ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

IMVANEX suspension for injection
Smallpox and monkeypox vaccine (Live Modified Vaccinia Virus Ankara)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:

Modified Vaccinia Ankara – Bavarian Nordic Live virus[1] no less than 5×10^7 Inf.U*

*infectious units
[1]Produced in chick embryo cells

This vaccine contains trace residues of chicken protein, benzonase, gentamicin and ciprofloxacin (see section 4.3).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

Light yellow to pale white, milky suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against smallpox, monkeypox and disease caused by vaccinia virus in individuals 12 years of age and older (see sections 4.4 and 5.1).

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Primary vaccination (individuals previously not vaccinated against smallpox, monkeypox or vaccinia viruses)
A first dose of 0.5 ml should be administered on an elected date.
A second dose of 0.5 ml should be administered no less than 28 days after the first dose, see sections 4.4 and 5.1.

Booster vaccination (individuals previously vaccinated against smallpox, monkeypox or vaccinia viruses)
There are inadequate data to determine the appropriate timing of booster doses. If a booster dose is considered necessary then a single dose of 0.5 ml should be administered, see sections 4.4 and 5.1.

Special population
Immunocompromised patients (e.g. HIV infected, patients under immunosuppressive therapy) who have been previously vaccinated against smallpox, monkeypox or vaccinia viruses should receive two booster doses. The second booster vaccination should be given no less than 28 days after the first booster dose.

Paediatric population
The safety and efficacy of IMVANEX in children below 12 years have not been established.
No data are available.

Method of administration

Immunisation should be carried out by subcutaneous injection, preferably into the upper arm.

For instructions on administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or trace residues (chicken protein, benzonase, gentamicin and ciprofloxacin).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and anaphylaxis

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

Concurrent illness

Immunisation should be postponed in individuals suffering from an acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not result in the deferral of vaccination.

General recommendations

IMVANEX should not be administered by intravascular injection.

Limitations of vaccine effectiveness

The protective efficacy of IMVANEX against smallpox, monkeypox and disease caused by vaccinia virus has not been studied in humans, see section 5.1.

A protective immune response may not be elicited in all vaccinees.

There are inadequate data to determine the appropriate timing of booster doses.

Prior vaccination with IMVANEX may modify the cutaneous response (‘take’) to subsequently administered replication-competent smallpox vaccine resulting in a reduced or absent take, see section 5.1.

Individuals with atopic dermatitis

Individuals with atopic dermatitis developed more local and general symptoms after vaccination (see section 4.8)

Immunocompromised individuals

Data have been generated in HIV infected individuals with CD4 counts ≥ 100 cells/µl and ≤ 750 cells/µl. Lower immune response data have been observed in HIV infected individuals compared to healthy individuals (see section 5.1). There are no data on the immune response to IMVANEX in other immunosuppressed individuals.

Two doses of IMVANEX given at a 7-day interval showed lower immune responses and slightly more local reactogenicity than two doses given at a 28-day interval. Therefore, dose intervals of less than 28 days should be avoided.

Anxiety-related reactions
Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with other vaccines or medicinal products have been performed. Therefore, concomitant administration of IMVANEX with other vaccines should be avoided.
The concomitant administration of the vaccine with any immunoglobulin including Vaccinia Immune Globulin (VIG) has not been studied and should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data (less than 300 pregnancy outcomes) from the use of IMVANEX in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of IMVANEX during pregnancy. Administration of Imvanex in pregnancy should only be considered when the potential benefits outweigh any potential risk to the mother and foetus.

Breast-feeding

It is not known whether IMVANEX is excreted in human milk. As a precautionary measure, it is preferable to avoid the use of IMVANEX during breast-feeding. Administration of Imvanex during breast-feeding should only be considered when the potential benefits outweigh any potential risks to the mother and baby.

Fertility

Animal studies did not reveal any evidence of impaired female and male fertility.

4.7 Effects on ability to drive and use machines

There is no information on the effect of IMVANEX on the ability to drive or use machines. However,

some of the undesirable effects mentioned in section 4.8 may affect the ability to drive or use machines (e.g. dizziness).

4.8 Undesirable effects

Summary of the safety profile

The safety of IMVANEX has been assessed in 20 clinical trials in which 5 261 Vaccinia-naïve individuals received two doses of no less than 5 x 10^7 Inf.U four weeks apart while 534 Vaccinia- and IMVANEX-experienced individuals received a single booster dose.

The most common adverse reactions observed in clinical trials were injection site reactions and common systemic reactions typical for vaccines which were mild to moderate in intensity and resolved without intervention within seven days following vaccination.

Adverse reaction rates reported after either vaccination dose (1^{st}, 2^{nd} or booster) were similar.

