06.12.2021

VERORAB (RABIES, INACTIVATED, WHOLE VIRUS 2.5 IU) powder and solvent for suspension for injection\ וראב אבקה וסולבנט לתרחיף להזרקה

רופא/ה נכבד/ה ,רוקח/ת נכבד/ה,

חברת מדיצ'י מדיקל בע"מ מודיעה על עדכון העלון לרופא. בהודעה זו מצוינים סעיפים בהם נעשה שינוי מהותי או שינוי המהווה החמרה. עדכונים נוספים אשר אינם מהווים החמרה או שאינם מהותיים, אינם נכללים בהודעה זו (שינוי שהינו הוספה או שינוי ניסוח מסומן כך,מחיקה מסומנת ~~כך~~ -והחמרה מסומנת ברקע צהוב).

ההתוויה הרשומה לתכשיר בישראל:

Verorab is indicated for the prevention of rabies in children and adults. It can be used before and after exposure to the rabies virus, as a primary vaccination or as a booster dose.

[....]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 mL) contains:

Rabies virus*, WISTAR Rabies PM/WI38 1503-3M strain (inactivated) ..... ≥ 2.5 IU**

* Produced in VERO cells

** Quantity measured according to the NIH test against the international standard

Excipient with known effect:
Phenylalanine ..... 41 micrograms

For the full list of excipients, see section 6.1.

Verorab may contain traces of polymyxin B, streptomycin and neomycin, used in the manufacturing process (see section 4.3~~.~~).

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection in prefilled syringe.

Before reconstitution, the powder is ~~a~~uniform white ~~and homogeneous pellet.~~in colour.

The solvent is a ~~limpid~~clear, colourless solution.

4. CLINICAL PARTICULARS

[....]

4.2 Posology and Method of Administration

[....]

Method of administration

~~VERORAB~~Precautions to be taken before handling or administering the medicinal product

The vaccine is administered ~~by~~via the intramuscular route ~~only, into the deltoid area in adults or the~~ , in the anterolateral ~~aspect~~region of the thigh muscle in infants and ~~toddlers (~~young children and in the deltoid muscle in older children and adults.

Do not inject in the buttocks region.

Do not inject via the intravascular route.

For instructions on reconstitution of the medicinal product before administration, see ~~also sections 4.4 and~~section 6.6~~).~~.

[....]

4.4. Special warnings and precautions for use

[....]

Precautions for use

Injection-schedule recommendations should be followed scrupulously.

~~Serological tests (assay of neutralising antibodies using the RFFIT - Rapid Fluorescent Focus Inhibition Test - method) should be performed regularly (see Table 1).~~
The need for serological tests (to assess seroconversion in subjects) should be determined in accordance with official recommendations.

When the vaccine is administered to subjects~~-~~ with a known immunodeficiency due to an immunosuppressive illness or a concomitant immunosuppressive treatment (such as corticosteroids), a serological test should be performed ~~2 to 4 weeks after vaccination~~to ensure that an immune response indicative of protection has been induced. In the case of post-exposure vaccination, all vaccine doses should be administered. Rabies immunoglobulins should also be administered concomitantly with the vaccine in the event of any category II or III exposure (see section 4.2).

Do not inject ~~-~~via the intravascular route: make sure the needle does not penetrate a blood vessel.

As with all injectable vaccines, appropriate medical treatment and supervision must be readily available in case of a rare anaphylactic reaction after vaccine administration, particularly in case of post-exposure in subjects with a known hypersensitivity to polymyxin B, to streptomycin, to neomycin or to any antibiotic of the same ~~group~~class.

As with all injectable vaccines, Verorab should be administered with caution in subjects with thrombocytopenia or coagulation disorders as intramuscular injection may induce bleeding in these subjects.

~~The potential risk of apnoea and the need for respiratory monitoring for 48-72 h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.~~

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs, such as transient visual disturbance and paraesthesia. It is important that procedures are in place to avoid injury from faints.

Traceability

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

Verorab contains phenylalanine, potassium and sodium

Verorab contains 41 micrograms phenylalanine per 0.5 mL dose which is equivalent to 0.68 microgram/kg for a 60 kg person. Phenylalanine may be harmful for people with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Verorab contains less than 1 mmol of potassium (39 mg) and less than 1 mmol of sodium (23 mg) per dose, that is to say essentially 'potassium-free' and 'sodium-free'.

Paediatric population

The potential risk of apnoea with the need for respiratory monitoring for 48-72 h must be carefully taken into account when administering the primary vaccination doses in very premature infants (born at 28 weeks' gestation or less) and particularly in those with a history of respiratory immaturity.

[....]

4.8. Undesirable effects

Summary of the safety profile

Over 13,000 subjects, including approximately 1,000 children and adolescents under the age of 18, have received at least one dose of Verorab in clinical studies.

Adverse reactions were generally moderate in intensity and occurred within 3 days of vaccination. Most reactions resolved spontaneously within 1 to 3 days of their onset.

The most common adverse reactions, in all age groups (except infants/young children less than 24 months) were headache, malaise, myalgia and pain at the injection site.

Tabulated list of adverse reactions

[....]

