1. NAME OF THE MEDICINAL PRODUCT

Rabipur
Potency ≥ 2.5 IU/ml
Powder and solvent for solution for injection
Rabies, inactivated, whole virus vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (1.0 ml) contains:

Rabies virus* (Inactivated, strain Flury LEP) .....≥ 2.5 International Units
*produced on purified chick embryo cells

The vaccine contains residues of chicken proteins (e.g. ovalbumin), Human Serum Albumin, and may contain traces of neomycin, chlortetracycline, and amphotericin B. See sections 4.3 Contraindications and 4.4 Special warnings and special precautions for use.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder is white. The solvent is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rabipur is indicated for active immunization against rabies in individuals of all ages. This includes pre-exposure prophylaxis (i.e. before possible risk of exposure to rabies), in both primary series and booster dose, and post-exposure prophylaxis (i.e. after suspected or proven exposure to rabies).

4.2 Posology and method of administration

The immunisation schedules for Rabipur should be based on official recommendations.

Posology
The recommended single intramuscular (IM) dose is 1.0 ml in individuals of all ages.

PRE-EXPOSURE PROPHYLAXIS (PrEP)
Pre-exposure prophylaxis is recommended for anyone who is at continual, frequent or increased risk for exposure to the rabies virus, as a result of their residence or occupation, such as laboratory workers dealing with rabies virus and other lyssaviruses, veterinarians and animal handlers. Travellers in high-risk areas should be vaccinated after a risk assessment. Children living in or visiting rabies-affected areas are at particular risk and should be given pre-exposure prophylaxis on an individual basis or in mass campaigns when there are no economic, programmatic or logistical obstacles.

Primary immunisation
In previously unvaccinated individuals, an initial course of PrEP consists of three doses (each of l.0 ml) administered IM, according to the conventional or rapid regimen, as follows:

	Conventional regimen	Rapid regimen[1]
1st dose	Day 0	Day 0
2nd dose	Day 7	Day 3
3rd dose	Day 21 (or 28)	Day 7

[1]For previously unvaccinated adult individuals aged 18-65 years who are not able to complete the conventional PrEP regimen within 21 or 28 days (e.g. individuals requiring PrEP on short notice).

Booster

Rabipur may be used for booster vaccination after prior immunisation with human diploid cell rabies vaccine (HDCV).

The need of intermittent serological testing for the presence of antibody ≥ 0.5 IU/ml and the administration of booster doses should be assessed in accordance with official recommendations.

The following provides general guidance:

- Testing for neutralising antibodies at 6 month intervals is usually recommended if the risk of exposure is high (e.g. laboratory staff working with rabies vaccine)
- In persons who are considered to be at continuing risk of exposure to rabies (e.g. veterinarians and their assistants, wildlife workers, hunters), a serological test should usually be performed at least every 2 years, with shorter intervals if appropriate to the perceived degree of risk.

A booster would be recommended only if Rabies Virus Neutralising Antibody (RVNA) concentration falls to less than 0.5 IU/ml (assessed by rapid fluorescent focus inhibition test [RFFIT]).

Alternatively, booster doses may be given at official recommended intervals without prior serological testing according to the perceived risk. Experience shows that booster doses are generally required every 2-5 years.

The individual IM booster dose is 1.0 ml.

POST-EXPOSURE PROPHYLAXIS PEP)
Post-exposure prophylaxis according to the WHO recommendations consists of

- local treatment of the wound as soon as possible after exposure,
- a course of rabies vaccine that meets WHO recommendations
- administration of rabies immunoglobulin, if indicated.

The indication for post-exposure prophylaxis (PEP) depends on the type of contact with the suspected rabid animal, as provided in the Table below. Post-exposure immunisation should begin as soon as possible after exposure and should be accompanied by local measures to the site of inoculation so as to reduce the risk of infection.

Official guidance according to WHO PEP prophylaxis guideline should be sought regarding the appropriate concomitant measures that should be taken to prevent establishment of infection (see also section 4.4 Special warnings and special precautions for use).

