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

Zabdeno suspension for injection
Ebola vaccine (Ad26.ZEBOV-GP [recombinant])

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 mL) contains:
Adenovirus type 26 encoding the *Zaire ebolavirus* (EBOV) Mayinga variant glycoprotein (GP)*, not less than 8.75 $\log_{10}$ infectious units (Inf.U)
* Produced in PER.C6 cells and by recombinant DNA technology.

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection

Colourless to slightly yellow, clear to very opalescent suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zabdeno, as part of the Zabdeno, Mvabea vaccine regimen, is indicated for active immunisation for prevention of disease caused by Ebola virus (*Zaire ebolavirus* species) in individuals ≥1 year of age (see sections 4.4 and 5.1).

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

4.2 Posology and method of administration

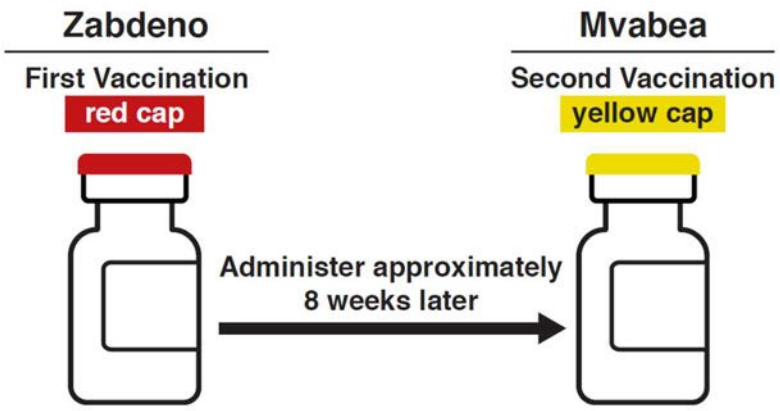
Zabdeno should be administered by a trained healthcare worker.

Zabdeno is the first vaccination in the prophylactic 2-dose heterologous Ebola vaccine regimen which consists of vaccination with Zabdeno followed by a second vaccination with Mvabea given approximately 8 weeks later (see sections 4.4 and 5.1) (refer to the SmPC for Mvabea).

Posology

Primary vaccination
A dose (0.5 mL) of Zabdeno (red cap vial) vaccine should be administered as the first vaccination.

A dose (0.5 mL) of Mvabea (yellow cap vial) vaccine should be administered as the second vaccination approximately 8 weeks after the first vaccination with Zabdeno (refer to the SmPC for Mvabea).



Booster vaccination with Zabdeno (individuals who previously received the Zabdeno, Mvabea 2-dose primary vaccination regimen)
Individuals who have previously completed the 2-dose primary vaccination regimen can receive a booster dose of Zabdeno. As a precautionary measure, a Zabdeno booster vaccination is recommended in individuals who are at imminent risk of exposure to Ebola virus and have completed the 2-dose primary vaccination regimen more than 4 months ago (see sections 4.4 and 5.1).

Corrective measures in case of inadvertent administration
If Mvabea is inadvertently administered as the first vaccination, administration of Zabdeno is recommended as the second vaccination approximately 8 weeks later.

If Zabdeno is inadvertently administered as the first and the second vaccination, additional immunisation with Mvabea is recommended approximately 8 weeks after the second vaccination with Zabdeno.

If Mvabea is inadvertently administered as the first and the second vaccination, additional immunisation with Zabdeno is recommended approximately 8 weeks after the second vaccination with Mvabea.

If the second vaccination (Mvabea) of the regimen has been delayed beyond the recommended 8 weeks after the first vaccination (Zabdeno) of the regimen, the Mvabea vaccine should be administered regardless of the elapsed time from the first vaccination with Zabdeno (see section 5.1).

Paediatric population
The posology in children aged 1 to <18 years is the same as in adults. No data are available on the safety and efficacy of the 2-dose primary vaccination regimen and the booster vaccination in children aged <1 year.

Elderly population
No dosage adjustment is required in elderly individuals ≥65 years of age.

HIV-infected individuals
No dosage adjustment is required in HIV-infected individuals with infection controlled through antiretroviral therapy (see section 5.1).

Method of administration

Zabdeno should be administered by the intramuscular (IM) route. The preferred site is the deltoid muscle of the upper arm. In younger children, either the deltoid region of the arm or anterolateral aspect of the thigh are acceptable sites for intramuscular injection.

Do not administer this vaccine intravenously or subcutaneously.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For precautions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of its excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

Hypersensitivity

Close observation is recommended following vaccination for the early signs of anaphylaxis or anaphylactoid reactions. 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. Individuals should be observed by a healthcare professional for at least 15 minutes after vaccination.

Anxiety-related reactions

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

Thrombocytopenia and coagulation disorders

The vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder because bleeding or bruising may occur following an intramuscular administration in these individuals.

Concurrent illness

Vaccination should be postponed in individuals suffering from an acute severe febrile illness or acute infection, unless the benefit of immediate vaccination outweighs the potential risks. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Immunocompromised individuals

Safety and immunogenicity of the Zabdeno, Mvabea vaccine regimen has not been assessed in immunocompromised individuals, including those receiving immunosuppressive therapy. Immunocompromised individuals may not respond as well as immunocompetent individuals to the Zabdeno, Mvabea vaccine regimen.

Level of protection

The exact level of protection afforded by the vaccine regimen is unknown.

In the absence of field efficacy data, the protective effect of the vaccine regimen in humans was inferred by the bridging of immunogenicity in humans to immunogenicity and efficacy data obtained in non-human primates (immunobridging) (see section 5.1).

