PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

IMVAMUNE®

Smallpox Vaccine Modified Vaccinia Ankara-Bavarian Nordic® (live-attenuated, non-replicating)

Suspension for Injection

at least 0.5 x 10^8 Inf.U/ per 0.5 mL single dose

ATC code: J07BX

Bavarian Nordic A/S
Hejreskovvej 10A
3490 Kvistgaard
Denmark

Manufactured for:
Progress Therapeutics Inc.
1151 Gorham Street, Suite #8
Newmarket, Ontario L3Y 8Y1

Date of Revision:
April 06, 2017

Submission Control No: 204531

Date of Approval: July 12, 2017

Table of Contents

IMVAMUNE®

Smallpox Vaccine Modified Vaccinia Ankara-Bavarian Nordic® (live-attenuated, non-replicating)

HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR VACCINATION AGAINST SMALLPOX INFECTION AND DISEASE BASED ON LIMITED CLINICAL TESTING IN HUMANS

PART I: HEALTH PROFESSIONAL INFORMATION

Health Canada has authorized the sale of the IMVAMUNE based on limited clinical testing in humans under the provision of the Extraordinary Use New Drug regulations. The authorization is based on the Health Canada review of the available quality, non-clinical and clinical data. Health Canada considers that the benefit/risk profile of IMVAMUNE is favourable for active immunization against small pox in individuals who have a contraindication to other approved smallpox vaccines.
As part of the authorization for sale for IMVAMUNE Health Canada has requested the sponsor agree to post-market commitments. Adherence to these commitments, as well as updates to information on quality, non-clinical, and clinical data will be continuously monitored by Health Canada.

SUMMARY PRODUCT INFORMATION

Pharmacotherapeutic group: Other viral vaccines.
ATC code: J07BX

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection (s.c.)	Suspension for injection at least 0.5 x 10^8 Inf.U/0.5 mL	Tris buffer (10 mM Tris containing 140 mM NaCl, pH 7.7): Tris-hydroxymethyl-amino methane, sodium chloride, water for injection and hydrochloric acid Tris-hydroxymethyl-amino methane, sodium chloride, water for injection *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

IMVAMUNE® is a live viral vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic® (MVA-BN®), an attenuated non-replicating orthopox virus. MVA-BN® is grown in chicken embryo fibroblast cells, harvested, concentrated, purified and suspended in a Tris buffer (10 mM Tris containing 140 mM NaCl, pH 7.7). The vaccine contains trace amounts of host cell DNA and protein, benzonase and gentamicin. No preservative or adjuvant is added to the formulation.

Each 0.5 mL dose of vaccine is supplied as a liquid frozen suspension in a 2 mL glass vial for subcutaneous use. Each single dose has a MVA-BN® titer of at least 0.5 x 10^8 Inf.U /0.5 mL (Inf.U = infectious units).

INDICATIONS AND CLINICAL USE

IMVAMUNE® (MVA-BN®) is indicated for limited use by the Canadian Government in an emergency situation for active immunization against smallpox infection and disease.

IMVAMUNE® is indicated for persons 18 years of age and older who have a contraindication to the first or second generation smallpox vaccines. This includes individuals with immune deficiencies and skin disorders.

The indication is supported by clinical trials which include individuals who are human immunodeficiency virus (HIV) infected (CD4 ≥ 200 cells/μL) and who have atopic dermatitis (AD).

The vaccine may be used for both primary vaccination and revaccination.

Geriatrics (≥ 56 years of age): IMVAMUNE® has been administered to 120 subjects 56 to 80 years of age. No overall differences in safety and immunogenicity were observed between these subjects and those < 56 years of age.

Pediatrics (< 18 years of age):
IMVAMUNE® has not been studied in subjects below 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to this vaccine or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Individuals who show hypersensitivity reactions after receiving the first dose of the vaccine should not be given the second dose.
- As with other vaccines, vaccination with IMVAMUNE® must be postponed in persons with acute febrile conditions if used for non-emergency (pre-event) prophylaxis.

WARNINGS AND PRECAUTIONS

General

- As with any other vaccine, vaccination with IMVAMUNE® may not result in protection in all cases.
- As with all injectable vaccines, appropriate medical treatment and supervision should always be available to treat rare cases of anaphylactic reactions following the administration of the vaccine.
- IMVAMUNE® should not be administered intravascularly

Special Populations

Pregnant Women:
There is no information on the use of IMVAMUNE® during pregnancy. Animal reproductive studies did not reveal any evidence of impaired fertility or harm to the fetus.

IMVAMUNE® should be administered to pregnant women only if they are at risk of infection with variola virus and if the benefit of immunization outweighs the potential risks to the mother and fetus.

Nursing Women:

Safety during lactation has not been established. It is not known whether vaccine antigens or antibodies are excreted in human milk.

IMVAMUNE® should be administered to women who are breastfeeding only if they are at risk of infection with variola virus and if the benefit of immunization outweighs the potential risks.

Pediatrics (< 18 years of age):
IMVAMUNE® has not been studied in subjects below 18 years of age. Before the eradication of smallpox disease, smallpox vaccination was administered routinely during childhood since the benefits were considered to outweigh the risks.

IMVAMUNE® should be administered to children only if they are at risk of infection with variola virus and if the benefit of immunization outweighs the potential risks to the child.

Geriatrics (> *56* years of age):
IMVAMUNE® has been administered to 120 subjects 56 to 80 years of age. No overall differences in safety and immunogenicity were observed between these subjects and those < 56 years of age.

Immunosuppressed Individuals:
Data are available only for HIV positive individuals with CD4 counts ≥ 200. An adequate immune response may be diminished in HIV positive individuals as well as in other patients with immunodeficiency or patients receiving immunosuppressive therapy.

