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 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 $TCID_{50}$ *

*50% tissue culture infectious dose
[1] Produced in chick embryo cells

This vaccine contains trace residues of gentamicin (see section 4.3).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

Pale milky coloured homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against smallpox 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):
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):
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 should receive two booster doses. The second booster vaccination should be given no less than 28 days after the first dose.

Paediatric population

The safety and efficacy of IMVANEX in individuals below 18 years of age have not been established.

Method of administration

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

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 and gentamicin).

4.4 Special warnings and precautions for use

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.

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.

IMVANEX should not be administered by intravascular injection.

The protective efficacy of IMVANEX against smallpox has not been studied. 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.

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

Data have been generated in HIV infected individuals with CD4 counts $\geq$ 200 cells/µl and $\leq$ 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 4 weeks should be avoided.

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 the use of IMVANEX should be avoided during pregnancy unless it is considered that the possible benefit in terms of preventing smallpox would outweigh the potential risk.

Breast-feeding

It is not known whether IMVANEX is excreted in human milk.

IMVANEX should be avoided during breastfeeding unless it is considered that the possible benefit in terms of preventing smallpox would outweigh the potential risk.

Fertility:

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

4.7 Effects on ability to drive and use machines

Some of the undesirable effects mentioned in section 4.8 may affect the ability to drive or operate machinery (e.g. dizziness).

4.8 Undesirable effects

Summary of the safety profile
The safety of IMVANEX has been assessed in 16 clinical trials in which 1855 Vaccinia-naïve individuals received two doses 1 x 10^8 $TCID_{50}$ 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 summary 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)

Table 1: **Adverse Reactions Reported in Completed Clinical Trials with IMVANEX (N = 3445 subjects)**

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)
Infections and Infestations	-	-	Nasopharyngitis Influenza Upper respiratory tract infection	Sinusitis Conjunctivitis
Blood and Lymphatic System Disorders	-	-	Lymphadenopathy	-
Metabolism and Nutrition Disorders	-	Appetite disorder	-	-
Psychiatric Disorders	-	-	Sleep disorder	-
Nervous System Disorders	Headache	Dizziness	Paraesthesia	Peripheral sensory neuropathy
Ear and Labyrinth Disorders	-	-	Vertigo	-
Cardiac Disorders	-	-	-	Tachycardia
Respiratory, Thoracic and Mediastinal Disorders	-	-	Pharyngolaryngeal pain Rhinitis Cough	-
Gastrointestinal Disorders	Nausea	-	Diarrhoea Vomiting Dry mouth Abdominal Pain	-
Skin and Subcutaneous Tissue Disorders	-	-	Rash Pruritus Dermatitis Skin discolouration Ecchymosis Hyperhidrosis Urticaria	Night sweats
Musculoskeletal and Connective Tissue Disorders	Myalgia	Pain in extremity Arthralgia	Back pain Neck pain Musculoskeletal stiffness Muscle spasms	Musculoskeletal pain Muscular weakness
General Disorders and Administration Site Conditions	Injection site pain Injection site erythema Injection site induration Injection site	Injection site discolouration Injection site nodule Injection site haematoma Injection site warmth Chills	Injection site irritation Injection site haemorrhage Injection site exfoliation Injection site paraesthesia	Oedema peripheral

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)
	swelling Injection site pruritus Fatigue	Underarm swelling	Injection site inflammation Injection site reaction Injection site rash Injection site movement impairment Application site anesthesia Flushing Axillary pain Chest pain Asthenia Malaise	
Investigations	-	Body temperature increased Troponin I increased Pyrexia	Hepatic enzyme increased White blood cell count decreased Mean platelet volume decreased White blood cell count increased	-
Injury, Poisoning and Procedural Complications	-	-	Contusion	-

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 0.64% 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.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccine, 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.

Immunogenicity in humans

Seroconversion rates 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 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:

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)

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)

[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; [2] Full Analysis Set (FAS); [3] Per Protocol Analysis Set (PPS), [4] seropositivity rates

Seroconversion rates 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.

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)

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);

Long-term immunogenicity 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:

		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; 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, induced by either licensed smallpox vaccines a long time ago or two years after IMVANEX.

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	1688
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; PRNT = plaque reduction neutralization test; S+ = Seropositivity rate; GMT = geometric mean titre.

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 infection by active immunisation against smallpox infection and disease (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under 'exceptional circumstances'.
This means that due to the lack of smallpox disease in the world 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 vaccine must not be mixed with other medicinal products.

6.3 Shelf life

2 years

After thawing, the vaccine should be used immediately. However, the physico-chemical in-use stability has been demonstrated for 12 hours when stored at 2°C -8°C in the dark.
Do not re-freeze a vial once it has been thawed.

6.4 Special precautions for storage

Store in a freezer (-20°C ± 5°C)
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 size of 20.

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature 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.

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

7. MARKETING AUTHORISATION HOLDER

Bavarian Nordic A/S
Hejreskovvej 10a
DK-3490 Kvistgaard
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/855/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 July 2013

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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