Tabulated list of adverse reactions

Adverse reactions from all clinical trials are listed according to the following frequency:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1 000 to <1/100)
Rare (≥1/10 000 to <1/1 000)
Unknown (cannot be estimated from the available data)

Table 1: **Adverse reactions reported in completed clinical trials (N = 7 082 subjects) and post-authorisation experience with IMVANEX**

MedDRA System Organ Class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1 000 to <1/100)**	**Rare (≥1/10 000 to <1/1 000)**	**Unknown (cannot be estimated from the available data)**
Infections and infestations	-	-	Nasopharyngitis Upper respiratory tract infection	Sinusitis Influenza Conjunctivitis	-
Blood and lymphatic system disorders	-	-	Lymphadenopathy	-	-
Metabolism and nutrition disorders	-	Appetite disorder	-	-	-
Psychiatric disorders	-	-	Sleep disorder	-	-
Nervous system disorders	Headache	-	Dizziness Paresthesia	Migraine Peripheral sensory neuropathy	Acute peripheral facial paralysis (Bell's palsy)

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to <1/100)	Rare (≥1/10 000 to <1/1 000)	Unknown (cannot be estimated from the available data)
				Somnolence	
Ear and labyrinth disorders	-	-	-	Vertigo	-
Cardiac disorders	-	-	-	Tachycardia	-
Respiratory, thoracic and mediastinal disorders	-	-	Pharyngolaryngeal pain Rhinitis Cough	Oropharyngeal pain	-
Gastrointestinal disorders	Nausea	-	Diarrhoea Vomiting	Dry mouth Abdominal Pain	-
Skin and subcutaneous tissue disorders	-	-	Rash Pruritus Dermatitis	Urticaria Skin discolouration Hyperhidrosis Ecchymosis Night sweats Subcutaneous nodule Angioedema	-
Musculoskeletal and connective tissue disorders	Myalgia	Pain in extremity Arthralgia	Musculoskeletal stiffness	Back pain Neck pain Muscle spasms Musculoskeletal pain Muscular weakness	-
General disorders and administration site conditions	Injection site pain Injection site erythema Injection site swelling Injection site induration	Rigor/Chills Injection site nodule Injection site discolouration Injection site haematoma Injection site warmth	Underarm swelling Malaise Injection site haemorrhage Injection site irritation Flushing Chest pain	Axillary pain Injection site exfoliation Injection site inflammation Injection site paraesthesia Injection site reaction Injection site rash	-

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to <1/100)	Rare (≥1/10 000 to <1/1 000)	Unknown (cannot be estimated from the available data)
	Injection site pruritus Fatigue			Oedema peripheral Asthenia Injection site anesthesia Injection site dryness Injection site movement impairment Influenza like illness Injection site vesicles	
Investigations	-	Body temperature increased Pyrexia	Troponin I increased Hepatic enzyme increased White blood cell count decreased Mean platelet volume decreased	White blood cell count increased	-
Injury, poisoning and procedural complications	-	-	-	Contusion	-

Description of selected adverse reactions

Individuals with atopic dermatitis (AD)
In a non-placebo controlled clinical trial that compared the safety of IMVANEX in individuals with AD to healthy individuals, individuals with AD reported erythema (61.2%) and swelling (52.2%) at the injection site with a higher frequency than healthy individuals (49.3% and 40.8%, respectively). The following general symptoms were reported more frequently in individuals with AD compared to healthy individuals: headache (33.1% vs. 24.8%), myalgia (31.8% vs. 22.3%), chills (10.7% vs. 3.8 %), nausea (11.9% vs. 6.8%), and fatigue (21.4% vs. 14.4%).
7% of the individuals with AD in clinical trials with IMVANEX experienced a flare-up or worsening of their skin condition during the course of the trial.

Rash
IMVANEX may trigger local rashes or more widespread eruptions. Events of rash after vaccination (related cases observed in 0.4% of subjects) with IMVANEX tend to occur within the first days after vaccination, are mild to moderate in intensity and usually resolve without sequelae.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

Paediatric population

Adolescents 12-18 years
Interim data from the currently ongoing study DMID 22-0020 suggest a mainly similar safety-profile in adolescents as in adults. The study enrolled 315 adolescents. Data up to Study Day 57 are considered clean. More than 99% received two vaccination doses. According to the current database, the most frequent injection site reaction was injection site pain (> 70%), and the most frequent systemic adverse reactions were fatigue (> 50%) and headache (50%).

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, other viral vaccines, ATC code: J07BX

Efficacy in animals

Non-human primate (NHP) studies have demonstrated that vaccination with IMVANEX induced a comparable immune response and protective efficacy to traditional smallpox vaccines used to eradicate smallpox and protected NHP from severe disease associated with a lethal challenge of monkeypox virus. As seen with traditional smallpox vaccines, a significant reduction in both mortality and morbidity (viral load, weight loss, number of pox lesions, etc.) compared to non-vaccinated controls was demonstrated for NHP vaccinated with IMVANEX.