If only one of the vaccines, Zabdeno or Mvabea, is received, the efficacy is expected to be reduced as compared to the 2-dose vaccine regimen.

The vaccine regimen might not protect all individuals against Ebola virus (*Zaire ebolavirus* species) disease, and ***does not replace precautions to avoid exposure to Ebola virus***. Vaccinated individuals should adhere to local guidelines and recommendations to prevent or treat exposure to Ebola virus.

The Zabdeno, Mvabea vaccine regimen should not be initiated for post-exposure prophylaxis against Ebola virus.

Duration of protection

The duration of protection is unknown. A booster dose of Zabdeno administered at various intervals after completion of a primary series with Zabdeno and Mvabea has been shown to elicit an anamnestic response (see section 5.1).As a precautionary measure, a Zabdeno booster vaccination should be considered for individuals at imminent risk of exposure to Ebola virus, for example healthcare professionals and those living in or visiting areas with an ongoing Ebola virus disease outbreak, who completed the 2-dose primary vaccination regimen more than 4 months ago (see sections 4.2 and 5.1).

Protection against Filovirus disease

The vaccine regimen is not intended to prevent diseases caused by Filoviruses other than *Zaire ebolavirus* species.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, and is considered to be essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

The safety, immunogenicity and efficacy of co-administration of Zabdeno with other vaccines have not been evaluated, and therefore, co-administration is not recommended.

If Zabdeno must be given at the same time as another injectable vaccine(s), then the vaccine(s) should always be administered at different injection sites. Do not mix Zabdeno with any other vaccine in the same syringe or vial.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Zabdeno in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Zabdeno and Mvabea vaccine regimens elicited detectable Ebola virus (EBOV) GP-specific maternal antibody titres that were transferred to the foetuses (see section 5.3).

As a precautionary measure, it is preferable to avoid vaccination with Zabdeno during pregnancy. Nevertheless, considering the severity of Ebola virus disease, vaccination should not be withheld when there is a clear risk of exposure to Ebola infection.

Breast-feeding

It is not known whether Zabdeno is excreted in human milk.
A risk to the newborns/infants from breast-feeding by vaccinated mothers cannot be excluded.

As a precautionary measure, it is preferable to avoid vaccination with Zabdeno during breast-feeding. Nevertheless, considering the severity of Ebola virus disease, vaccination should not be withheld when there is a clear risk of exposure to Ebola infection.

Fertility

No data are available on fertility in humans. A reproductive toxicity study in animals with Zabdeno and Mvabea vaccine regimens did not reveal any evidence of impaired female fertility. General toxicity studies have not revealed any effects on male sex organs that would impair male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Zabdeno has no known effect on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common local adverse reactions reported in adults who received Zabdeno were pain (47%), warmth (24%) and swelling (11%) at the injection site. The most common systemic adverse reactions were fatigue (46%), headache (45%), myalgia (36%), arthralgia (24%) and chills (23%). Most adverse reactions occurred within 7 days following vaccination and were mild to moderate in severity and of short duration (2-3 days).

The most common local adverse reaction reported in children 1 to 17 years of age who received Zabdeno was pain (24%) at the injection site. The most common systemic adverse reactions were fatigue (19%), decreased activity (16%), decreased appetite (14%) and irritability (14%). Most adverse reactions occurred within 7 days following vaccination. Most adverse reactions were mild to moderate in severity and of short duration (1-4 days).

Pyrexia was reported more frequently for younger children 1 to 3 years of age (11%) and 4 to 11 years of age (12%) compared to adolescents 12 to 17 years of age (4%) and adults (7%). The frequency of pyrexia in younger children was similar to that observed in the active control group receiving a licensed paediatric vaccine.

The safety profile of Zabdeno in children 1 to 17 years of age was generally similar to that observed in adults.

Tabulated list of adverse reactions

Adverse reactions observed during clinical studies are listed below by the following frequency categories:
very common (≥1/10);
common (≥1/100 to <1/10);
uncommon (≥1/1000 to <1/100);
rare (≥1/10000 to <1/1000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adults
Table 1 shows the adverse reactions reported from clinical trials in adults.

Table 1: Adverse Reactions Reported in Adults Following Vaccination with Zabdeno

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	very common	headache
	uncommon	dizziness postural
Gastrointestinal disorders	common	vomiting
Musculoskeletal and connective tissue disorders	very common	arthralgia, myalgia
Skin and subcutaneous tissue disorders	common	pruritus
General disorders and administration site conditions	very common	chills, fatigue, injection site pain, injection site swelling, injection site warmth
	common	pyrexia, injection site pruritus
	uncommon	injection site induration, injection site erythema

There were no new adverse reactions reported in adults after receiving the booster vaccination with Zabdeno.

Children 1 to 17 years of age
Table 2 shows the adverse reactions reported from clinical trials in children 1 to 17 years of age.

Table 2: Adverse Reactions Reported in Children 1 to 17 Years of Age Following Vaccination with Zabdeno

System Organ Class	Frequency	Adverse reactions
Metabolism and nutrition disorders	very common	decreased appetite
Psychiatric disorders	very common	irritability
Gastrointestinal disorders	common	vomiting, nausea
Musculoskeletal and connective tissue disorders	common	arthralgia, myalgia
General disorders and administration site conditions	very common	fatigue, decreased activity, injection site pain
	common	pyrexia, injection site pruritus, injection site swelling, injection site erythema

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: J07BX02

Mechanism of action

Zabdeno is a monovalent vaccine composed of a single recombinant, replication-incompetent human adenovirus type 26 vectored vaccine that encodes the *Zaire ebolavirus* Mayinga variant GP. The EBOV GP encoded by Zabdeno has 100% homology to the one encoded by Mvabea. Following administration, the EBOV GP is expressed locally and stimulates an immune response.