Monitoring and Laboratory Tests
Replicating smallpox vaccines have been associated with myopericarditis. If a vaccinated subject exhibits signs and symptoms potentially associated with cardiac disorder (e.g., chest pain or discomfort, dyspnea, palpitations), ECG and troponin I test should be performed. In case of ECG changes or troponin I elevations, further cardiologic examination should be performed

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Safety was assessed in 17 completed clinical trials where approximately 12,000 doses were given to 6448 subjects. The most common local adverse drug reactions at the injection site after vaccine administration are pain, erythema, induration and swelling. The most common systemic adverse drug reactions observed after vaccination are fatigue, headache, myalgia, and nausea. Most of the reported adverse drug reactions were of mild to moderate intensity and resolved within the first seven days following vaccination. No trends have been identified suggesting the occurrence of any particular unexpected adverse reactions or classes of adverse reactions following the administration of IMVAMUNE®. In particular, despite close cardiac monitoring no confirmed case of myocarditis, pericarditis, endocarditis or any other type of cardiac inflammatory disease (or related syndromes) was recorded.
In addition, IMVAMUNE® has been tested in individuals with contraindications to receiving

traditional, replicating smallpox vaccines, i.e. HIV infected persons and AD patients. The safety profile of IMVAMUNE® in immune compromised subjects has been shown to be comparable to that recorded for healthy individuals. IMVAMUNE® has been studied in more than 600 subjects infected with HIV to evaluate its immunogenicity and safety in an immunocompromised population. Since HIV directly infects T helper cells, and also indirectly impairs other immune system responses, HIV infection can be considered as being exemplary also for other forms of immunodeficiency.
AD subjects developed slightly more frequent and more intense reactions that are typically observed after vaccination (local skin reactions such as injection site erythema, injection site swelling and injection site pruritus; general symptoms like headache, myalgia, chills, nausea, and fatigue). No indication or trend could be detected that a vaccination with IMVAMUNE® worsens the intensity of AD.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates and is provided below for reference.

Data sources: Summarized 6-month safety data of all completed clinical Phase I trials POX-MVA-001, POX-MVA-002, POX-MVA-004, POX-MVA-007; Phase I/II trials POX-MVA-010 and HIV-POL-002 (IMVAMUNE® control group only); Phase II trials POX-MVA-005, POX-MVA-008, POX-MVA-009, POX-MVA-011, POX-MVA-023, POX-MVA-024, POX-MVA-028, POX-MVA-029, POX-MVA-030 and HIV-NEF-004 (IMVAMUNE® control group only) ; and Phase III trial POX-MVA-013 (total N=6448)

Doses ranging from $1x10^6$ to $1x10^8$ Inf.U were administered in studies POX-MVA-001, POX-MVA-002 and POX-MVA-004; in all remaining studies, only the standard dose was utilized. The following populations were included:

- Vaccinia-naïve, healthy, 18-55 years of age
- Vaccinia-experienced, healthy, 18-55 years of age
- IMVAMUNE® -experienced, healthy, 20-57 years of age
- Vaccinia-experienced, healthy, elderly 56-80 years of age
- Vaccinia-naïve, HIV-1 infected, 18-55 years of age
- Vaccinia-experienced, HIV-1 infected, 18-55 years of age
- Vaccinia-naïve, atopic dermatitis (AD), 18-40 years of age
- Vaccinia-naïve, allergic rhinitis (AR), 18-40 years of age

The following frequencies of Adverse Drug Reactions (n= 6448) have been reported in these completed clinical trials with IMVAMUNE® (Table 1).

Table 1 - Adverse Drug Reactions Reported by ≥ 1% of Subjects in Completed IMVAMUNE® Clinical Trials (N=6448)

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 Conjunctivitis Influenza
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
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	Urticaria Ecchymosis Hyperhidrosis 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	Rigor/Chills Injection site discolouration Injection site nodule	Underarm swelling Injection site warmth Injection site haemorrhage	Injection site rash Oedema peripheral Asthenia Injection site

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)
	erythema Injection site swelling Injection site induration Injection site pruritus Fatigue	Injection site haematoma	Injection site irritation Flushing Axillary pain Chest pain Injection site exfoliation Injection site inflammation Injection site paraesthesia Injection site reaction	anesthesia Injection site dryness Injection site movement impairment Malaise 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.

Abnormal Hematologic and Clinical Chemistry Findings
There were no safety concerns with regard to haematological parameters, clinical chemistry or urine analysis across studies.

Post-Market Adverse Drug Reactions
Not applicable

DRUG INTERACTIONS

Use with other vaccines:
Interactions with other vaccines have not been established. Therefore, concomitant administration of other vaccines should be avoided. If co-administration with another vaccine is indicated, immunization should be carried out on separate limbs. To minimize the potential risk of interactions, it is recommended to administer killed vaccines > 2 weeks and live vaccines ≥ 4 weeks before or after administration of IMVAMUNE®.

Use with immunoglobulins:
Interaction with concomitant administration of immunoglobulins has not been established.

Drug-Drug Interactions
Concomitant administration of combination antiretroviral therapy in the majority of the HIV-1 infected study population did not reveal any undesirable interaction regarding the efficacy and safety of IMVAMUNE®.
Interactions with other drugs have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Not applicable.

Recommended Dose and Dosage Adjustment
The primary vaccination schedule in Vaccinia-naïve individuals consists of two doses of 0.5 mL four weeks apart administered by the subcutaneous route.
Missed Dose
If the primary vaccination schedule in Vaccinia-naïve individuals is not completed full protection against smallpox might not be achieved. The second dose, if missed, should be given as soon as possible (see CLINICAL TRIALS, Study Results POX-MVA-005).

