of Imvanex in adolescents was based on the results of a clinical trial (DMID 22-0020) that included 315 adolescents (12 to 17 years of age) and 211 adults (18 to 50 years of age). The neutralizing antibody response in adolescents was non-inferior to the response in adults who received the same standard dose and posology of the vaccine in the trial. Based on this, the CHMP concluded that Imvanex will provide similar protection in adolescents to that expected in adults, in whom the vaccine was shown to be effective in real world observational studies[3;5]. Importantly, the safety profile in adolescents was similar to that seen in adults, with no additional risks identified.

During the 2022-2023 outbreak, one single dose of Imvanex (0.5-3.95x10^8 Inf.U) was offered in the United Kingdom (UK) to children who had been exposed to the monkeypox virus. Surveillance data were collected by the UK Health Security Agency on 87 children from birth to 16 years (median age 5 years). In terms of safety, 45 of the 87 children completed a follow-up questionnaire. Of these, 36% reported no symptoms, 40% reported mild injection-site reactions only, and 24% reported systemic symptoms with/without local reactions. None developed any serious adverse event or mpox disease after vaccination. The immune response could be evaluated only in 8 children and showed development of specific humoral and cellular immune responses up to 15 weeks after vaccination[6].

As a third-generation non-replicating orthopoxvirus vaccine, Imvanex also has better safety profile than earlier generation vaccines, which contain live replicating vaccinia virus, for which serious adverse events have been described, including frequent myocarditis, neuro-encephalitis and severe cutaneous reactions[7].

Data from other vaccines using the Modified Vaccinia Ankara virus platform in paediatric populations

Although the MVA-BN vaccine is not licensed in children, paediatric studies of other vaccines using it as a vector (often at a considerably higher dose than used in MVA-BN) have been undertaken with a reassuring safety profile. One of such vaccines is Mvabea, a recombinant MVA-BN virus modified to add genetic material from three variants of Ebola virus and one of Marburg virus. Mvabea is registered in the EU since 2020 in individuals older than 1 year of age for the prevention of Zaire ebolavirus disease, as part of the Zabdeno, Mvabea vaccine regimen.

Clinical trials with Mvabea were conducted in more than 3,300 individuals in the EU, US, and Africa, including over 800 children from 1 year to 17 years of age. The same dosing regimen (0.7 x 10^8 Inf.U) was used in adults and across the whole paediatric population. The safety profile of Mvabea in children was benign, similarly to what observed in adults; the most common reactions were pain at the injection site (21% of children), and fatigue (11%). Adverse reactions were mild to moderate in severity and of short duration (1-3 days). Immune responses in children were higher than those observed in adults in the same studies.[9].

Additional data with Mvabea in the context of Zabdeno/Mvabea vaccination regimen are available from a clinical trial (EBL2005) conducted in Guinea and Sierra Leone, which included 75 infants from 4 to 11 months of age, receiving the same dose as the standard one authorized for children and adults in the EU. In the trial, the safety profile in infants was similar to that observed in children from 1 to 17 years of age[9,10].

Additional trials in which MVA was used as vaccine platform included a tuberculosis (TB) vaccine trial of around 1500 infants aged approximately 5 to 6 months[11], and a trial of 200 Gambian infants who received an MVA malaria vaccine[12]. In both trials the vaccines showed an acceptable safety profile.

Key considerations

The data from the clinical trials of Imvanex in adults and adolescents and the available surveillance data on the use of Imvanex in children from birth during the 2022-2023 mpox outbreak show a reassuring reactogenicity and safety profile.

This is further supported by similar safety profile of the Ebola vaccine Mvabea in children and infants and by the data from paediatric trials of TB and malaria candidate vaccines where Imvanex was used as viral vector, since no relevant differences in safety are expected with the vaccine used as vector versus its use as standalone monkeypox vaccine.

In all keys studies so far, Imvanex and Mvabea were administered subcutaneously, using the same standard dose and posology in adults and in paediatric populations.

Based on the non-inferior immune response to Imvanex in adolescents compared to adults and on the higher immune response to Mvabea in children, it is expected that the immune response to Imvanex in children below 12 years of age will be at least similar to that of adults and adolescents.

As a third-generation non-replicating orthopoxvirus vaccine, Imvanex has better safety profile than earlier generation vaccines, which contain live replicating vaccinia virus for which serious adverse events have been described.

Conclusion

Taking into account the currently limited options for the prevention of mpox in the paediatric population, and the safety data of Imvanex and MVA-based vaccines reported so far in different age groups, the ETF considers that Imvanex could be used for the prevention of mpox in children below 12 years of age who are at risk of mpox disease during the current international public health emergency[1]. Decision to use Imvanex in this age group remains at discretion and under the responsibility of national health authorities in the countries affected.

References

1. Mpox – African Region (who.int)
2. The global alarm bell is ringing due to the threat of potential severe cases and deaths caused by clade I of monkeypox virus - The Lancet Infectious Diseases
3. Imvanex Summary of Product Characteristics: IMVANEX, INN-Smallpox and monkeypox vaccine (Live Modified Vaccinia Virus Ankara)
4. Statement of the WHO Global Advisory Committee on Vaccine Safety (GACVS) on the safety of the mpox vaccines for use in high-risk groups
5. Pischel L et al. Vaccine effectiveness of 3rd generation mpox vaccines against mpox and disease severity: a systematic review and meta-analysis. Vaccine. 2024.
6. Ladhani SN, et al. Early evaluation of the safety, reactogenicity, and immune response after a single dose of modified vaccinia Ankaraâ€"Bavaria Nordic vaccine against mpox in children: a national outbreak response
7. Second generation vaccines serious adverse events Green Book Chapter 29 Smallpox and monkeypox
8. Phase 3 Efficacy Trial of Modified Vaccinia Ankara as a Vaccine against Smallpox | New England Journal of Medicine (nejm.org)
9. MVABEA, Ebola vaccine (MVA-BN-Filo [recombinant])

[1] This statement is not to be intended as a formal change of the conditions of use in the existing marketing authorization.

10. Safety and immunogenicity of the two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in infants: a phase 2, randomised, double-blind, active-controlled trial in Guinea and Sierra Leone - The Lancet Global Health
11. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial - PubMed
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