Efficacy

In the absence of efficacy data from clinical studies, the efficacy of the 2-dose primary vaccination regimen has been assessed through challenge studies in non-human primates (NHP, Cynomolgus macaques, *Macaca fascicularis*), the most relevant animal model for EBOV disease. The 2-dose primary vaccination regimen administered at an interval of 8 weeks was protective down to a first dose of 2 x 10^9 VP of Zabdeno, in combination with 1 x 10^8 Inf.U of Mvabea, in a lethal intramuscular EBOV Kikwit NHP challenge model. Humoral immune responses, as measured by the level of EBOV GP-binding antibodies, were strongly correlated to survival in NHP. Protective effect in humans has been inferred through comparison of EBOV GP-binding antibody concentrations (immunobridging).

Clinical immunogenicity

In the absence of efficacy data from clinical studies, the protective effect of the vaccine has been inferred from immunogenicity data. Data from 5 clinical studies conducted in Europe, the United States, and Africa in 764 adults 18 to 50 years of age who had received the 2-dose primary vaccination regimen at the 8-week interval were used in this analysis. Anti-EBOV GP binding antibodies were correlated with a protective effect against a rapidly progressing fully lethal Ebola virus infection in non-human primates. The human immune responses measured 21 days post-dose 2 were associated with an increase of the predicted survival probability from 0% (i.e., fully lethal) to 53.4% (98.68%CI: 33.8%; 70.9%) using the animal model. Based on this analysis, the Zabdeno, Mvabea vaccine regimen can be anticipated to have a protective effect against EBOV disease in humans. Although the relationship between antibody titre and survival has been studied only in adult NHP, immunobridging performed on paediatric subjects, the elderly and HIV-infected subjects suggests that the potential protective effects for these populations are consistent with the one estimated in adults.

Immunogenicity
Immunogenicity data are presented for a total of 842 adults and 509 children (1 to 17 years of age) who had received the 2-dose primary vaccination regimen in Phase II and III clinical studies: study EBL2001 in the UK and France, studies EBL3002 and EBL3003 in the United States, study EBL2002 in Uganda, Kenya, Burkina Faso and Cote d'Ivoire, and study EBL3001 in Sierra Leone. The concentrations of EBOV GP-specific binding antibodies were measured approximately 3 weeks after completion of the 2-dose primary vaccination regimen. These are presented as geometric mean concentrations (GMC).

Immunogenicity data in adults after the 2-dose primary vaccination regimen
The immune response to the 2-dose primary vaccination regimen given in an 8-week interval was assessed in 5 Phase II and III studies conducted in Europe, Africa and the USA (see Table 3). In all studies, 98% to 100% of study participants mounted a binding antibody response to EBOV GP, defined as more than 2.5-fold increase in binding antibody concentration over baseline value.

Table 3: EBOV GP-specific Binding Antibody Responses to the Zabdeno, Mvabea 2-dose Vaccine Regimen in Adults (8 week interval): GMC EU/mL (95% CI)

Study	Baseline	21 days post-dose 2	6 months post-dose 2	10 months post-dose 2
EBL2001	(N=70) <LLOQ (<LLOQ; <LLOQ)	(N=69) 10131 (8554; 11999)	-	(N=50) 1205 (971; 1497)
EBL2002	(N=134) 39 (<LLOQ; 48)	(N=136) 7518 (6468; 8740)	-	(N=133) 342 (291; 401)

EBL3001	(N=231) 68 (56; 81)	(N=224) 3976 (3517; 4495)	-	(N=199) 268 (234; 307)
EBL3002	(N=140) <LLOQ (<LLOQ; <LLOQ)	(N=135) 11054 (9673; 12633)	(N=131) 1263 (1100; 1450)	-
EBL3003	(N=258) <LLOQ (<LLOQ; <LLOQ)	(N=254) 11052 (9959; 12265)	(N=244) 1151 (1024; 1294)	-

Data shown for vaccinated participants who received the 2-dose vaccine regimen in the Per Protocol Analysis Set.
EU = ELISA Units
CI = Confidence interval
N = Number of participants with data
LLOQ = Lower limit of quantification

The interval between doses in these studies was 8 weeks +/- 3 days. While the immunogenicity of vaccine regimens with a longer interval between doses up to 69 weeks (483 days) was similar, vaccine regimens with an interval of 4 weeks were less immunogenic.

Following the 2-dose primary vaccination regimen with an 8-week interval, GMCs EU/mL (95% CI) of 5283 (4094; 6817) were observed in HIV-infected adults on antiretroviral therapy, with CD4+ cells >350 cells/microlitre and no signs of immunosuppression (N=59).

Immunogenicity data in children after the 2-dose primary vaccination regimen
The immune response to the 2-dose primary vaccination regimen given in an 8-week interval was assessed in children (1 to 17 years of age) in two studies conducted in Africa (see Table 4). In the two studies, 98% to 100% of study participants mounted a binding antibody response to EBOV GP. Immune responses in children were higher than those observed in adults in the same studies.