Booster Dose
Individuals previously vaccinated against smallpox with either a traditional smallpox vaccine or IMVAMUNE® can be re-vaccinated with a single subcutaneous 0.5 mL dose of IMVAMUNE® to boost their immune response.
Since no persistency data beyond two years after priming are available for IMVAMUNE®-experienced persons, the recommended booster schedule is to administer a single dose of IMVAMUNE® every two years (see CLINICAL TRIALS, Study Results POX-MVA-023).

Administration
IMVAMUNE® should be administered by subcutaneous injection, preferably in the deltoid region of the non-dominant upper arm. The vaccine must not be administered intravascularly.

Each vial is for single use only and should not be used for more than one individual. The entire contents of the vial should be injected.

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

OVERDOSAGE

No case of overdose has been reported.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

IMVAMUNE® does not contain smallpox virus (variola) and cannot spread or cause smallpox.

Smallpox Disease
Smallpox is caused by variola virus, an orthopoxvirus of the *Poxviridae* family. Variola can only infect humans and has no animal reservoir. It is transmitted from person-to-person, mainly via the respiratory route, and has a high mortality rate (30%). There is no specific treatment and the only prevention is vaccination.

Following eradication of smallpox in 1980, smallpox vaccination was discontinued. Evidence that smallpox virus may be in the possession or is recreated by DNA synthesis by nations with militant intent or terrorist organizations has led to concerns regarding its use for biological warfare and/or bio-terrorism At present the majority of the world's population has no existing immunity to smallpox. The intentional release of this highly contagious virus would therefore have devastating effects. Vaccination against smallpox remains the single most important control measure. There is no drug treatment available for smallpox and thus pre-exposure protection against the disease is essential.

Mechanism of Action
Clinical and pre-clinical studies have shown that both humoral and cellular immune responses induced in animal species (i.e. mice and monkeys) and individuals vaccinated with IMVAMUNE® are comparable to immune responses induced by traditional vaccines used to eradicate smallpox. Furthermore, animal model challenge studies performed in mice and monkeys have shown that IMVAMUNE® confers protection against other pox virus infections and disease comparable to that conferred by traditional vaccines used to eradicate smallpox. This is particularly important since there is no known single correlate of protection against smallpox infection.

Duration of Effect
Data on long-term immunogenicity covering a period of 24 months following primary vaccination with IMVAMUNE® are currently available. Although antibody titers tend to decrease to low levels two years after priming, these can be readily boosted following a single booster dose of IMVAMUNE® to even higher peak GMT responses (ELISA and PRNT) compared to the primary response. Repeated exposure to IMVAMUNE® (booster vaccination) increases the antibody titers (3.4-fold higher GMTs by ELISA and 2.7-fold higher GMT by PRNT) compared to the priming vaccination (see CLINICAL TRIALS, Study Results POX-MVA-005 and POX-MVA-023).

Booster Dose
There is limited data on long-term immunogenicity following a booster dose in vaccinia-experienced and in IMVAMUNE®-experienced, healthy subjects. However, two weeks after a single booster dose, even higher antibody titers (ELISA and PRNT) are observed than after priming. Assuming a similar decline of antibody titers as in the primed population, data suggests that a booster dose every two years is sufficient in vaccinia-experienced and in IMVAMUNE®-experienced, healthy subjects (see CLINICAL TRIALS, Study Results POX-MVA-023).

STORAGE AND STABILITY

Store frozen at -20°C ± 5°C or -50°C ±10°C or -80°C ±10°C .
Expiry date depends on storage temperature.
Can be stored at 2°C – 8°C for up to 2 weeks.

After thawing, the vaccine should be used immediately or can be stored at 2°C – 8°C for up to 2 weeks prior to use.

Do not refreeze a vial once it has been thawed.

Store in the original package in order to protect from light.

Do not use after the expiry date shown on the label.

SPECIAL HANDLING INSTRUCTIONS

Thaw at room temperature. To ensure homogeneity upon thawing, the vial should be swirled gently (not shaken) for at least 30 seconds. After thawing, the drug product should appear as a pale milky colored homogeneous suspension. The liquid vaccine should be visually inspected for any foreign particulate matter prior to administration. In case of foreign particulate matter being visible, the vaccine must not be used.

After thawing, the vaccine should be used immediately or can be stored at 2°C – 8°C for up to 2 weeks prior to use.
Do not re-freeze a vial once it has been thawed.

Store in the original package in order to protect from light.

The injection volume of 0.5 mL per dose should be withdrawn with a syringe using an injection needle long enough to reach the bottom of the vial. After withdrawal of the vaccine, the injection needle should be changed to a s.c. injection needle and the vaccine administered to the subject immediately.

Sterile needles should be used for withdrawal and administration of IMVAMUNE®.
Needles and vial should be properly disposed.

IMVAMUNE® is a vaccine suspension and is supplied in a package of twenty 2 mL injection vials each containing one single standard dose (at least $0.5x10^8$ Inf.U per dose) of liquid-frozen vaccine.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

Suspension for injection

Composition

Each vial of liquid-frozen IMVAMUNE® is formulated to have a titer of at least $0.5x10^8$ Inf.U per 0.5 mL (1 dose) of MVA-BN®.
Each dose contains 0.61 mg Tris-hydroxymethyl-amino methane and 4.1 mg sodium chloride.
The product contains no preservatives and no adjuvants.

Packaging

IMVAMUNE® is supplied as a single dose in a 2 mL type I borosilicate glass vial closed with a sterile bromobutyl rubber stopper, crimped with an aluminium cap and covered with a polypropylene closure

IMVAMUNE® is supplied in a package of twenty 2 mL single dose vials.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Smallpox Vaccine Modified Vaccinia Ankara-Bavarian Nordic® (live-attenuated, non-replicating)

Product Characteristics

IMVAMUNE® is a live viral vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic® (MVA-BN®), a highly attenuated orthopox virus. MVA-BN® is grown in chicken embryo fibroblast cells, harvested, concentrated, purified and suspended in a Tris buffer (10 mM Tris containing 140 mM NaCl, pH 7.7). The vaccine contains trace amounts of host cell DNA and protein, benzonase and gentamicin. No preservative or adjuvant is added to the formulation.