Category of exposure	Type of exposure to a domestic or wild[a] animal suspected or confirmed to be rabid, or animal unavailable for testing	Recommended post-exposure prophylaxis
I	Touching or feeding animals. Licks on intact skin. Contact of intact skin with secretions or excretions of a rabid animal or human case.	None, if reliable case history is available.
II	Nibbling of uncovered skin. Minor scratches or abrasions without bleeding.	Administer vaccine immediately[b]. Stop treatment if animal remains healthy throughout an observation period of 10 days[c] or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques.
III	Single or multiple transdermal bites[d] or scratches, licks on broken skin. Contamination of mucous membrane with saliva (i.e. licks). Exposure to bats[e].	Administer rabies vaccine immediately, and rabies immunoglobulin, preferably as soon as possible after initiation of post-exposure prophylaxis. Rabies immunoglobulin can be injected up to 7 days after first vaccine dose administration. Stop treatment if animal remains healthy throughout an observation period of 10 days or is proven to be negative for rabies by reliable laboratory using appropriate diagnostic techniques.

[a] Exposure to rodents, rabbits or hares does not routinely require rabies post-exposure prophylaxis.
[b] If an apparently healthy dog or cat in or from a low-risk area is placed under observation, treatment may be delayed.
[c] This observation period applies only to dogs and cats. Except for threatened or endangered species, other domestic and wild animals suspected of being rabid should be euthanized and their tissues examined for the presence of rabies antigen by appropriate laboratory techniques.
[d] Bites especially on the head, neck, face, hands and genitals are category III exposures because of the rich innervation of these areas.
[e] Post-exposure prophylaxis should be considered when contact between a human and a bat has occurred, unless the exposed person can rule out a bite or scratch or exposure of a mucous membrane.

Previously unvaccinated individuals

The dose for intramuscular injection is 1.0 ml, according to the following regimens:

	Essen regimen (5 doses)	Zagreb regimen (4 doses)	Reduced Essen regimen (4 doses)[2]
1st dose	Day 0	Day 0, 2 doses[1]	Day 0
2nd dose	Day 3		Day 3
3rd dose	Day 7	Day 7	Day 7
4th dose	Day 14	Day 21	Day 14
5th dose	Day 28		

[1] One injection in each of the two deltoids or thigh sites.

[2] This shortened Essen regimen may be used as an alternative for healthy, fully immune competent, exposed people provided they receive wound care plus rabies immunoglobulin in category III as well as in category II exposures and a WHO-prequalified rabies vaccine.

Previously vaccinated individuals
In previously vaccinated individuals, post-exposure prophylaxis consists of two doses administered as follows:

	IM (1.0 ml dose)
1st dose	Day 0
2nd dose	Day 3

Rabies immunoglobulin is not indicated in such cases.

Dosing in different populations:

Post-exposure prophylaxis (PEP) for immunocompromised individuals
For category II and III exposures, a complete series of 5 doses is required in combination with comprehensive wound management and local infiltration of rabies immunoglobulin, according to the following regimens:

	Essen regimen[1]	Alternative to Essen[1]
1st dose	Day 0	Day 0, 2 doses[2]
2nd dose	Day 3	Day 3
3rd dose	Day 7	Day 7
4th dose	Day 14	Day 14
5th dose	Day 28	Day 28

[1] Each dose consists of 1.0 ml injected intramuscularly.
[2] Two doses of vaccine may be given on day 0, that is, a single dose of 1.0 ml vaccine should be injected into the right deltoid and another single dose into the left deltoid muscle. In small children, one dose should be given into the anterolateral region of each thigh. This would result in a total of 6 doses.

Severely immunosuppressed patients may not develop an immunologic response after rabies vaccination.

In immunocompromised patients, the neutralising antibody titre should be measured 14 days after the first injection. Patients with a titre that is less than 0.5 IU/ml should be given another two doses of vaccine simultaneously and as soon as possible. Further checks on the antibody titre should be made and further doses of vaccine should be administered as necessary. Immunosuppressive agents should not be administered during post-exposure therapy unless essential for the treatment of other conditions.