Mouse studies have demonstrated that vaccination with IMVANEX protected mice from a lethal challenge of replicating vaccinia virus.

Immunogenicity

Seroconversion to vaccinia in Vaccinia-naïve healthy and special populations
The Vaccinia-naïve study population included healthy individuals as well as individuals with HIV infection and AD who received 2 doses of IMVANEX 4 weeks apart. Seroconversion rates in Vaccinia-naïve individuals were defined as appearance of vaccinia antibody titers equal or greater than the assay cut-off value following receipt of two doses of IMVANEX. Seroconversion by ELISA and PRNT were as follows:

Table 2 Seroconversion rates by ELISA in Vaccinia-naïve healthy and special populations

SCR - ELISA			Day 7/14[1]	Day 28[1]	Day 42[1]
Study	**Health status**	**N**	**SCR % (95% CI)**	**SCR % (95% CI)**	**SCR % (95% CI)**
POX-MVA-005[2]	Healthy	183	70.9 (63.7, 77.4)	88.9 (83.4, 93.1)	98.9 (96.0, 99.9)
POX-MVA-008[3]	Healthy	194	12.5 (8.1, 18.2)	85.4 (79.6, 90.1)	98.5 (95.5, 99.7)
	Atopic Dermatitis	257	22.9 (17.8, 28.6)	85.4 (80.5, 89.5)	97.3 (94.5, 98.9)
POX-MVA-009[4]	Healthy	66	69.7 (57.1, 80.4)	72.2 (60.4, 83.0)	96.8 (89.0, 99.6)
POX-MVA-011[2]	Healthy	88	29.6 (20.0, 40.8)	83.7 (74.2, 90.8)	98.7 (93.1, 100)
	HIV	351	29.2 (24.3, 34.5)	67.5 (62.1, 72.5)	96.2 (93.4, 98.0)
POX-MVA-013[2]	Healthy	2,119[6]	N/A[5]	N/A[5]	99.7 (99.4; 99.9)

Table 3 Seroconversion rates by PRNT in Vaccinia-naïve healthy (including adults and adolescents aged 12 to 17 years) and special populations

SCR - PRNT			Day 7/14[1]	Day 28[1]	Day 42[1]
Studies in adults					
Study	**Health Status**	**N**	**SCR % (95% CI)**	**SCR % (95% CI)**	**SCR % (95% CI)**
POX-MVA-005[2]	Healthy	183	45.1 (37.7, 52.6)	56.7 (49.1, 64.0)	89.2 (83.7, 93.4)
POX-MVA-008[3]	Healthy	194	5.4 (2.6, 9.8)	24.5 (18.6, 31.2)	86.6 (81.0, 91.1)
	Atopic Dermatitis	257	5.6 (3.1, 9.3)	26.8 (21.4, 32.7)	90.3 (86.0, 93.6)
POX-MVA-009[4]	Healthy	66	12.1 (5.4, 22.5)	10.6 (4.4, 20.6)	82.5 (70.9, 90.9)
POX-MVA-011[2]	Healthy	88	11.1 (5.2, 20.0)	20.9 (12.9, 31.0)	77.2 (66.4, 85.9)
	HIV	351	15.7 (11.9, 20.1)	22.5 (18.1, 27.4)	60.3 (54.7, 65.8)
POX-MVA-013[2]	Healthy	2119[6]	N/A[5]	N/A[5]	99.8 (99.5; 99.9)
Study in adolescents (12 to 17 years) and aduls (18 to 50 years) – data from interim analysis					
DMID 22-0020[7]	Adolescents (Arm 5)	310	N/A[5]	82.6 (77.9, 86.6)	99.0 (97.1, 99.8)
	Healthy adults (Arms 3 and 4) [8]	210	N/A[5]	75.2 (68.8, 80.9)	97.6 (94.5, 99.2)
	Healthy adults (Arm 4 only) [8]	134	N/A[5]	76.9 (68.8, 83.7)	97.7 (93.5, 99.5)

[1]Day 7/14 corresponding to 1 or 2 weeks after the first IMVANEX dose (analysis time point at day 7 only in studies POX-MVA-008 and POX-MVA-011; POX-MVA-005 had the first post vaccination analysis at day 14); day 28 corresponding to 4 weeks after the first IMVANEX dose; day 42 corresponding to 2 weeks following the second dose of IMVANEX;

SCR = Seroconversion rate; PRNT = plaque reduction neutralisation test; ELISA = enzyme-linked immunosorbent assay using MVA as an antigen [2] Full Analysis Set (FAS) (for POX-MVA-013: Immunogenicity Analysis Set; IAS); [3] Per Protocol Analysis Set (PPS), [4] seropositivity rates, [5] no immunogenicity sample taken, [6] combined Groups 1-3; [7] Number of participants in the mITT population [8] Arms 3 and 4 were combined as a comparator group in the primary analysis.