Each vial of liquid-frozen IMVAMUNE® is formulated to have a titer of at least $0.5x10^8$ Inf.U per dose (0.5 mL) of MVA-BN® (standard dose).

The vaccine is stored frozen at -20°C ± 5°C or -50°C ±10°C or -80°C ±10°C.
Expiry date depends on storage temperature.
Can be stored at 2°C – 8°C for up to 2 weeks.

After thawing, the vaccine should be used immediately or can be stored at 2°C – 8°C for up to 2 weeks prior to use.

Do not refreeze a vial once it has been thawed.

Store in the original package in order to protect from light.

After thawing, IMVAMUNE® is a pale milky colored homogeneous suspension.

CLINICAL TRIALS

An overview with regard to the main 6 pivotal clinical trials with IMVAMUNE® is given below. Overall, 7 pivotal and several supportive trials have been completed to gather data about IMVAMUNE®.

Study demographics and trial design

Clinical trials included vaccinia-naïve and vaccinia-experienced adults (age 18 – 55) and vaccinia-experienced elderly (age 56 – 80) subjects. IMVAMUNE® has been studied in healthy subjects, > 600 subjects infected with HIV and in 381 subjects with atopic dermatitis.

Table 2: Trial Design and Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
POX-MVA-005	Phase II, partially double-blind, partially randomized, placebo-controlled, non-inferiority study Safety and immunogenicity of IMVAMUNE® in vaccinia-naïve and vaccinia-experienced subjects (18-55 years)	One or two standard doses of MVA-BN® s.c. administration at Day 0 (1 dose schedule) or Day 0 and 28 (2 dose schedule) **Group 1:** 2 doses IMVAMUNE® **Group 2**: 1 dose IMVAMUNE®, 1 dose Placebo **Group 3**: Placebo **Group 4:** 1 dose IMVAMUNE®	N total = 745 **Vaccinia-naïve** **Group 1** N=183 **Group 2** N= 181 **Group 3** N=181 **Vaccinia-experienced** **Group 4** N=200	**Overall** 29.8 years (18-55) **Vaccinia-naïve** **Group 1** 25.3 years (18- 50) **Group 2** 25.4 years (18-44) **Group 3** 26.0 years (18- 50) **Vaccinia-experienced** **Group 4** 41.5 years (22- 55)	**Overall** M: 314 (42.1%) F: 431 (57.9%) **Vaccinia-naïve** **Group 1** M: 86 (47.0%) F: 97 (53.0%) **Group 2** M: 69 (38.1%) F: 112 (61.9%) **Group 3** M: 74 (40.9%) F: 107 (59.1%) **Vaccinia-experienced** **Group 4** M: 85 (42.5%) F: 115 (57.5%)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
POX-MVA-023	Phase II, open-label booster study Safety and immunogenicity of single booster with IMVAMUNE® in former POX-MVA-005 vaccinees	One standard dose of MVA-BN® two years after priming with either one or two doses of IMVAMUNE® s.c. administration at Day 0	**Booster Set**[1] N total = 152 **Group 1** N = 75 **Group 2** N = 77 **Persistence Set**[2] N total = 304 (152 + 152) **Group 1** N = 92 (75+17) **Group 2** N = 91 (77+14) **Group 4** N = 121	**Booster Set**[1] **Overall** 27.6 years (20-52) **Group 1** 27.3 years (20-52) **Group 2** 27.9 years (20- 46) **Persistence Set**[2] **Overall** 34.6 years (20 -57) **Group 1** 27.7 years (20- 52) **Group 2** 27.7 years (20-46) **Group 4** 44.9 years (26-57)	**Booster Set**[1] **Overall** M: 67 (44.1%) F: 85 (55.9%) **Group 1** M: 35 (46.7%) F: 40 (53.3%) **Group 2** M: 32 (41.6%) F: 45 (58.4%) **Persistence Set**[2] **Overall** M: 132 (43.4%) F: 172 (56.6%) **Group 1** M: 42 (45.7%) F: 50 (54.3%) **Group 2** M: 36 (39.6%) F: 55 (60.4%) **Group 4** M: 54 (44.6%) F: 67 (55.4%)
POX-MVA-008	Phase II, open-label, controlled, multicenter Safety and immunogenicity of IMVAMUNE® in vaccinia-naïve AD subjects compared to healthy subjects	Two standard doses of MVA-BN® s.c. administration at Day 0 and 28	**N = 632** **AD subjects N = 350** **Healthy subjects N = 282**	**AD subjects 27.9 years (18-42)** **Healthy subjects 27.4 years (18-41)**	**Males:** **AD subjects 127 (36.3%)** **Healthy 132 (46.8%)** **Females:** **AD subjects 223 (63.7%)** **Healthy subjects 150 (53.2%)**