Table 4: EBOV GP-specific Binding Antibody Responses to the Zabdeno, Mvabea 2-dose Vaccine Regimen in Children 1 to 17 years of age (8 week interval): GMC EU/mL (95% CI)

Age	**Study**	**Baseline**	**21 days post-dose 2**	**6 months post-dose 2**	**10 months post-dose 2**
1-3 years	EBL3001	(N=123) <LLOQ (<LLOQ; <LLOQ)	(N=124) 22568 (18426; 27642)	(N=122) 713 (598; 849)	(N=120) 750 (629; 894)
4-11 years	EBL2002	(N=52) <LLOQ (<LLOQ; <LLOQ)	(N=53) 17388 (12973; 23306)	(N=53) 715 (602; 851)	(N=54) 637 (529; 767)
	EBL3001	(N=130) 62 (49; 78)	(N=124) 10212 (8419; 12388)	(N=126) 442 (377; 518)	(N=123) 436 (375; 506)
12-17 years	EBL2002	(N=53) <LLOQ (<LLOQ; 37)	(N=53) 13532 (10732; 17061)	(N=41) 577 (454; 734)	(N=52) 541 (433; 678)
	EBL3001	(N=142) 65 (52; 81)	(N=134) 9929 (8172; 12064)	(N=135) 469 (397; 554)	(N=132) 386 (326; 457)

Data shown for vaccinated participants who received the 2-dose vaccine regimen in the Per Protocol Analysis Set.
EU = ELISA Units
CI = Confidence interval
N = Number of participants with data
LLOQ = Lower limit of quantification

Immunogenicity data in adults after Zabdeno booster vaccination
The immune response to a booster vaccination of Zabdeno administered 1 or 2 years after the primary vaccination regimen was evaluated in 2 clinical studies (see Table 5). Booster vaccination resulted in the rapid activation of an anamnestic response, with a 40- to 56-fold increase in antibody concentrations within 7 days. The magnitude of the response in terms of fold-increase and post-booster GMC was similar irrespective of the time since primary vaccination (1 or 2 years).

Table 5: EBOV GP-specific Binding Antibody Responses to Zabdeno Booster Vaccination in Adults: GMC EU/mL (95% CI)				
Study	**Pre-booster**	**7 days post-booster**	**21 days post-booster**	**1 year post-booster**
EBL2002[a]	(N=39) 366 (273; 491)	(N=39) 20416 (15432; 27009)	(N=39) 41643 (32045; 54116)	(N=37) 4383 (2969; 6470)
EBL3001[b]	(N=29) 274 (193; 387)	(N=25) 11166 (5881; 21201)	(N=29) 30411 (21972; 42091)	(N=26) 3237 (2305; 4547)

[a] booster vaccination administered 1 year after primary vaccination

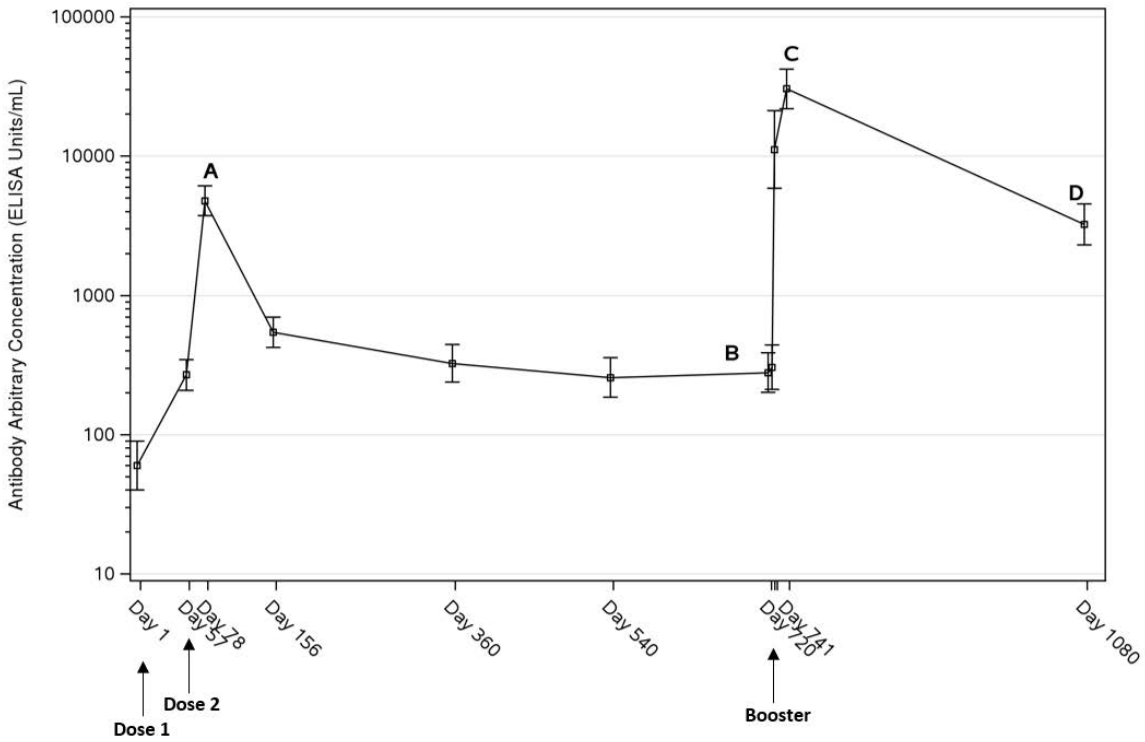
[b] booster vaccination administered 2 years after primary vaccination

Data shown for vaccinated participants who received the booster vaccination in the Per Protocol Analysis Set.
EU = ELISA Units
CI = Confidence interval
N = Number of participants with data

Long term persistence of antibodies in adults

Three weeks after completion of the 2-dose primary vaccination regimen, the immune response (GMC) reaches its peak ("A" in figure 1 below). After the peak the response declines by 6 months and remains stable at least 1 year post-dose 1 (Table 3). As illustrated by the data on 43 adults in study EBL3001, the response remains stable also at two years post-dose 1 (latest time point available) ("B" in figure 1 below). After administration of a booster dose of Zabdeno, a rapid anamnestic response is observed within 7 days. The highest binding antibody concentrations are observed 21 days post-booster dose ("C" in figure 1 below), followed by a decline in antibody concentrations. At 1 year post-booster dose, GMCs were higher than before administration of the booster dose ("D" in figure 1 below).

