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 x 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 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 children below 18 years 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, 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.

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. See section 5.1.

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 ≥ 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 4 weeks should be avoided.

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 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 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 5×10^7 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 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)
Rare (≥1/10,000 to <1/1,000)

Table 1: **Adverse Reactions Reported in Completed Clinical Trials with IMVANEX (N = 7,082 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 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 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	Rigor/Chills Injection site nodule	Underarm swelling Malaise	Axillary pain Injection site exfoliation

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)
	Injection site erythema Injection site swelling Injection site induration Injection site pruritus Fatigue	Injection site discolouration Injection site haematoma Injection site warmth	Injection site haemorrhage Injection site irritation Flushing Chest pain	Injection site inflammation Injection site paraesthesia 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

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.

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

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)
POX-MVA-013[2]	Healthy	2,119[6]	N/A[5]	N/A[5]	99.7 (99.4; 99.9)

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; [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

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	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; 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 randomized 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).

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 because of 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 at -20°C +/-5°C
5 years at -50°C +/-10°C
5 years at -80°C +/-10°C

After thawing, the vaccine should be used immediately or if previously stored at -20°C +/-5°C, the vaccine can be stored at 2°C–8°C in the dark for up to 8 weeks 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.

If previously stored at -20°C +/-5°C, the vaccine can be stored short-term in a refrigerator at 2°C–8°C for up to 8 weeks 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 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
Philip Heymans Allé 3
DK-2900 Hellerup
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
Date of the last renewal: 23 April 2018

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.

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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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:

Description	Due date
To ensure adequate monitoring of effectiveness, the applicant should 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 re-assessment application

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK OF 20 VIALS

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Trometamol
Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.

20 single dose vials.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Thaw at room temperature. Gently swirl for at least 30 seconds.
Read the package leaflet before use.

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.

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

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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® suspension for injection
Smallpox vaccine

2. METHOD OF ADMINISTRATION

Subcutaneous use

3. EXPIRY DATE

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

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

Store in a freezer (at -20°C +/-5°C or -50°C +/-10°C or -80°C +/-10°C) protected from light.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

IMVANEX suspension for injection
Smallpox 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 infection in adults.

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 virus.
IMVANEX does not contain smallpox virus (Variola) and cannot spread or cause smallpox.

2. What you need to know before you receive IMVANEX

You must not receive IMVANEX:

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

- if you are ill with a high temperature. In this case, 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.

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.

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

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 would outweigh the potential risks of giving you this vaccine.

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 medicinal product 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:

- 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:

- 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 forget to receive 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 1000 people):
- sinus infection,
- influenza,
- pink 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.

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 should be used immediately or if previously stored at -20°C +/-5°C, the vaccine can be stored at 2°C–8°C in the dark for up to 8 weeks 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 5×10^7 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 pack containing 20 vials.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Bavarian Nordic A/S
Philip Heymans Allé 3
DK-2900 Hellerup
Denmark
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 {**MM/YYYY**}

This medicine has been authorised under 'exceptional circumstances'.
This means that because of scientific reasons 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

---

The following information is intended for healthcare professionals only:

Instructions for preparation and administration of the vaccine:

The vaccine should be allowed to reach room temperature 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.

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

After thawing, the vaccine should be used immediately or if previously stored at -20°C +/-5°C, the vaccine can be stored at 2°C–8°C in the dark for up to 8 weeks 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.