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
POX-MVA-011	Phase II Safety and immunogenicity of IMVAMUNE® in vaccinia-naïve and vaccinia-experienced HIV infected subjects compared to healthy subjects	Two standard doses of MVA-BN® s.c. administration at Day 0 and 28	**N total= 579** **Healthy naïve N = 88**	**Healthy naïve 28.9 years (18-52)**	**Healthy naïve Male: 38 (43.2%) Female: 50 (56.8%)**
			Healthy experienced N = 9	**Healthy experienced 45.6 years (25-56)**	**Healthy experienced Male: 5 (55.6%) Females: 4 (44.4%)**
			HIV infected naïve N = 351	**HIV infected naïve 36.8 years (18-54)**	**HIV infected naïve Male: 287 (81.8%) Female: 64 (18.2%)**
			HIV infected experienced N = 131	**HIV infected experienced 44.6 years (25-55)**	**HIV infected experienced Male: 110 (84.0%) Female: 21 (16.0%)**
POX MVA-024	Phase II Safety and immunogenicity of one and two doses of IMVAMUNE® smallpox vaccine in 56-80 year old vaccinia-experienced subjects	Two standard doses of MVA-BN® or one Placebo dose and one standard dose s.c. administration at Day 28 or Day 0 and 28	**N total = 120**	**Overall 63.7 years (56 – 80)**	**Male total = 43 (35.8 %)** **Female Total= 77 (64.2 %)**
			2 doses IMVAMUNE® N = 62	**2 doses IMVAMUNE® 64.6 years (56 – 77)**	**2 doses IMVAMUNE® Male: 25 (40.3 %)** **Female: 37 (59.7%)**
			1 dose Placebo/ 1 dose IMVAMUNE® N = 58	**1 dose Placebo/ 1 dose IMVAMUNE® 62.6 (56 – 80)**	**1 dose Placebo/ 1 dose IMVAMUNE® Male: 18 (31.0%)** **Female: 40 (69.0%)**

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Mean age (Range)	Gender
POX-MVA-013	Phase III, randomised, double-blind, placebo-controlled, non-inferiority trial Immunogenicity and safety of three consecutive production lots of IMVAMUNE® in healthy, vaccinia-naïve subjects	Two standard doses of MVA-BN® or two Placebo doses s.c. administration at Day 0 and 28	**N total = 4005** **2 doses IMVAMUNE® N = 3003** **2 doses Placebo N = 1002**	**Overall 27.7 years (18 – 40)** **2 doses IMVAMUNE® 27.7 years (18 – 40)** **2 doses Placebo 27.7 years (18 – 40)**	**Male total = 1919 (47.9 %)** **Female total = 2086 (52.1 %)** **2 doses IMVAMUNE® Male: 1456 (48.5 %)** **Female: 1547 (51.5%) 2 doses Placebo Male: 463 (46.2%)** **Female: 539 (53.8%)**

1 Subjects of Groups 1 and 2 who received a booster vaccination in study POX-MVA-023.
2 Subjects of Groups 1 and 2 who received a booster vaccination (booster set) in study POX-MVA-023 plus Group 1, 2 and 4 subjects who had a blood draw only in POX-MVA-023.

Study results

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 IMVAMUNE® 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 IMVAMUNE®. Seroconversion by ELISA and PRNT were as follows:

Table 3: Seroconversion rates 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-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[4]	Healthy	2119[6]	NA[5]	NA[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-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[4]	Healthy	2119[6]	NA[5]	NA[5]	99.8 (99.5, 99.9)

[1]Day 7/14 corresponding to 1 or 2 weeks after the first IMVAMUNE® 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 IMVAMUNE® dose; Day 42 corresponding to 2 weeks following the second dose of IMVAMUNE®; SCR = Seroconversion rate; [2] Full Analysis Set (FAS); [3] Per Protocol Analysis Set (PPS);[4] Immunogenicity Analysis Set (IAS) subset used for immunogenicity analysis (first 700 subjects enrolled per group); [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 titers following a single vaccination with IMVAMUNE®.

Table 4: Seroconversion rates 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)

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 IMVAMUNE®; Day 7/14 corresponding to 1 or 2 weeks after vaccination with IMVAMUNE® (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 IMVAMUNE®; 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 IMVAMUNE® are currently available as shown below:

Table 5: Long-term immunogenicity in human

		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 neutralization test; SCR = seroconversion rate;
*represents seropositivity rates

Booster Dose

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

Table 6: Booster Dose

Primary immunization		**N**	**Day 0[1]**		**N**	**Day 7[1]**		**Day 14[1]**	
	ELISA		**S+ %**	**GMT**		**S+ %**	**GMT**	**S+ %**	**GMT**
2 doses of IMVAMUNE®		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 IMVAMUNE®		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 IMVAMUNE® (pre-booster); Day 7 and 14 corresponding to 1 or 2 weeks after booster vaccination with IMVAMUNE®; 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.

DETAILED PHARMACOLOGY

Due to the absence of naturally occurring smallpox, the clinical efficacy of a smallpox vaccine cannot be directly demonstrated in humans, since it is not feasible and would not be ethical to expose people to an artificial smallpox infection (challenge). Therefore, clinical efficacy was inferred from nonclinical studies using animal challenge models as well as in clinical studies where immune responses induced by IMVAMUNE® and by licensed smallpox vaccines were compared.

Non-clinical pharmacology data

The pharmacodynamic properties of IMVAMUNE® were assessed in mice and non-human primates (NHP). Variola, the causative agent of smallpox in humans, belongs to the orthopox family of viruses, which includes a number of closely related poxviruses e.g. mousepox virus (ectromelia virus [ECTV]), cowpox virus, monkeypox virus (MPXV) and vaccinia virus (VV). It has been well established that exposure to one of the poxviruses provides protection from some of the other orthopox family members and indeed, smallpox has been eradicated by a worldwide vaccination campaign using various VV strains e.g. Lister-Elstree or New York City Board of Healthy (e.g. Dryvax®).

Animal efficacy data have been generated in four separate animal models that have been specifically developed to demonstrate the efficacy of IMVAMUNE® in comparison to traditional smallpox vaccines.

Two NHP studies using either a systemic (i.v.) or respiratory (i.t..) lethal challenge with MPXV have demonstrated:

- A single vaccination of IMVAMUNE® ($1x10^8$ Inf.U) induces a comparable peak immune response (antibody and T cell) compared to ACAM2000™ in cynomolgus macaques. A prime-boost regime of IMVAMUNE® induced a higher peak antibody response (by ELISA and PRNT) compared to ACAM2000™.
- A single or prime-boost vaccination of IMVAMUNE® ($1x10^8$ Inf.U) induced a comparable efficacy as afforded by ACAM2000™ and protected NHP from severe disease associated with a lethal challenge (i.v. or i.t.) of MPXV.
- There were no differences in the associated blood viral loads, weight loss or clinical scores between the animals vaccinated with either a single or prime-boost regime of IMVAMUNE® compared to ACAM2000™ treated animals following the lethal MPXV challenge (i.v. or i.t.).