Figure 1. EBOV GP-specific Binding Antibody Responses after the Zabdeno, Mvabea 2-dose vaccine regimen and Zabdeno booster vaccination 2 years after the primary vaccination regimen in adults in study EBL3001[a]; GMC (95% CI)



[a] The analysis is based on the per protocol analysis set.

The error bars represent the Geometric Mean Concentration and its 95% confidence interval.

The European Medicines Agency has deferred the obligation to submit the results of studies with Zabdeno for the prevention of Ebola virus disease in one or more subsets of the paediatric population (see section 4.2 for information on paediatric use).

This vaccine has been authorised under 'exceptional circumstances'. This means that for scientific reasons it has been impossible to get complete information on this vaccine. 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 revealed no special hazard for humans based on repeated dose toxicity and local tolerance studies, and a reproductive toxicity study in rabbits.

General (repeated dose) toxicity studies, including local tolerance

Vaccination of rabbits with various Zabdeno and Mvabea vaccine regimens was well tolerated when administered intramuscularly at full human dose levels. The vaccine-related findings (reflected by inflammatory changes at the injection site, increases in fibrinogen, C-reactive protein and globulin, and microscopic findings of increased lymphoid cellularity and/or germinal centres in the draining lymph nodes and spleen) were noted to be recovering 2 weeks after the last vaccination, and reflect a normal, physiological response associated with vaccination. There were no effects noted that were considered to be adverse.

Fertility/Reproductive and Developmental Toxicity

Biodistribution studies conducted in the rabbit did not show distribution of the Ad26 vector to the gonads (testes, ovaries) following IM injection.

The general (repeated dose) toxicity studies with Zabdeno and Mvabea vaccine regimens have not revealed any effects on male sex organs that would impair male fertility. In addition, the general and/or reproductive toxicity studies did not reveal any evidence of impaired female fertility. In a reproductive toxicity study, Zabdeno and Mvabea vaccine regimens did not induce maternal or developmental toxicity following maternal exposure during the premating and gestation period. In this study, the vaccine regimens elicited detectable EBOV GP-specific maternal antibody titres that were transferred to the foetuses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Ethanol
Histidine hydrochloride monohydrate
Polysorbate-80
Sodium chloride
Sucrose
Water for injections
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

4 years at -85°C to -55°C

6.4 Special precautions for storage

Transport frozen at -25°C to -15°C. Upon receipt, the product can be stored as indicated below:

Store in a freezer at -85°C to -55°C at the distributor in case of stockpiling. The expiry date for storage at -85°C to -55°C is printed on the vial and outer carton after EXP.

The vaccine can also be stored by the distributor or end user in a freezer at -25°C to -15°C for a single period of up to 20 months. Upon removal from the -85°C to -55°C freezer, the new expiry date must be written by the distributor or end user on the outer carton and the vaccine should be used or discarded at the end of the 20 months. This new expiry date should not exceed the original expiry date (EXP). The original expiry date should be made unreadable.

The vaccine can also be stored by the distributor or end user in a refrigerator at 2°C to 8°C for a single period of up to 8 months. Upon moving the product to 2°C to 8°C storage, the discard date must be written by the distributor or end user on the outer carton and the vaccine should be used or discarded at the end of the 8 months period. This discard date should not exceed the original expiry date (EXP), or the new expiry date assigned for the -25°C to -15°C storage condition. The original expiry date and/or the new expiry date assigned for the -25°C to -15°C storage condition should be made unreadable.

Once thawed, the vaccine cannot be refrozen.

The vial must be kept in the original package in order to protect from light and to track the expiry or discard date for the different storage conditions.

6.5 Nature and contents of container

0.5 mL suspension in a single-dose Type I glass vial with a rubber stopper (chlorobutyl with fluoropolymer coated surface), aluminium crimp and red plastic cap.

Pack size of 20 single-dose vials.

6.6 Special precautions for disposal and other handling

Zabdeno is a colourless to slightly yellow, clear to very opalescent suspension. The vaccine should be inspected visually for particulate matter and discolouration prior to administration. The vial should be inspected visually for cracks or any abnormalities, such as evidence of tampering prior to administration. If any of these should exist, do not administer the vaccine.

Once the vaccine has been removed from the freezer and thawed, use immediately or store in a refrigerator at 2°C to 8°C (see section 6.4). Once removed from the refrigerator for administration, it should be used immediately.

Gently mix the contents of the vial by swirling for 10 seconds. Do not shake. Use a sterile needle and sterile syringe to extract the entire contents from the vial for administration.