Seroconversion to vaccinia in Vaccinia-experienced healthy and special populations

Seroconversion in Vaccinia-experienced individuals was defined as at least a two-fold increase in base titres following a single vaccination with IMVANEX.

Table 4 Seroconversion rates by ELISA in Vaccinia-experienced healthy and special populations

SCR - ELISA			Day 0[1]	Day 7/14[1]	Day 28[1]	Day 42[1]
Study	**Health status**	**N**	**SCR %**	**SCR % (95% CI)**	**SCR % (95% CI)**	**SCR % (95% CI)**
POX-MVA-005[2]	Healthy	200	-	95.5 (91.6, 97.9)	93.0 (88.5, 96.1)	NA
POX-MVA-024[2]	Healthy	61	-	83.6 (71.9, 91.8)	79.7 (67.2, 89.0)	NA
POX-MVA-011[2]	Healthy	9	-	62.5 (24.5, 91.5)	100 (63.1, 100)	100 (59.0, 100.0)
	HIV	131	-	57.3 (48.1, 66.1)	76.6 (68.2, 83.7)	92.7 (86.6, 96.6)

Table 5 Seroconversion rates by PRNT in Vaccinia-experienced healthy and special populations

SCR - PRNT			Day 0[1]	Day 7/14[1]	Day 28[1]	Day 42[1]
Study	**Health status**	**N**	**SCR %**	**SCR % (95% CI)**	**SCR % (95% CI)**	**SCR % (95% CI)**
POX-MVA-005[2]	Healthy	200	-	78.5 (72.2, 84.0)	69.8 (63.0, 76.1)	NA
POX-MVA-024[2]	Healthy	61	-	73.8 (60.9, 84.2)	71.2 (57.9, 82.2)	NA
POX-MVA-011[2]	Healthy	9	-	75.0 (34.9, 96.8)	62.5 (24.5, 91.5)	85.7 (42.1, 99.6)
	HIV	131	-	46.0 (37.0, 55.1)	59.7 (50.5, 68.4)	75.6 (67.0, 82.9)

[1]Day 0 corresponding to day of vaccination with IMVANEX; day 7/14 corresponding to 1 or 2 weeks after vaccination with IMVANEX (first post vaccination analysis at day 7 in study POX-MVA-011, and at day 14 in studies POX-MVA-005 and POX-MVA-024); day 28 corresponding to 4 weeks after vaccination with IMVANEX; SCR = Seroconversion rate; [2] Full Analysis Set (FAS); PRNT = plaque reduction neutralisation test; ELISA = enzyme-linked immunosorbent assay using MVA as an antigen.

Long-term immunogenicity to vaccinia in humans

Limited data on long-term immunogenicity covering a period of 24 months following primary vaccination of Vaccinia-naïve individuals with IMVANEX are currently available as shown below:

Table 6 Seroconversion rates by ELISA and PRNT in Vaccinia-naïve healthy over a period of 24 months

		ELISA		PRNT	
Month	**N**	**SCR % (95% CI)**	**GMT (95% CI)**	**SCR % (95% CI)**	**GMT (95% CI)**
2	178	98.9 (96.0, 99.9)	328.7 (288.5, 374.4)	86.0 (80.0, 90.7)	34.0 (26.4, 43.9)
6	178	73.0 (65.9, 79.4)	27.9 (20.7, 37.6)	65.2 (57.7, 72.1)	7.2 (5.6, 9.4)
24*	92	71.7	23.3	5.4	1.3

		(61.4, 80.6)	(15.2, 35.9)	(1.8, 12.2)	(1.0, 1.5)

ELISA = enzyme-linked immunosorbent assay using MVA as an antigen; GMT= geometric mean titre; N = number of subjects in the specific study group; PRNT = plaque reduction neutralisation test; SCR = seroconversion rate;
*represents seropositivity rates

Booster dose

Two clinical studies have demonstrated that IMVANEX is able to boost a pre-existing immunological memory response to vaccinia, induced by either licensed smallpox vaccines a long time ago or two years after IMVANEX.

Table 7 Seroconversion rates by ELISA and PRNT after a booster dose

Primary immunisation		**N**	**Day 0[1]**		**N**	**Day 7[1]**		**Day 14[1]**	
	ELISA		**S+ %**	**GMT**		**S+ %**	**GMT**	**S+ %**	**GMT**
2 doses of IMVANEX		92	72	23	75	100	738	100	1,688
Licensed smallpox vaccine		200	79	39	195	-	-	98	621
	PRNT		**S+ %**	**GMT**		**S+ %**	**GMT**	**S+ %**	**GMT**
2 doses of IMVANEX		92	5.4	1	75	92	54	99	125
Licensed smallpox vaccine		200	77	22	195	-	-	98	190

[1]Day 0 corresponding to day of booster vaccination with IMVANEX (pre-booster); day 7 and 14 corresponding to 1 or 2 weeks after booster vaccination with IMVANEX; N = number of subjects in the specific study group; ELISA = enzyme-linked immunosorbent assay using MVA as an antigen; PRNT = plaque reduction neutralization test; S+ = Seropositivity rate; GMT = geometric mean titre.