Two murine models that utilize a lethal intranasal (i.n.) challenge with either VV Western Reserve (WR) or ECTV that closely mimic smallpox infection in humans were used to test vaccine efficacy. Findings from these studies demonstrated the following:

- A single vaccination with IMVAMUNE® induces a comparable immune response (antibody and T cells) as traditional smallpox vaccines (Elstree, Dryvax® and ACAM2000™).
- A single vaccination with IMVAMUNE® induces comparable protection in mice challenged (i.n.) with 50x murine lethal dose 50 (MLD_{50}) VV-WR as traditional smallpox vaccines (Elstree, Dryvax® and ACAM2000™).
- Similarly, vaccination of IMVAMUNE® induces a robust protection in mice challenged (i.n.) with lethal doses of ECTV (58x to 580x MLD_{50}).
- Within 3-4 days of a single IMVAMUNE® vaccination, mice are protected from a lethal (50x MLD_{50}) challenge (i.n.) with VV-WR, while animals vaccinated with traditional smallpox vaccines (e.g. Dryvax®) are only protected 10-14 days later.
- A single vaccination with IMVAMUNE® can induce protection in immune suppressed animals on the same day as a lethal challenge with ECTV. IMVAMUNE® can protect all animals when given 2 days post challenge (post exposure) with a lethal dose of ECTV [(1)].
- There was a negative correlation between seroconversion (by ELISA) and VV titers in the lungs following a lethal challenge with VV-WR, pointing towards antibody responses as a good predictor for protection. Seroconversion by ELISA was correlated to the ability to predict protection in the mouse VV-WR challenge model. Using the optimal dose of IMVAMUNE® ($1x10^8$ Inf.U) or 10-fold less, seroconversion by PRNT also correlated with protection.

Clinical pharmacology data

A direct comparison of immune responses (ELISA and PRNT) in humans to a licensed smallpox vaccine (e.g. Dryvax®) provided a means of inferring efficacy, taking into account comparative ELISA and PRNT responses in animal challenge studies. These lethal animal challenge studies in two species have shown protection in mice and NHP while using a traditional licensed smallpox vaccine (e.g. Dryvax® or ACAM2000™) as a comparator. Additional immunogenicity data generated in humans provide further support of clinical efficacy as follows:

- The ability of IMVAMUNE® to boost a pre-existing immunity in vaccinia-experienced subjects (ELISA and PRNT) can be seen as supporting clinical efficacy, as demonstrated for ACAM2000™. Boosting an immune response in subjects previously vaccinated with a smallpox vaccine with a proven efficacy was evidence that ACAM2000™ is capable of providing protection against smallpox in this population. The same effect has been demonstrated for IMVAMUNE® in two large clinical Phase II trials (POX-MVA-005 and POX-MVA-011 that enrolled vaccinia-experienced subjects: IMVAMUNE® provided a strong booster response (ELISA and PRNT) in healthy and HIV infected subjects previously vaccinated with a smallpox vaccine of proven efficacy against smallpox.
- A single dose of IMVAMUNE® in vaccinia-naive subjects induces a long-lived B cell memory that can be boosted to the same antibody levels as in subjects vaccinated according to the standard schedule (2 IMVAMUNE® doses): Two years after priming with either one or two doses of IMVAMUNE®, the memory response (ELISA and

PRNT) to a single booster dose of IMVAMUNE® is rapid (within 7 days), stronger compared to the primary responses (> 2.5-fold), and comparable to that observed in people previously vaccinated with a licensed smallpox vaccine with proven efficacy (POX-MVA-023).

- A Phase I study (POX-MVA-002) performed at a time when Dryvax® was still licensed in the US and permitted for use in clinical trials demonstrated that the peak and long-term immune responses (ELISA and PRNT) induced by IMVAMUNE® were comparable to those induced by Dryvax® in healthy vaccinia-naïve subjects.
- In the same phase I study, prior vaccination of healthy, vaccinia-naïve subjects with two doses of IMVAMUNE® prevented or attenuated the vaccine take following a subsequent vaccination with Dryvax® as judged by either the absence of or a significant reduction in redness/ swelling, healing time and VV titers in the skin pustule. The prevention and/or attenuation of the Dryvax® lesion has historically been associated with pre-existing immunity against smallpox infections, acquired either by previous vaccination(s) using conventional smallpox vaccines or a prior smallpox infection.
- IMVAMUNE® induced comparable, Variola virus neutralizing titers compared to subjects vaccinated with Dryvax®. In vitro evaluation of the peak response sera obtained from study POX-MVA-002 demonstrated that the immune response elicited by IMVAMUNE®, measured by the ability to neutralize variola virus (PRNT), was comparable to that elicited by Dryvax®. In addition, 90% titers at serum dilutions > 1:160 were only observed with IMVAMUNE® and not with Dryvax®.
- A retrospective study demonstrated comparability of total (ELISA) and neutralizing antibodies (PRNT) induced in healthy vaccinia-naïve subjects after vaccination with IMVAMUNE®. Responses from 2 clinical studies (POX-MVA-005 and POX-MVA-011) were compared to responses obtained from 5 NIH / DMID sponsored studies with Dryvax®/Wetvax.
- In a Phase III Study (POX-MVA-013) consistency of three consecutively produced MVA-BN lots was proven in terms of humoral immunogenicity (PRNT GMT equivalence).
- In 17 completed clinical trials, IMVAMUNE® has demonstrated the ability to induce a fast and strong, vaccinia-specific immune response. Included are healthy vaccinia-naïve and vaccinia-experienced populations as well as populations that are contraindicated to receive traditional smallpox vaccines, such as HIV-1 infected and AD patients. The immunogenicity endpoints of these studies (seroconversion rates and GMTs by ELISA and PRNT) were based on historical (epidemiological and immunological) evidence that a measurable immune response against orthopoxviruses is correlated with the appearance of a take and/or protection and therefore likely to predict clinical benefit.