In all cases, the immunisation schedule must be followed exactly as recommended, even if the patient does not present for treatment until a considerable time has elapsed since exposure.

Method of Administration
For adults and children ≥ 2 years of age, the vaccine should be given by intramuscular injection into the deltoid muscle;
For children < 2 years, the anterolateral region of the thigh is recommended.

For instructions on reconstitution of the medicinal product before administration, see Section 6.5 Instructions for use and handling.

4.3 Contraindications

Pre-exposure prophylaxis
Rabipur should not be administered to subjects with a known hypersensitivity to any of the components of the vaccine (see sections 2. Qualitative and quantitative composition and 6.1 List of excipients).

Individuals with acute diseases requiring treatment should not be vaccinated until at least 2 weeks after recovery. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

Post-exposure prophylaxis (PEP)
In view of the almost invariably fatal outcome of rabies, no contraindication to post-exposure prophylaxis is indicated, including pregnancy.

4.4 Special warnings and special precautions for use

Patients considered to be at risk of a severe hypersensitivity reaction to the vaccine or any of the vaccine components should receive an alternative rabies vaccine if a suitable product is available.

As with all vaccines, appropriate medical treatment and supervision should be always readily available in case of a rare anaphylactic event following administration of the vaccine.

Rabipur contains residues of egg and chicken proteins, such as ovalbumin. In instances in which individuals have developed clinical symptoms of anaphylaxis such as generalized urticaria, upper airway (lip, tongue, throat, laryngeal or epiglottal) oedema, laryngeal or bronchospasm, hypotension or shock, following exposure to egg or chicken protein, the vaccination should only be administered by personnel with the capability and facilities to manage anaphylaxis post-vaccination.

Rabies vaccine must not be given by intra-gluteal injection or subcutaneously, as the induction of an adequate immune response may be less reliable. Do not administer the vaccine intradermally.

Do not inject intravascularly. Unintentional intravascular injection may result in systemic reactions, including shock.

The vaccine must not be mixed in the same syringe with other medicinal products.

If rabies immunoglobulin is indicated in addition to Rabipur vaccine, then it must be administered at an anatomical site distant to the vaccination (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Encephalitis and Guillain-Barré Syndrome have been reported to be temporally associated with the use of Rabipur (see section 4.8 Undesirable effects). The use of corticosteroids to treat adverse reactions such as these may inhibit the development of immunity to rabies (see section 4.5 Interactions). A patient's risk of developing rabies must be carefully considered, before deciding to discontinue immunisation.

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 (see section 4.8 Undesirable effects). It is important that procedures are in place to avoid injury from fainting.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

4.5 Interaction with other medicinal products and other forms of interaction

Immunocompromising conditions and immunosuppressive agents can interfere with the development of an adequate response to the rabies vaccine. Therefore, it is recommended that serological responses should be monitored in such subjects and additional doses given as necessary.

Administration of rabies immunoglobulin may be necessary for management but may attenuate the effects of concomitantly administered rabies vaccine. Therefore, it is important that rabies immunoglobulin should be administered once only for treating each at-risk exposure and with adherence to the recommended dose.

All of the rabies immunoglobulin, or as much as anatomically possible (but avoiding possible compartment syndrome), should be administered into or around the wound sites. The remaining immunoglobulin, if any, should be injected intramuscularly at a site distant from the site of the vaccine administration to avoid possible interference with simultaneously administered rabies vaccine.

Other essential inactivated vaccines may be given at the same time as Rabipur. Available clinical data support concomitant administration of Rabipur with inactivated Japanese encephalitis vaccine and conjugated MenACWY meningococcal vaccine in adult subjects (≥ 18 years); limited data are available in the paediatric population.

Concomitant vaccines should always be administered at separate injection sites and preferably into different limbs.