Immunogenicity and attenuation of take of ACAM2000 in healthy subjects

Imvanex was compared to ACAM2000 (a 'second generation' live attenuated smallpox vaccine produced in cell culture and licenced in the United States of America) in a randomized, open-label non-inferiority clinical trial in healthy adults (US military personnel) aged 18 to 42 years and who were naïve to smallpox vaccine (Study POX-MVA-006).

A total of 433 subjects were randomised in a 1 : 1 ratio to receive either two doses of Imvanex followed by a single dose of ACAM2000 at four weeks intervals or to receive a single dose of ACAM2000. ACAM2000 was administered via scarification.

The first co-primary endpoint compared vaccinia-specific neutralizing antibody responses at the peak visits (day 42 after first vaccination for Imvanex where the subjects received two doses according to the standard vaccination schedule and day 28 for ACAM2000). Imvanex induced a peak neutralizing antibody geometric mean titer (GMT) of 153.5 (n = 185; 95% CI 134.3, 175.6), which was non-inferior to the GMT of 79.3 (n = 186; 95% CI 67.1, 93.8) obtained after scarification with ACAM2000.

The second co-primary endpoint evaluated if vaccination with Imvanex (n = 165) prior to administration of ACAM2000 results in an attenuation of the cutaneous reaction to ACAM2000 (n = 161) as measured by maximum lesion area in mm^2. At day 13-15, the median maximum lesion area for subjects who were administered ACAM2000 was $75mm^2$ (95% CI 69.0, 85.0) and for those who received Imvanex it was 0.0 (95% CI 0.0, 2.0).

Vaccine effectiveness

In real-world observational studies conducted in vaccine-eligible individuals (according to local recommendations), vaccine effectiveness against mpox disease was demonstrated at least 14 days after vaccination[a], with adjusted vaccine effectiveness estimates ranging from 35% (95% CI, -2-59) to 89% (95% CI, 76-95) after one IMVANEX dose and from 66% (95% CI, 47-78) to 90% (95% CI, 86-92) after two IMVANEX doses.

Table 8 Vaccine effectiveness at least 14 days after vaccination[a]

Country	Study Design, Period	Vaccination strategy	1-dose effectiveness % [95% CI]	2-dose effectiveness % [95% CI]
US	Case-control Aug 2022-Mar 2023	PrEP/PEP	77% (60-87)	89% (56-97)
	Case-control Aug 2022-Nov 2022	PrEP	36% (22-47)*	66% (47-78)*
	Retrospective cohort May 2022-Dec 2022	PrEP/PEP	81% (64-90)*	83% (28-96)*
	Case-coverage Jul 2022-Oct 2022	PrEP/PEP	86% (83-89)*	90% (86-92)*
	Case-control Jun 2022-Dec 2022	PrEP/PEP	68% (25-87)*	89% (44-98)*
Spain	Retrospective cohort Jul 2022-Dec 2022	PrEP	79% (33-100)*,**	-
	Prospective cohort May 2022-Aug 2022	PEP	89% (76-95)[a]	-
Canada	Case-control Jun 2022-Sep 2022	PrEP	35% (-2-59) 65% (1-87)***	-
UK	Case-coverage Jul 2022-Dec 2022	PrEP	78% (54-89)**	-

Note: all data are adjusted vaccine effectiveness, based on subcutaneous administration, unless indicated otherwise.
*Covers both subcutaneous and intradermal administrations.
**Crude vaccine effectiveness.
***Based on individual-level data supplemented with questionnaire responses on risk behaviour.
[a] PEP administered ≤ 14 days after exposure.

Impact on hospitalisation

In a surveillance study conducted from May 2022 to May 2023 in the US, IMVANEX was shown to reduce the risks of mpox-related hospitalisation. Compared with unvaccinated mpox patients, the odds of hospitalisation were 0.27 (95% CI, 0.08-0.65) after one IMVANEX dose, and 0.20 (95% CI, 0.01-0.90) after two IMVANEX doses. The estimated relative risk reduction was 73% after one IMVANEX dose and 80% after two IMVANEX doses.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with IMVANEX in one or more subsets of the paediatric population for prevention of smallpox, monkeypox and disease caused by vaccinia virus by active immunisation against smallpox, monkeypox and disease caused by vaccinia virus infection and disease (see section 4.2 for information on paediatric use).