Use a separate sterile needle and syringe for each individual. It is not necessary to change needles between drawing up the vaccine from a vial and injecting it into a recipient, unless the needle has been damaged or contaminated. Any remaining content in the vial should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance to local requirements. Potential spills should be disinfected with agents with viricidal activity against adenovirus.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1444/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

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 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)
Cilag GmbH International,
Janssen Vaccines,
branch of Cilag GmbH International
Rehhagstrasse 79
3018 Bern
Switzerland

Name and address of the manufacturer(s) responsible for batch release
Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

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

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

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

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
To ensure adequate monitoring of effectiveness, the applicant will perform the following study to collect data in the context of the intended use of the Ad26.ZEBOV, MVA-BN-Filo prophylactic vaccine regimen. Post-authorisation non-interventional study: - VAC52150EBLXXXX: Evaluation of a heterologous, two-dose preventive Ebola vaccine for field effectiveness	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 SIZE OF 20 SINGLE-DOSE VIALS

1. NAME OF THE MEDICINAL PRODUCT

Zabdeno suspension for injection
Ebola vaccine (Ad26.ZEBOV-GP [recombinant])

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Single-dose of 8.75 $\log_{10}$ infectious units (Inf.U) in 0.5 mL

Adenovirus type 26 encoding the *Zaire ebolavirus* (EBOV) Mayinga variant glycoprotein

3. LIST OF EXCIPIENTS

Disodium edetate, ethanol, histidine hydrochloride monohydrate, polysorbate-80, sodium chloride, sucrose, water for injections, sodium hydroxide (for pH adjustment)

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
20 single-dose vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
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

See EXP for expiry date at -85°C to -55°C.
Write new expiry date at -25°C to -15°C (maximum 20 months):_____
Write discard date at 2°C to 8°C (maximum 8 months):_____
When writing new expiry/discard date, make former expiry date unreadable.

9. SPECIAL STORAGE CONDITIONS

Store vial in the original package to protect from light and track expiry/discard date.

Store at -85°C to -55°C or at -25°C to -15°C or at 2°C to 8°C.

See the Package Leaflet to determine the expiry or discard date at the different conditions.

Transport frozen at -25°C to -15°C.

Do not refreeze the vaccine once it has been thawed.

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1444/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SINGLE-DOSE VIAL

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

Zabdeno
8.75 $\log_{10}$ Inf.U/0.5 mL
suspension for injection
Ebola vaccine (Ad26.ZEBOV-GP [recombinant])
IM

2. METHOD OF ADMINISTRATION

Intramuscular use

3. EXPIRY DATE

EXP
-85 – -55°C

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zabdeno suspension for injection
Ebola vaccine (Ad26.ZEBOV-GP [recombinant])

▼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 or your child is vaccinated 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, pharmacist or nurse.
- This vaccine has been prescribed for you or your child only. Do not pass it on to others.
- If you or your child get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zabdeno is and what it is used for

What is Zabdeno
Zabdeno is a vaccine used to protect against Ebola virus disease in the future.
It is given to people aged 1 year and older who may possibly come into contact with Ebola virus.

Zabdeno is given as the first dose of a 2-dose course of vaccinations to protect you from getting Ebola virus disease caused by the *Zaire ebolavirus*, which is a type of Filovirus. This vaccine will not protect you against the other types of Filovirus.

Because Zabdeno does not contain the whole Ebola virus, it cannot give you Ebola virus disease.

The 2-dose course of vaccinations consists of:
- a first dose of Zabdeno vaccine,
- followed around 8 weeks later by a dose with Mvabea vaccine.

Even after you have had the course of Zabdeno and Mvabea vaccination you should be **very careful** not to come into contact with Ebola virus. As with all vaccinations, the vaccination course may not fully protect everyone from Ebola virus disease.

The Zabdeno and Mvabea 2-dose course of vaccinations should be used according to official recommendations.

What is Ebola
- Ebola is a serious disease caused by a virus. People catch Ebola from people or animals who are infected with Ebola virus or who died from Ebola.
- You can catch Ebola from blood and body fluids like urine, stools, saliva, vomit, sweat, breast milk, semen and vaginal fluids of people who are infected with Ebola virus.
- You can also catch Ebola from things that have touched the blood or body fluids of a person or animal with Ebola (like clothes or objects in direct contact).

- Ebola is not spread through the air, water or food.

Ebola virus disease usually causes a high fever – and it can stop the blood from clotting, causing severe bleeding ('severe haemorrhagic fever'). This can lead to serious illness, and in some cases **death**.

- First signs and symptoms may be fever, feeling tired, weak or dizzy, and muscle aches.
- Later signs and symptoms may include bleeding under the skin, into organs in the body such as the liver or kidneys and from the mouth, eyes or ears. Some people get severe diarrhea, sudden drop in blood pressure or blood flow to the organs in the body (shock) which may cause serious and permanent damage to these organs, severe confusion (delirium), fits (seizures), kidney failure and coma.

Talk to your doctor, pharmacist or nurse first to decide if you should be given this vaccine.

How the vaccine works
The Zabdeno and Mvabea 2-dose vaccine course stimulates the body's natural defences (immune system). The vaccine works by causing the body to produce its own protection (antibodies) against the virus that causes the Ebola infection. This will help to protect against Ebola virus disease in the future.

2. What you need to know before you or your child are given Zabdeno

To make sure that the vaccination course is suitable for you or your child, it is important to tell your doctor, pharmacist or nurse if any of the points below apply to you or your child. If there is anything you do not understand, ask your doctor, pharmacist or nurse to explain.

Do not have the vaccine if

- you or your child have ever had a severe allergic reaction to any of the active substances or any of the other ingredients listed in section 6.

If you are not sure, talk to your doctor, pharmacist or nurse before you are given the vaccine.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given Zabdeno if you or your child:

- have ever had a severe allergic reaction after any other vaccine injection,
- have ever fainted, after having an injection,
- have a problem with bleeding or you bruise easily,
- currently have a fever or an infection,
- are taking medicines that weaken the immune system, such as high-dose corticosteroids (such as prednisone) or chemotherapy (cancer medicines),
- have a weak immune system – for example, due to HIV infection or an illness that runs in the family ('genetic disorder').