Almost all adult subjects achieved an adequate immune response (Rabies Viral Neutralizing Antibodies (RVNAs) ≥ 0.5 IU/ml) within 7 days after the end of a primary series of three injections of Rabipur when given concomitantly with inactivated JE vaccine according to either a rapid or the conventional PrEP schedule by the intramuscular route. From day 57 after vaccination a faster decline in immune response to rabies was observed in individuals vaccinated concomitantly with JE vaccine according to the rapid PrEP schedule compared with the concomitant conventional PrEP schedule and the rabies only conventional PrEP schedule. At day 366, percentages of subjects with RVNA concentration ≥ 0.5 IU/mL were 68%, 76%, and 80% for vaccine groups rabies/JE accelerated, rabies/JE conventional, and rabies conventional, respectively.

All adult subjects achieved an adequate immune response (RVNAs ≥ 0.5 IU/ml) within 28 days after the end of a primary series of three injections of Rabipur when given concomitantly with conjugated MenACWY vaccine according to the recommended conventional schedule by the intramuscular route.

4.6 Pregnancy and lactation

Pregnancy
No cases of harm attributable to the use of Rabipur during pregnancy have been observed.

Rabipur may be administered to pregnant women when post-exposure prophylaxis is required.

The vaccine may also be used for pre-exposure prophylaxis during pregnancy if it is considered that the potential benefit outweighs any possible risk to the foetus.

Breastfeeding
While it is not known whether Rabipur enters breast milk, no risk to the breast-feeding infant has been identified. Rabipur may be administered to pregnant and breastfeeding women when post-exposure prophylaxis is required.

The vaccine may also be used for pre-exposure prophylaxis in breastfeeding women if it is considered that the potential benefit outweighs any possible risk to the infant.

Fertility
Non-clinical reproductive and developmental toxicity studies have not been performed.

4.7 Effects on ability to drive and use machines

No studies have been carried out with Rabipur to assess the effect on the ability to drive or use machines (see section 4.8 Undesirable effects).

Some of the adverse effects described in section 4.8 Undesirable effects, may affect the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions from clinical trials
In clinical studies the most commonly reported solicited adverse reactions were injection site pain (30-85%, mainly pain due to injection) or injection site induration (15-35%). Most injection site reactions were not severe and resolved within 24 to 48 hours after injection.

Adverse reactions reported are listed according to the following frequency:
Very common ≥ 1/10
Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1,000 to < 1/100
Rare ≥ 1/10,000 to < 1/1,000
Very rare < 1/10,000.

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Common	Lymphadenopathy
Immune system disorders	Rare	Hypersensitivity
Metabolism and nutrition disorders	Common	Decreased appetite
Nervous system disorders	Very common	Headache, Dizziness
	Rare	Paraesthesia
Gastrointestinal disorders	Common	Nausea, vomiting, diarrhoea, abdominal pain/discomfort
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Urticaria
	Rare	Hyperhidrosis (sweating)
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia
General disorders and administration site conditions	Very common	Injection site reactions, malaise, fatigue, asthenia, fever
	Rare	Chills

Statistically there is no indication of increasing frequencies of primary manifestations or triggered attacks of autoimmune diseases (e.g. multiple sclerosis) after vaccination. However, in individual cases it cannot be absolutely excluded that a vaccination may trigger an episode in patients with corresponding genetic disposition. According to the current state of scientific knowledge, vaccinations are not the cause of autoimmune disease.

Adverse reactions from post-marketing spontaneous reports
The following adverse reactions have been identified during post-approval use of Rabipur. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

System Organ Class	**Adverse reactions**
Immune system disorders	Anaphylaxis including anaphylactic shock
Nervous system disorders	Encephalitis, Guillain-Barré Syndrome (see *section 4.4 Special warnings and special precautions for use*), presyncope, syncope, vertigo
Skin and subcutaneous tissue disorders	Angioedema

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually such reactions can be successfully managed with anti-inflammatory and antipyretic agents. Please see section 4.4 Special warnings and special precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction.

4.9 Overdose

Insufficient data are available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: viral vaccines, ATC-Code: J07B G01

The minimum rabies virus antibody titre recommended as being proof of an adequate immune response after vaccination is ≥ 0.5 IU/ml concentration as specified by the WHO, or a 1:5 titre (complete inhibition in the rapid fluorescent focus inhibition test [RFFIT] at 1:5 dilution) as specified by the Centers for Disease Control and Prevention (CDC). In healthy vaccinees, this level should be achieved in most individuals by Day 14 of a post-exposure regimen, with or without simultaneous administration of Rabies Immunoglobulin (RIG) and irrespective of age.