A study in adolescents (DMID 22-0020[7]) is currently ongoing with immunogenicity data up to Study Day 43 (14 days Post Dose 2) already available. The results of the primary endpoint show non-inferiority regarding antibody response of adolescents to adults in the vaccinia specific neutralization assay.

Table 9 Vaccinia Virus Specific PRNT Primary Hypothesis Testing, mITT Population

Hypothesis	Statistic	Adolescents (N=313)	Adults[c] (N=211)	Adults - Arm 4 Only (N=135)
At Day 43 the humoral immune response in adolescents is non-inferior to adults, as assessed by Vaccinia specific PRNT GMT	n	304	208	132
	GMT (95% CI)	470.3 (422.3, 523.8)	293.2 (249.8, 344.2)	295.7 (240.8, 363.2)
	GMTR (95% CI)	N/A	1.60 (1.32, 1.95)	1.59 (1.26, 2.00)
	p-value[a]	N/A	<0.001	<0.001
	Non-inferiority result[b]	N/A	Yes	Yes

N = Number of participants in the mITT Population; n = Number of participants with data at time point;
GMT = Geometric mean titer; GMTR = Geometric mean titer ratio of adolescents to adults;
CI = Confidence Interval, calculated using Student's t distribution for GMT and Welch-Satterthwaite t test for GMTR.
[a] Two-sample t-test with unequal variance, non-inferiority (NI) margin of 0.67 and two-sided type I error rate of 0.05 to test the null hypothesis that humoral immune response in adolescents will be noninferior to adults.
[b] If the lower bound of the GMTR 95% CI is greater than or equal to 0.67 (NI=0.174 log10 scale) prior to rounding, the result is "Yes".
[c] Arms 3 and 4 were combined as a comparator group in the primary analysis. Arm 3 participants were excluded for a sensitivity analysis.

Exceptional circumstances

This medicinal product has been authorised under 'exceptional circumstances'.
This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on repeated dose toxicity, local tolerance, female fertility, embryo-foetal and postnatal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years at -20°C +/-5°C
5 years at -50°C +/-10°C
9 years at -80°C +/-10°C

After thawing, the vaccine can be stored at 2°C–8°C in the dark for up to 2 months within the approved shelf-life prior to use.
Do not re-freeze a vial once it has been thawed.

6.4 Special precautions for storage

Store in a freezer (at -20°C +/-5°C or -50°C +/-10°C or -80°C +/-10°C). Expiry date depends on storage temperature.
The vaccine can be stored short-term in a refrigerator at 2°C–8°C for up to 2 months within the approved shelf-life prior to use.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

0.5 ml suspension in a vial (Type I glass) with stopper (bromobutyl rubber).

Pack sizes of 1 single dose vial, 10 single dose vials or 20 single dose vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vial should be allowed to reach a temperature between 8°C and 25°C before use. Swirl the vial gently before use for at least 30 seconds.

The suspension should be visually inspected for particulate matter and discoloration before use. In the event of any damage to the vial, foreign particulate matter and/or variation of physical aspect being observed, discard the vaccine.
A dose of 0.5 ml is withdrawn into a syringe for injection.
Each vial is for single use.

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bavarian Nordic A/S
Philip Heymans Allé 3
DK-2900 Hellerup
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/855/001
EU/1/13/855/002
EU/1/13/855/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 July 2013
Date of lastest renewal: 23 April 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Bavarian Nordic A/S
Hejreskovvej 10 A, Kvistgård, 3490, Denmark

Name and address of the manufacturer(s) responsible for batch release
Bavarian Nordic A/S
Hejreskovvej 10 A, Kvistgård, 3490, Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authoristion holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of

Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measure:

Number	Description	Due date
SOB-002	To ensure adequate monitoring of safety and effectiveness, the MAH shall perform the following study to collect data where IMVANEX is used as a prophylactic vaccine and/or use in case of re-emergence of circulating smallpox. • Non-interventional post-authorisation efficacy study (PAES) POX-MVA-039: An observational, non-interventional post-authorisation safety and efficacy study for the prophylactic vaccination with IMVANEX following re-emergence of circulating smallpox infections.	Status to be reported annually within each annual reassessment
SOB-004	In order to further characterise the safety information of IMVANEX in adolescents 12 to 17 years of age, the MAH shall submit the final clinical study report of study DMID 22-0020: • A Phase 2 Randomised, Open-Label, Multisite Trial to Inform Public Health Strategies Involving the Use of MVA-BN Vaccine for mpox.	30-May-2025
SOB-005	In order to ensure adequate monitoring of safety and efficacy of IMVANEX in the active immunisation against smallpox and disease caused by vaccinia virus, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of IMVANEX.	Status to be reported annually within each annual reassessment

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK OF 1 VIAL
PACK OF 10 VIALS
PACK OF 20 VIALS

1. NAME OF THE MEDICINAL PRODUCT

IMVANEX suspension for injection
Smallpox and monkeypox vaccine (Live Modified Vaccinia Virus Ankara)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) has a titre of no less than 5 x 10^7 Inf.U (Inf.U = infectious units)

3. LIST OF EXCIPIENTS

Trometamol
Sodium chloride
Water for injections
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.