TOXICOLOGY

The safety and toxicity of IMVAMUNE® was evaluated in repeated dose studies in rats and rabbits. Embryo-fetal development studies (segment II) were performed in rats and rabbits, and a peri- and postnatal development toxicity study (segment III) was performed in rats. The local tolerance of IMVAMUNE® was evaluated as part of the repeat-dose toxicity studies.

Table 7: Toxicology Studies Overview

Type of Study	Species	Route of Administration	Dosing level (Inf.U)	Schedule/Duration
Repeat-dose toxicity	Rats / Crl:CD(SD)	Subcutaneous	4.9×10^8	4 applications within 22 days
	Rabbits / New Zealand White	Subcutaneous	4.9×10^8	2 applications at 8 days interval
	Rabbits / New Zealand White	Subcutaneous	1×10^7, 1×10^8	3 applications within 42 days
	Rabbits / New Zealand White	Subcutaneous	1×10^7, 1×10^8	3 applications within 42 days
Reproductive and develop-mental toxicity	Rats / Crl(Wi)BR-Wistar	Subcutaneous	1×10^7, 1×10^8	2 immunizations at 2 weeks interval
	Rabbits / New Zealand White	Subcutaneous	1×10^7, 1×10^8	3 immunizations at 2 weeks interval
	Rats / Crl:(Wi)BR-Wistar	Subcutaneous	1×10^7, 1×10^8	3 immunizations at 2 weeks interval

IMVAMUNE® did not cause any life-threatening toxicity and there were no adverse changes in observed clinical signs, ophthalmology, clinical chemistry, urinalyses, gross tissue evaluation, organ weights or histopathologic tissue evaluation indicative of direct target organ toxicity when administered to rats and rabbits at doses up to 4.9×10^8 Inf.U applied up to 4 times within a period of 42 days. The dose of 4.9×10^8 Inf.U is approx. 5 times the dose (in absolute terms) and 20 - 200 times the dose (based on mg/kg) to be used in humans (i.e. 1×10^8 Inf.U of IMVAMUNE®; two-dose vaccination regimen).

Haematological parameters did not provide any evidence for immunotoxic effects.

Local tolerance was evaluated in biodistribution studies as well as in the repeat-dose toxicity studies. The only reported clinical observations were swelling and red discoloration at the injection site.

In development toxicity studies, IMVAMUNE® (up to 1×10^8 Inf.U; highest tested dose) had no adverse effect on gestation, lactation and maternal behaviour in female dams and on the behavioural/functional development of the offspring (F1 generation) of treated female rats and rabbits. No adverse effects on embryo-fetal development were observed when dosing IMVAMUNE® 14 days prior to the day of sperm positivity (Day –14) and on the day of sperm positivity (Day 0) in rats and at 14 days prior to the day of sperm positivity (Day –14), on the

day of sperm positivity (gestation Day 0), and on gestation Day 14 in rabbits. Vaccination with IMVAMUNE® yielded a robust, dose dependent antibody response in dams and conferred passive immunity to their litters, confirming this species as relevant animal model for toxicity testing. Overall, nonclinical studies provided no evidence of perinatal toxicity or teratogenicity IMVAMUNE®.

No specific juvenile animal studies were performed.

The toxicity study results demonstrate that IMVAMUNE® induces reversible and vaccine expected side effects.

REFERENCES

1 Samuelsson, C., Hausmann, J., Lauterbach, H., Schmidt, M., Akira, S., Wagner, H., Chaplin, P., Suter, M., O'Keeffe, M., and Hochrein, H. (2008). Survival of lethal poxvirus infection in mice depends on TLR9, and therapeutic vaccination provides protection. *J Clin Invest* **118**, 1776-1784.

2 Damon I, Davidson W, Hughes C, Olson V, Smith S, Holman R, Frey S, Newman F, Belshe R, Yan L and Karem K (2009) Evaluation of smallpox vaccines using variola neutralization. JGenVirol (Pt 8):1962-1966.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

IMVAMUNE®
Smallpox Vaccine Modified Vaccinia Ankara-BN® (live-attenuated, non-replicating)

HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR VACCINATION AGAINST SMALLPOX INFECTION AND DISEASE BASED ON LIMITED CLINICAL TESTING IN HUMANS

Health Canada has authorized the sale of the IMVAMUNE based on limited clinical testing in humans under the provision of the Extraordinary Use New Drug regulations. The authorization is based on the Health Canada review of the available quality, non-clinical and clinical data. Health Canada considers that the benefit/risk profile of IMVAMUNE is favourable for active immunization against smallpox in individuals who have a contraindication to other approved smallpox vaccines.
As part of the authorization for sale for IMVAMUNE Health Canada has requested the sponsor agree to post-market commitments. Adherence to these commitments, as well as updates to information on quality, non-clinical, and clinical data will be continuously monitored by Health Canada.
This vaccine is for exclusive use by the Canadian Government.

Read this carefully before you start taking **IMVAMUNE®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IMVAMUNE®**.

What is IMVAMUNE® used for?
- IMVAMUNE® is a vaccine that helps protect against smallpox infection and disease.
- IMVAMUNE® is indicated for individuals 18 years of age and older who have a contraindication to other approved smallpox vaccines. This could include individuals:
  - Who are human immunodeficiency virus infected (CD4 $\geq$ 200 cells/µL)
  - Who have atopic dermatitis

How does IMVAMUNE® work?
IMVAMUNE® is used for vaccination (active immunization) against smallpox virus.
IMVAMUNE® activates your immune system to help protect you from smallpox infection and disease.
IMVAMUNE® does not contain smallpox virus (variola virus) and cannot spread or cause smallpox.