If any of the above apply to you or your child (or you are not sure), talk to your doctor, pharmacist or nurse before you are given Zabdeno.

If you are at high risk of being in contact with the Ebola virus, a booster vaccination with Zabdeno may be recommended for you or your child. Talk to your doctor, pharmacist or nurse if this applies to you or your child.

If you or your child only has one of the vaccines, Zabdeno or Mvabea, it may give less protection from Ebola virus disease than having a course of both vaccines.

As with all vaccines, the Zabdeno and Mvabea 2-dose course of vaccination may not fully protect everyone from Ebola virus disease and it is not known how long you will be protected.

- **People who have been given the 2-dose course of vaccination should still take precautions to avoid coming into contact with Ebola virus.**

Washing your hands correctly is the most effective way to prevent the spread of dangerous germs, like Ebola virus. It reduces the number of germs on the hands and so reduces their spread from person to person.

Proper hand washing methods are described below.
- Use soap and water when hands are soiled with dirt, blood, or other body fluids. There is no need to use antimicrobial soaps for washing hands.
- Use alcohol-based hand sanitiser when hands are not dirty. Do not use alcohol-based hand sanitiser when hands are soiled with dirt, blood, or other body fluids.

While in an area affected by Ebola, it is important to avoid the following:
- Contact with blood and body fluids (such as urine, faeces, saliva, sweat, vomit, breast milk, semen, and vaginal fluids).
- Items that may have come in contact with an infected person's blood or body fluids (such as clothes, bedding, needles, and medical equipment).
- Funeral or burial rituals that require handling the body of someone who died from Ebola.
- Contact with bats, apes and monkeys or with blood, fluids and raw meat prepared from these animals (bushmeat) or meat from an unknown source.
- Contact with semen from a man who had Ebola. You should follow safe sex practices until the virus is gone from the semen. Talk to your doctor, pharmacist or nurse for advice about how long to maintain safe sex practices.

Children younger than 1 year of age
Zabdeno must not be used in children younger than 1 year of age.

Other medicines and Zabdeno
Tell your doctor or pharmacist if you or your child are taking, have recently taken or might take, any other medicines or vaccines.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before having this vaccine if you or your child is pregnant or breast-feeding. Also do this if you think you or your child may be pregnant or are planning to have a baby.

Driving and using machines
Zabdeno has no known effect on the ability to drive and use machines.

Zabdeno contains Sodium
Zabdeno contains less than 1mmol sodium (23 mg) per dose of 0.5 mL, that is to say essentially 'sodium-free'.

Zabdeno contains ethanol (alcohol)
This medicine contains .002 mg of alcohol (ethanol) per dose of 0.5 mL. The small amount of alcohol in this medicine will not have any noticeable effects.

3. How Zabdeno is given

Your doctor or nurse will inject the vaccine into a muscle (intramuscular injection) in the upper arm or thigh.

Zabdeno must not be injected into a blood vessel.

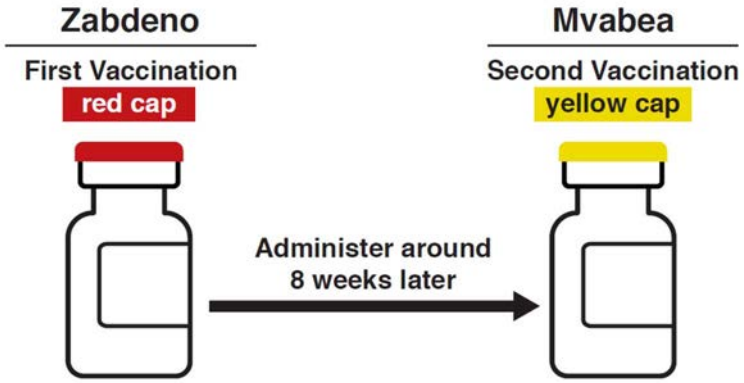
The 2-dose course of vaccination consists of:
- a dose of Zabdeno vaccine,
- followed around 8 weeks later by a dose of Mvabea vaccine.

Your doctor will tell you the date for the second vaccine.

How much vaccine will you or your child get

Primary vaccination

- First vaccination with Zabdeno – red cap vial (0.5 mL).
- Second vaccination with Mvabea – yellow cap vial (0.5 mL), given around 8 weeks after the first vaccination with Zabdeno.



Booster vaccination with Zabdeno (an extra dose of Zabdeno to increase or renew the effect of an earlier Zabdeno and Mvabea 2-dose course of vaccination)

- The booster vaccination is recommended for you or your child if you are at high risk of being in contact with the Ebola virus and you completed the 2-dose course of vaccination more than 4 months ago.
- Ask your doctor if you or your child should consider getting the booster vaccination.

During and after the injection of the vaccine, the doctor will watch over you or your child for around 15 minutes or longer as necessary in case of a severe allergic reaction.

Instructions for preparing the vaccine – for medical and healthcare professionals – are included at the end of the leaflet.

If you have an unintended or accidental injection of Zabdeno or Mvabea

- If you or your child are accidently given Mvabea as the first vaccination – you will get Zabdeno as the second vaccination around 8 weeks later.
- If you or your child are accidently given Zabdeno as the first and the second vaccination – you will get Mvabea around 8 weeks after the second vaccination with Zabdeno.
- If you or your child are accidently given Mvabea as the first and the second vaccination – you will get Zabdeno around 8 weeks after the second vaccination with Mvabea.
- If you or your child have not been given Mvabea around 8 weeks after vaccination with Zabdeno – talk to your doctor, pharmacist or nurse about getting the second vaccination with Mvabea.