1 single dose vial.
10 single dose vials.
20 single dose vials.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Thaw at room temperature (15°C - 25°C). Gently swirl for at least 30 seconds.
Read the package leaflet before use.

For more information, scan here or visit https://imvanex.qrdoc.bavarian-nordic.com
QR code to be included

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (-20°C +/-5°C):
EXP (-50°C +/-10°C):
EXP (-80°C +/-10°C):

9. SPECIAL STORAGE CONDITIONS

Store in a freezer (at -20°C +/-5°C or -50°C +/-10°C or -80°C +/-10°C) protected from light. Expiry date depends on storage temperature.
For additional information on thawing, shelf-life and storage, see package leaflet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirement.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bavarian Nordic A/S
Philip Heymans Allé 3
DK-2900 Hellerup
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/855/001
EU/1/13/855/002
EU/1/13/855/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IMVANEX® injection
Smallpox and monkeypox vaccine
SC

2. METHOD OF ADMINISTRATION

Subcutaneous use

3. EXPIRY DATE

EXP (-20°C):
EXP (-50°C):
EXP (-80°C):

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

IMVANEX suspension for injection
Smallpox and monkeypox vaccine (Live Modified Vaccinia Virus Ankara)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IMVANEX is and what it is used for

IMVANEX is a vaccine used to prevent smallpox, monkeypox and disease caused by vaccinia virus in adults and adolescents aged 12 years and older.

When a person is given the vaccine, the immune system (the body's natural defence system) will produce its own protection in the form of antibodies against the smallpox, monkeypox and vaccinia viruses.
IMVANEX does not contain smallpox virus (Variola) or monkeypox virus or vaccinia viruses. It cannot spread or cause smallpox, monkeypox or vaccinia infection and disease.

2. What you need to know before you are given IMVANEX

You must not receive IMVANEX:

- if you are allergic or have previously had a sudden life-threatening allergic reaction to the active substance or any of the other ingredients of this medicine (listed in section 6) or chicken protein, benzonase, gentamicin or ciprofloxacin which may be present in the vaccine in very small amounts.

Warnings and precautions

Talk to your doctor or nurse before receiving IMVANEX:
- if you have atopic dermatitis (see section 4).
- if you have HIV infection or any other condition or treatment leading to a weakened immune system.
- if you are feeling nervous about the vaccination process or have ever fainted following any needle injection.

The protective efficacy of IMVANEX against smallpox, monkeypox and disease caused by vaccinia virus has not been studied in humans.

In case of illness with high temperature, your doctor will postpone the vaccination until you are feeling better. The presence of a minor infection, such as a cold, should not require postponement of the vaccination, but talk to your doctor or nurse first.

IMVANEX may not fully protect all people who are vaccinated.

Prior vaccination with IMVANEX may modify the cutaneous response (‘take’) to subsequently administered replication-competent smallpox vaccine resulting in a reduced or absent take.

Other medicines or vaccines and IMVANEX

Tell your doctor or nurse if you are taking or have recently taken any other medicines or if you have recently received any other vaccine.

Pregnancy and breast-feeding

If you are a pregnant or breast feeding, think you may be pregnant or are planning to have a baby, ask to your doctor for advice. The use of this vaccine during pregnancy and breast-feeding is not recommended. However, your doctor will assess whether the possible benefit in terms of preventing smallpox, monkeypox and disease caused by vaccinia virus would outweigh the potential risks to you and your foetus/baby.

Driving and using machines

There is no information on the effect of IMVANEX on your ability to drive or use machines. However, it is possible that if you experience any of the side effects listed in section 4, then some of these may affect your ability to drive or use machines (e.g. dizziness).

IMVANEX contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ’sodium-free’.

3. How IMVANEX is given

You can be given this vaccine whether or not you have received smallpox vaccination in the past.

The vaccine will be injected under the skin, preferably into the upper arm, by your doctor or a nurse. It must not be injected into a blood vessel.

If you have never been vaccinated against smallpox, monkeypox or vaccinia viruses:
- You will receive two injections.
- The second injection will be given no less than 28 days after the first.
- Make sure you complete the vaccination course of two injections.

If you have previously been vaccinated against smallpox, monkeypox or vaccinia viruses:
- You will receive one injection.
- If your immune system is weakened you will receive two injections with the second injection no less than 28 days after the first.

If you miss an appointment for your injection of IMVANEX

If you miss a scheduled injection, tell your doctor or nurse and arrange another visit.