Pre-exposure Prophylaxis
In clinical trials with previously unimmunised subjects,

- Almost all subjects achieved an adequate immune response (Rabies Virus Neutralising Antibodies (RVNA) ≥ 0.5 IU/ml) by day 28 of a primary series of three injections of Rabipur when given according to the recommended schedule by the intramuscular route.
- Almost all subjects achieved an adequate immune response (RVNAs ≥ 0.5 IU/ml) within 7 days after the end of a primary series of three injections of Rabipur when given concomitantly with inactivated Japanese encephalitis vaccine according to either a rapid or the conventional PrEP schedule by the intramuscular route.
- All subjects achieved an adequate immune response (RVNAs ≥ 0.5 IU/ml) within 28 days after the end of a primary series of three injections of Rabipur when given concomitantly with conjugated MenACWY vaccine according to the recommended conventional schedule by the intramuscular route.

As antibody titres slowly decrease, booster doses are required to maintain antibody levels above 0.5 IU/ml. However, persistence of adequate antibody concentrations for up to 2 years after immunisation with Rabipur without additional booster has been found to be 100 % in clinical trials.

In clinical trials, a booster dose of Rabipur elicited a 10-fold or higher increase in Geometric Mean Concentrations (GMCs) by day 30. It has also been demonstrated that individuals who had previously been immunised with HDCV developed a rapid anamnestic response when boosted with Rabipur.

Post-exposure Prophylaxis
In clinical studies, Rabipur elicited adequate neutralising antibodies (≥ 0.5 IU/ml) in almost all subjects by day 14 or 30, when administered according to the WHO-recommended 5-dose (day 0, 3, 7, 14 and 28; 1.0 ml each, intramuscular) regimen or to the WHO recommended 4-dose (day 0 (2 doses), 7, 21; 1.0 ml each, intramuscular) regimen.

Concomitant administration of either Human Rabies Immunoglobulin (HRIG) with the first dose of rabies vaccine caused a slight decrease in GMCs. However, this was not considered to be clinically relevant nor statistically significant.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Preclinical data including single-dose, repeated dose and local tolerance studies revealed no unexpected findings and no target organ toxicity. No genotoxicity and reproductive toxicity studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
TRIS-(hydroxymethyl)-aminomethane
Sodium chloride
Disodium edetate (Titriplex III)
Potassium-L-glutamate
Polygeline
Sucrose

Solvent (syringe):
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, Rabipur must not be mixed in the same syringe with other medicinal products.

6.3 Shelf life

4 years

For shelf life after reconstitution of the medicinal product, see Section 6.5 Instructions for use and handling.

6.4 Special precautions for storage

Store at +2° to +8°C (in a refrigerator). Protect from light. Do not freeze.

For storage conditions after reconstitution of the medicinal product, see Section 6.5 Instructions for use and handling.

Nature and contents of container

Powder for 1 dose in a vial with a stopper (chlorobutyl) and 1 ml of solvent for 1 dose in a disposable pre-filled syringe (type I glass) with a plunger-stopper (bromobutyl) without needle and with a tip-cap (bromobutyl).

