SUMMARY OF PRODUCT CHARACTERISTICS

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 adults (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 18 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 (1st, 2nd 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	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)**
				Peripheral sensory neuropathy 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	Rigor/Chills Injection site nodule Injection site discolouration Injection site haematoma	Underarm swelling Malaise Injection site haemorrhage Injection site irritation Flushing	Axillary pain Injection site exfoliation Injection site inflammation Injection site paraesthesia	-
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 induration Injection site pruritus Fatigue	Injection site warmth	Chest pain	Injection site reaction Injection site rash 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:
Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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)
	AD	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 and special populations

SCR - PRNT			**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	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)
	AD	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)

[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 13

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-0242	Healthy	61	-	83.6 (71.9, 91.8)	79.7 (67.2, 89.0)	NA
POX-MVA-0112	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-0242	Healthy	61	-	73.8 (60.9, 84.2)	71.2 (57.9, 82.2)	NA
POX-MVA-	Healthy	9	-	75.0 (34.9, 96.8)	62.5 (24.5, 91.5)	85.7 (42.1, 99.6)

0112	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 (61.4, 80.6)	23.3 (15.2, 35.9)	5.4 (1.8, 12.2)	1.3 (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 = enzymelinked 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 noninferior 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).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with IMVANEX in all 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).

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 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)

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