What are the ingredients in IMVAMUNE®?

Medicinal ingredients: Smallpox Vaccine Modified Vaccinia Ankara-BN® (live-attenuated, non-replicating)

Non-medicinal ingredients: sodium chloride
Trometamol
Traces of gentamicin and residual host cell DNA and protein

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

IMVAMUNE® comes in the following dosage forms:
Suspension for injection, at least 0.5 x 10^8 Inf.U MVA-BN® / dose

Do not use IMVAMUNE® if:
$ you are below 18 years of age

Individuals with the following conditions should discuss vaccination with their physician, who will be able to advise on safe vaccination or on alternative preventative measures to avoid infection with smallpox:

- Pregnant or breast feeding woman
- Persons with fever (temperature above 38.5 °C)
- Persons with allergies to the active substance or any of the excipients (see ingredients)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IMVAMUNE®. Talk about any health conditions or problems you may have, including if you:
$ are or think you are pregnant or if you are breast feeding
$ have any known allergies
$ have a fever or you think you may be getting a fever

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines or vaccines.

How to take IMVAMUNE®:
The vaccine is to be given as a single dose by injection under the skin.

DO NOT INJECT INTRAVASCULARLY.

Usual dose:
The primary vaccination series consists of two doses of 0.5 mL each according to the following schedule:
First dose: Day 0
Second dose: 28 days after first dose
Your doctor will advise on the need for a booster dose.

Overdose:

No case of overdose has been reported.

Missed Dose:
Make sure you finish the complete vaccination course of two injections. If not, you may not be fully protected against the disease. If you miss a scheduled injection, talk to your doctor and arrange another visit.

What are possible side effects from using IMVAMUNE®?

These are not all the possible side effects you may feel when taking IMVAMUNE®. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.
Like all vaccines, IMVAMUNE® can cause side effects, although not everybody gets them.

Anaphylactic shock is a rare but very serious event. Although no cases have been observed during clinical development of IMVAMUNE®, these events may occur with any injectable vaccine. An allergic reaction causes symptoms in many parts of the body, often starting with tingling or swelling around the mouth and lips. The face and neck may swell and breathing may become difficult. Heartbeat is fast and may be irregular. A rash, hives or redness of the skin may occur and there may be diarrhea. If these symptoms occur, contact your physician or call your emergency services immediately.

The adverse reactions listed below have been observed during clinical studies. The most common side effects reported were at the injection site. Most of the reported adverse reactions are mild to moderate in intensity and resolving without intervention within seven days following vaccination.
Very common side effects reported in at least 1 in 10 persons were:
Pain, redness, swelling, hardness, or itching at the injection site.
Tiredness, headache, aching muscles, nausea.

Common side effects reported in at least 1 in 100 but less than 1 in 10 persons were:
Discolouration, nodule, bruising at the injection site, chills, fever, pain in extremity, joint pain, or loss of appetite.

Uncommon side effects reported in at least 1 in 1,000 but less than 1 in 100 persons were:
Warmth, bleeding, irritation, scaling, inflammation, sensibility disorder, or reaction at the injection site.
Underarm swelling, flushing, axillary pain, chest pain, dizziness, sensibility disorder, musculoskeletal stiffness, back pain, neck pain, rash, pruritus, dermatitis, skin discolouration, diarrhea, vomiting, dry mouth, throat pain, flu-like symptoms, cough, sleep disorder, clinically not relevant increase of cardiac enzymes, hepatic enzyme increased, white blood cell count decreased, mean platelet volume decreased, contusion, nose and throat infection, upper respiratory tract infection or temporarily enlarged lymph nodes.

Rare side effects reported in at least 1 in 1000 persons were:
Rash, anaesthesia, dryness, movement impairment or vesicles at the injection site.

Weakness, malaise, influenza like illness, oedema peripheral, migraine, peripheral nerve sensations, muscle spasms, musculoskeletal pain, muscular weakness, urticarial, ecchymosis, increased sweating, night sweats, subcutaneous nodule, angioedema, abdominal pain, increased heartbeat, sinusitis, pink eye, influenza, white blood cell count increased, vertigo.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE Angioedema (swelling of the face, mouth and throat)		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Suspected Vaccine Adverse Events

For the general public:
If you suspect you have had a serious or unexpected event following receipt of a vaccine, please ask your healthcare professional to complete the Adverse Events Following Immunization (AEFI) Form and send it to your local health unit in your province/territory.

For healthcare professionals:
If a patient experiences an adverse event following immunization, please complete the Adverse Events Following Immunization (AEFI) Form and send it to your local health unit in your province/territory.

If you have any questions or have difficulty contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:
Toll-free telephone: 1-866-844-0018
Toll-free fax: 1-866-844-5931
By email: caefi@phac-aspc.gc.ca

NOTE: Should you require information related to the management of the adverse events, please contact your health professional before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

Storage:

Store frozen at -20°C ± 5°C or -50°C ±10°C or -80°C ±10°C.
Expiry date depends on storage temperature.
Can be stored at 2°C – 8°C for up to 2 weeks.

After thawing, the vaccine should be used immediately or can be stored at 2°C – 8°C for up to 2 weeks prior to use.

Do not re-freeze a vial once it has been thawed.

Store in the original package in order to protect from light.

Do not use after the expiry date stated on the label.

Keep out of reach and sight of children.

If you want more information about IMVAMUNE®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.bavarian-nordic.com, or by calling +45-3326-8383.

This leaflet was prepared by Bavarian Nordic A/S

Last Revised April 06, 2017