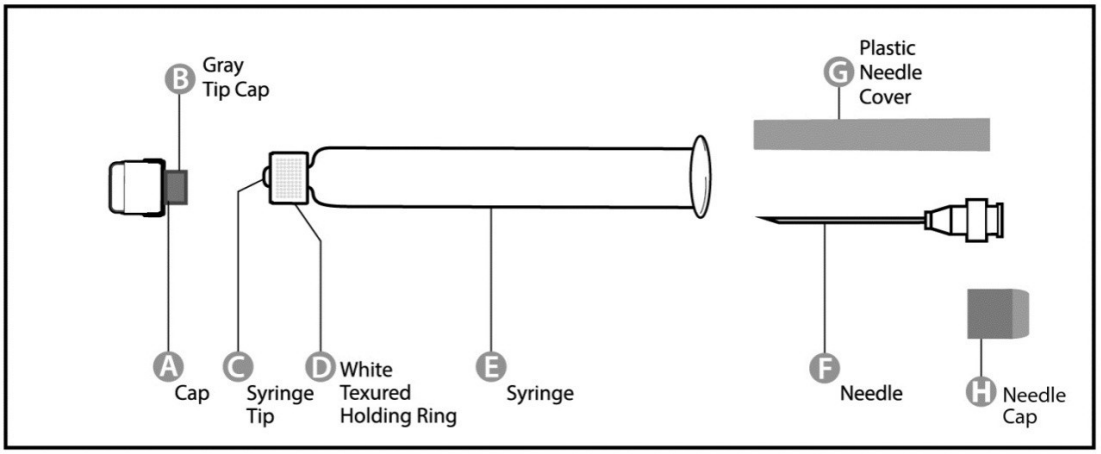
1 administration needle for injection and one needle for reconstitution.

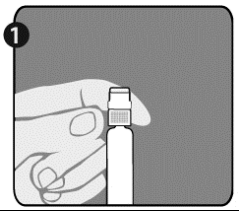
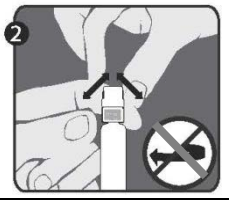
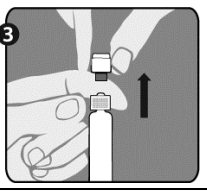
Not all pack sizes may be marketed.

6.5 Instructions for use and handling

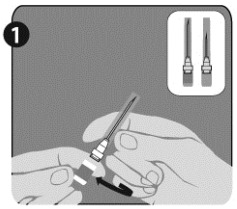
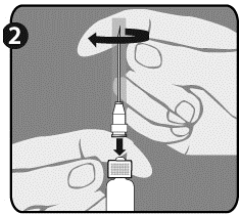
Instructions for use of Rabipur disposable pre-filled syringe

Pre-filled syringe



Step 1: With one hand, hold the syringe (E) with the cap pointing upward. Be sure to hold the syringe by the white textured holding ring (D).	
Step 2: With the other hand, grasp the cap (A) and firmly rock it back and forth to break its connection to the white textured holding ring (D). **Do not twist or turn the cap.**	
Step 3: Lift up to remove the cap (A) and the attached gray tip cap (B). Be careful not to touch the sterile syringe tip (C).	

Needle application (these instructions apply to both the green and the orange needles)

Step 1: Twist to remove the cap (H) from the green reconstitution needle. Do not remove the plastic cover (G). This needle is the longer of the two needles.	
Step 2: With one hand, firmly hold syringe (E) by white textured holding ring (D). With your other hand, insert needle (F) and twist clockwise until it locks into place. Once needle is locked, remove its plastic cover (G). The syringe (E) is now ready for use.	

Instructions for reconstituting Rabipur with the use of pre-filled syringe
The powder and solvent should be inspected visually for any foreign particulate matter and/or variation of appearance. If either is observed, do not reconstitute the vaccine.

The powder for solution should be reconstituted using the solvent for solution supplied.

Mix gently to avoid foaming.

The reconstituted vaccine is clear to slightly opalescent and colourless to slightly pink.

The reconstituted vaccine should be used immediately.

The vial of vaccine contains negative pressure. After reconstitution of the vaccine, it is recommended to unscrew the syringe from the needle to eliminate the negative pressure. After that, the vaccine can be easily withdrawn from the vial. It is not recommended to induce excessive pressure, since over-pressurization will create problems in withdrawing the proper amount of the vaccine.

For presentations where needles are provided with the pre-filled syringe presentation
After completing the reconstitution of the vaccine, remove the cap from the administration needle (as explained in step 1 for the reconstitution needle) and replace the reconstitution needle with the administration needle.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Bavarian Nordic A/S
Philip Heymans Alle 3
2900Hellerup
Denmark

8. MARKETING AUTHORISATION NUMBER

SIN13202P

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT

03 May 2021