Adverse reactions	Adults ≥ 18 years	Paediatric population under 18 years old
	Frequency	Frequency
Blood and lymphatic system disorders		
Lymphadenopathy	Common	Common
Immune system disorders		
Allergic reactions (e.g., rash, urticaria, pruritus)	Uncommon	Uncommon
Anaphylactic reactions and angioedema	Not known	Not known
Metabolism and nutrition disorders		
Decreased appetite	Uncommon	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness/vertigo	Uncommon	-
Irritability (in infants/young children)	-	Very common
Somnolence (in infants/young children)	-	Very common
Insomnia (in infants/young children)	-	Common
Ear and labyrinth disorders		
Sudden hearing loss, which may persist	Not known	Not known
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	Rare	-
Gastrointestinal disorders		
Nausea	Uncommon	-
Abdominal pain	Uncommon	Uncommon
Diarrhoea	Uncommon	-
Vomiting	-	Uncommon
Musculoskeletal and connective tissue disorders		
Myalgia	Very common	Very common
Arthralgia	Uncommon	-
General disorders and administration site conditions		
Injection site pain	Very common	Very common
Injection site erythema	Common	Common
Injection site pruritus	Common	-
Injection site swelling	Common	Common
Injection site induration	Common	-
Malaise	Very common	Very common
Influenza-like syndrome	Common	
Fever	Common	Common
Asthenia	Uncommon	-
Chills	Uncommon	Uncommon
Inconsolable crying (in infants/young children)	-	Very common

[....]

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Rabies vaccines, ATC code: ~~J07BG01~~J07BG.

[....]

~~immunoglobulins.~~ Mechanism of action

Protection after vaccination is provided by the induction of anti-rabies neutralising antibodies.

Clinical studies have been conducted to assess the immunogenicity of the vaccine for pre-exposure and post-exposure prophylaxis. A titre of anti-rabies neutralising antibodies ≥ 0.5 IU/mL is considered protective.

Pre-exposure prophylaxis

In clinical trials assessing a 3-dose regimen (D0, D7, D28 (or D21) by IM route) in adults and children, all subjects~~, the serum antibody level exceeded the threshold of 0.5 IU/mL,considered as protective by WHO, from the third injection at D14.~~

~~For subjects already immunised, the administration of 2 doses 3 days apart (D0 and D3) postexposure makes it possible to achieve a serum antibody level > 0.5 IU/mL, considered as protective by WHO. The administration of~~ achieved an adequate immune response with anti-rabies ~~immunoglobulins is not necessary in this case.~~

~~Slightly lower mean neutralizing~~neutralising antibody titres ~~may be observed when human rabies immunoglobulins (HRIG) or equine rabies immunoglobulins (ERIG) are administered at the same time as the first~~≥ 0.5 IU/mL two ~~doses of rabies vaccine, in accordance with the Zagreb regimen~~weeks after the end of primary vaccination.

A ten-year follow-up in 49 subjects who received the vaccine according to a 3-dose schedule (D0, D7, D28) followed by a booster dose one year later showed the persistence of the immune response with anti-rabies neutralising antibody titres ≥ 0.5 IU/mL for up to 10 years in 96.9% of vaccinated subjects.

Post-exposure prophylaxis

In clinical trials assessing the 5-dose Essen regimen (D0, D3, D7, D14, D28 by IM route) and the 4-dose Zagreb regimen (2 doses at D0, then 1 dose at D7 and 1 dose at D21 by IM route) in adults and children, Verorab induced adequate titres of anti-rabies neutralising antibodies (≥ 0.5 IU/mL) in nearly all subjects at D14 and in all subjects at D28.

The administration of human rabies immunoglobulin (HRIG) or equine rabies immunoglobulin (ERIG) concomitantly with the rabies vaccine may cause slightly lower mean neutralising antibody titres due to immune interference.

The effectiveness of Verorab was evaluated in 44 adult subjects bitten by animals confirmed to be rabid. The subjects received the vaccine according to the 5-dose Essen regimen (D0, D3, D7, D14 and D28 by IM route) and immunoglobulins, where necessary. Three years after vaccination, none of the subjects had developed rabies.

Paediatric population

There are no clinically significant differences in the immunogenicity of the vaccine in the paediatric population compared to adults.

[....]

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder*:

Maltose.

20% human albumin~~,~~ solution.

Basal Medium Eagle~~ (~~: mixture of mineral salts~~,~~ (including potassium), vitamins, dextrose and amino~~-~~ acids (including L-~~Phenylalanine),~~ phenylalanine).

Hydrochloric acid and sodium hydroxide for pH adjustment.

Water for injections.

* Composition of the powder before the freeze-drying step.

[....]

קיימים עדכונים נוספים . למידע נוסף יש לעיין בעלון לרופא המעודכן.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות:

https://data.health.gov.il/drugs/index.html#!/byDrug

וניתן לקבלו מודפס על ידי פניה לבעל הרישום מדיצ'י מדיקל בע"מ, רחוב המחשב 3 נתניה טלפון 7446170-09

בברכה,

ירון חסיד

רוקח ממונה