If you miss an appointment for vaccination of Zabdeno or Mvabea

- If you miss an appointment, tell your doctor and arrange another visit.
- If you miss a scheduled injection, you may not be fully protected from Ebola virus.
- If you have any further questions on the use of this vaccine, ask your doctor.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them. Most of the side effects happen within 7 days of getting the injection.

The following side effects can happen in adults.

Very common (may affect more than 1 in 10 people)
- pain, warmth, or swelling where the injection is given
- feeling very tired
- headache or muscle ache
- joint pain
- chills

Common (may affect up to 1 in 10 people)
- being sick (vomiting)
- itching where the injection is given
- generalised itching
- fever

Uncommon (may affect up to 1 in 100 people)
- feeling dizzy
- redness and skin hardness where the injection is given

The following side effects can happen in children and young people 1 to 17 years of age.

Very common (may affect more than 1 in 10 people)
- pain where the injection is given
- decreased activity
- decreased appetite
- feeling irritable
- feeling very tired

Common (may affect up to 1 in 10 people)
- swelling, itching or redness where the injection is given
- being sick (vomiting)
- feeling sick (nausea)
- joint pain
- muscle ache
- fever

Most of these side effects are mild to moderate in intensity and are not long-lasting.

Reporting of side effects
If you get any side effects, talk to your doctor , pharmacist 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 Zabdeno

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

Information about storage, expiry, and use and handling are described in the section intended for healthcare professionals at the end of the leaflet.

Your doctor or pharmacist is responsible for storing this vaccine and disposing of any unused product correctly.

6. Contents of the pack and other information

What Zabdeno contains
One dose (0.5 mL) contains:

- The active substance is Adenovirus type 26 encoding the *Zaire ebolavirus* Mayinga variant glycoprotein*, not less than 8.75 $\log_{10}$ infectious units
  * Produced in PER.C6 cells and by recombinant DNA technology.

  This product contains genetically modified organisms (GMOs).

- The other ingredients (excipients) are disodium edetate, ethanol, histidine hydrochloride monohydrate, polysorbate-80, sodium chloride, sucrose, water for injections and sodium hydroxide (for pH adjustment).

What Zabdeno looks like and contents of the pack
Zabdeno is a suspension in a single-dose glass vial (0.5 mL) with a rubber stopper and red cap.

Colourless to slightly yellow, clear to very opalescent suspension.

Zabdeno is available in a pack containing 20 single-dose vials.

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Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Biologics B.V.
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This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.
This vaccine has been authorised under 'exceptional circumstances'. This means that for scientific reasons it has been impossible to get complete information on this medicine. The European Medicines Agency will review any new information on this vaccine every year and this leaflet will be updated as necessary.

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

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

The following information is intended for healthcare professionals only:
- As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in the event of an anaphylactic reaction following the administration of Zabdeno. Individuals should be observed by a healthcare professional for at least 15 minutes after vaccination.
- Zabdeno must not be mixed with other medicinal products in the same syringe.
- Zabdeno must not be administered by intravascular injection under any circumstances.
- Immunisation should be carried out by intramuscular (IM) injection preferably in the upper arm in the region of the deltoid or in the thigh.
- Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to injection with a needle. Procedures should be in place to prevent injury from falling and to manage syncopal reactions.

Instructions for administration and handling
Zabdeno is a colourless to slightly yellow, clear to very opalescent suspension. The vaccine should be inspected visually for particulate matter and discolouration prior to administration. The vial should be inspected visually for cracks or any abnormalities, such as evidence of tampering prior to administration. If there are signs of any of these, do not administer the vaccine.

Once the vaccine has been removed from the freezer and thawed, use immediately or store in a refrigerator at 2°C to 8°C (see section 6.4). Once removed from the refrigerator for administration, it should be used immediately.

Gently mix the contents of the vial by swirling for 10 seconds. Do not shake. Use a sterile needle and sterile syringe to extract the entire contents from the vial for administration.

Use a separate sterile needle and syringe for each individual. It is not necessary to change needles between drawing up the vaccine from a vial and injecting it into a recipient, unless the needle has been damaged or contaminated. Any remaining content in the vial should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance to local requirements. Potential spills should be disinfected with agents with viricidal activity against adenovirus.

Information about storage
Do not use this vaccine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Transport frozen at -25°C to -15°C. Upon receipt, the product can be stored as indicated below:

Store in a freezer at -85°C to -55°C at the distributor in case of stockpiling. The expiry date for storage at -85°C to -55°C is printed on the vial and outer carton after EXP.

The vaccine can also be stored by the distributor or end user in a freezer at -25°C to -15°C for a single period of up to 20 months. Upon removal from the -85°C to -55°C freezer, the new expiry date must be written by the distributor or end user on the outer carton and the vaccine should be used or discarded at the end of the 20 months. This new expiry date should not exceed the original expiry date (EXP). The original expiry date should be made unreadable.

The vaccine can also be stored by the distributor or end user in a refrigerator at 2°C to 8°C for a single period of up to 8 months. Upon moving the product to 2°C to 8°C storage, the discard date must be written by the distributor or end user on the outer carton and the vaccine should be used or discarded at the end of the 8 months period. This discard date should not exceed the original expiry date (EXP), or the new expiry date assigned for the -25°C to -15°C storage condition. The original expiry date and/or the new expiry date assigned for the -25°C to -15°C storage condition should be made unreadable.

Once thawed, the vaccine cannot be refrozen.

The vial must be kept in the original package in order to protect from light and to track the expiry or discard date for the different storage conditions.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES AND PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.