If you have any further questions on the use of this vaccine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Serious side effects
Contact a doctor immediately, or go immediately to the emergency department of your nearest hospital if you experience any of the following symptoms:
- difficulty in breathing
- dizziness
- swelling of the face and neck.

These symptoms may be a sign of a serious allergic reaction.

Other side effects

If you already have atopic dermatitis, you may experience more intense local skin reactions (such as redness, swelling and itching) and other general symptoms (such as headache, muscle pain, feeling sick or tired), as well as a flare-up or worsening of your skin condition.

The most common side effects reported were at the site of injection. Most of them were mild to moderate in nature and resolved without any treatment within seven days.

If you get any of the following side effects, tell your doctor.

Very common (may affect more than 1 in 10 people):
- headache,
- aching muscles,
- feeling sick,
- tiredness,
- pain, redness, swelling, hardness or itching at the injection site.

Common (may affect up to 1 in 10 people):
- chills,
- fever,
- joint pain, pain in extremities,
- loss of appetite,
- lump, discolouration, bruising or warmth at the injection site.

Uncommon (may affect up to 1 in 100 people):
- nose and throat infection, upper respiratory tract infection,
- swollen lymph nodes,
- abnormal sleep,
- dizziness, abnormal skin sensations,
- muscle stiffness,
- sore throat, runny nose, cough,
- diarrhea, vomiting,
- rash, itch, skin inflammation,
- bleeding, irritation,
- underarm swelling, feeling unwell, flushing, chest pain, pain in the armpit,
- increase of cardiac laboratory values (like Troponin I), liver enzyme increased, white blood cell count decreased, mean platelet volume decreased.

Rare (may affect up to 1 in 1 000 people):
- sinus infection,
- influenza,
- redness and discomfort in the eye,
- hives (nettle rash),
- skin discolouration,
- sweating,
- skin bruising,
- night sweats,
- lump in skin,
- back pain,
- neck pain,
- muscle cramps,
- muscle pain,
- muscle weakness,
- swelling of the ankles, feet or fingers,
- faster heart beat,
- ear and throat ache,
- abdominal pain,
- dry mouth,
- spinning sensation (vertigo),
- migraine,
- nerve disorder causing weakness, tingling or numbness,
- drowsiness,
- scaling, inflammation, abnormal skin sensation, reaction at the injection site, rash, numbness, dryness, movement impairment, vesicles at the injection site,
- weakness,
- influenza like illness,
- swelling of the face, mouth and throat,
- white blood cell count increased,
- bruising.

Unknown (cannot be estimated from the available data):
- temporary one-sided facial drooping (Bell's palsy).

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IMVANEX

Keep this medicine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the label after Exp. The expiry date refers to the last day of that month.

Store in a freezer (at -20°C +/-5°C or -50°C +/-10°C or -80°C +/-10°C). Expiry date depends on storage temperature. Do not refreeze the vaccine once thawed. After thawing, the vaccine can be stored at 2°C–8°C in the dark for up to 2 months within the approved shelf-life prior to use.

Store in the original package to protect from light.

6. Contents of the pack and other information

What IMVANEX contains
One dose (0.5 ml) contains:
- The active substance is Modified Vaccinia Ankara – Bavarian Nordic Live virus[1], no less than 5 x 10^7 Inf.U*
  *infectious units
  [1]Produced in chick-embryo cells

- The other ingredients are: trometamol, sodium chloride, and water for injections.

This vaccine contains trace residues of chicken protein, benzonase, gentamicin and ciprofloxacin.

What IMVANEX looks like and contents of the pack

Once the frozen vaccine has been thawed, IMVANEX is a light yellow to pale white, milky suspension for injection.

IMVANEX is provided as a suspension for injection in a vial (0.5 ml).
IMVANEX is available in packs containing 1 single dose vial, 10 single dose vials or 20 single dose vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Bavarian Nordic A/S
Philip Heymans Allé 3
DK-2900 Hellerup
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tel +45 3326 8383
e-mail regulatory@bavarian-nordic.com

Manufacturer
Bavarian Nordic A/S
Hejreskovvej 10A,
3490 Kvistgaard
Denmark

This leaflet was last revised in

This medicine has been authorised under ‘exceptional circumstances’.
This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Instructions for preparation and administration of the vaccine:

The vial should be allowed to reach a temperature between 8°C and 25°C before use. Swirl gently before use. Visually inspect the suspension prior to administration. In case of any particles and/or abnormal appearance, the vaccine should be discarded.
Each vial is for single use.

A dose of 0.5 ml is withdrawn into a syringe for injection.

After thawing, the vaccine can be stored at 2°C–8°C in the dark for up to 2 months within the approved shelf-life prior to use.

Do not refreeze the vaccine once thawed.

In the absence of compatibility studies, this vaccine must not be mixed with other vaccines.