

Registration No......1C 1/63 (B)

Importer / Manufacturer: Biogenetech Co., Ltd. / Chiron Behring Vaccine Pvt.,Ltd.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT

CHIRORAB®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder and solvent for solution for injection for one immunisation dose (1 ml) contains: inactivated rabies virus (strain flury LEP), potency ≥ 2.5 IU.

Host system: primary chicken fibroblast cell cultures.

3. PHARMACEUTICAL FORM

Lyophilised powder and solvent for solution for injection.

After reconstitution of the white lyophilisate (powder), a clear colourless solution is obtained

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against rabies.

a.) Pre-exposure immunisation (preventative, prior to exposure):

Immunisation prior to possible infection with rabies, particularly for vets, veterinary medicine students, animal keepers, hunters, forestry workers, animal handlers, butchers, personnel in rabies research laboratories etc., or prior to visit to areas in which rabies is endemic (rabies infected areas)

b.) Post-exposure treatment (after exposure):

Treatment after contact with animals which are rabid or suspected to be rabid, or after contact with an inoculated rabies carcass.

4.2 Posology and method of administration

Dosage

With ChiroRab®, it is possible to vaccinate persons of any age group. The recommended single dose is 1 ml.

PRE-EXPOSURE IMMUNISATION (prior to exposure) Immunisation according to schedule A (see Table 2). One vaccination (1 ml) on days: 0, 7 and 21 or 28.

BOOSTER DOSES

International recommendations (WHO, ACIP-US) are as follows:

- For persons at continuous risk, evaluate the rabies virus neutralizing antibody titres by RFFIT, every 6 months.
- For persons at frequent risk, the WHO recommends antibody titre estimations every year, whereas the ACIP advocates testing every 2 years.

If titres are below 0.5 IU/ml at any time, one booster dose should be administered.

Considering the long term satisfactory antibody titres observed with ChiroRab[®], if serological tests cannot be conducted due to cost considerations or inaccessible medical facilities, a booster dose one year after primary immunisation followed by one dose every 5 years would be advisable.

POST-EXPOSURE TREATMENT (after exposure)

Begin with the course of immunisation immediately. For “immediate wound treatment”, see “Special precaution for use”!

For indication for use. See Table 1

(1) *Unimmunised or incompletely immunised individuals* (including those who have previously received fewer than 3 doses of vaccine, or who have received a vaccine of doubtful potency or origin):

Treatment according to schedule B or C. (see also Table 2)

One single dose of vaccine on days 0, 3, 7, 14, 28 (5-dose schedule).

As an alternative to the above mentioned 5-dose schedule, the World Health Organisation (WHO) also recommends the abbreviated 2-1-1 regimen as being effective: Two doses on day 0 (one dose given into the right and one dose into the left deltoid muscle [upper-arm muscle] or, in small children, one dose each into the anterolateral region of the right and left thigh), and one dose each on days 7 and 21 (see also Table 2, schedule B or C)

In all injuries caused by rabid animals or animals suspected to be rabid, or after contact between the saliva of these animals and the mucous membranes or damaged skin of the patient (see Table 1), the 5-dose schedule or 2-1-1 schedule along with additional passive immunisation are required (see Table 2, schedule C). 20 IU/kg bodyweight (BW) of human rabies immunoglobulin or 40 IU/kg of equine rabies immunoglobulin are to be given once at the time of the first vaccination. As much of the rabies immunoglobulin preparation as is anatomically feasible should be applied as deeply as possible in and around the wound. Any remaining rabies immunoglobulin should be administered intramuscularly (preferably intragluteally) at a site distant from the site of the vaccine injection.

If rabies immunoglobulin is not available at the time of the first vaccination it must be administered no later than 7 days after the first vaccination since later administration would result in interference with antibody formation.

Rabies immunoglobulin should only be administered at the recommended dose.

The recommended immunoglobulin dose should neither be increased, nor decreased, nor should rabies immunoglobulin administration be repeated (for further details refer to the manufacturer’s information).

The immunisation schedule must be followed exactly, even if considerable time has elapsed since exposure.

In subjects at particularly high risk of contracting rabies infection (e. g. with multiple wounds, particularly on the head or other markedly innervated

parts of the body), or for those who have delayed initiation of treatment, the patient must be vaccinated on each of the days 0, 3, 7, 14, 28. Additionally the initial immunisation dose should be doubled: a single dose of vaccine should be given by injection as soon as possible after exposure into the right deltoid and another single dose into the left deltoid muscle, or in small children, a single dose given into the anterolateral region of the right thigh with another single dose given into the left thigh.

(2) Previously fully immunised individuals:

Patients who have previously received a complete course of primary immunisation (pre- or post-exposure) should receive two doses of ChiroRab[®]; one on each of days 0 and 3, respectively. This is independent of the interval to the last immunisation. No administration of rabies immunoglobulin is required.

(3) Immunocompromised individuals:

Patients receiving immunosuppressive therapy, or who have congenital or acquired immunodeficiency, should be vaccinated once on each of the days 0, 3, 7, 14, 28. In addition, the initial immunisation dose (day 0) should be doubled with a single dose of vaccine being administered as soon as possible after exposure into each of the right and left deltoid muscles (upper-arm muscle) or, in small children, into the anterolateral region of each of the right and left thighs.

If immunocompromised patients (with impaired defence system) are treated after exposure to rabies, it is advisable that the antibody titre be measured 14 days after the first dose. If a titre of at least 0.5 IU/ml, which is considered adequate to confer protection, is not present, a dose of vaccine should be immediately administered into each upper-arm (or into each thigh in the case of small children). Depending on the immunisation status of these patients, additional doses may be necessary to achieve appropriate antibody titres in serum (for information on immunoglobulin administration see Section (1) “Unimmunised or incompletely immunised individuals”).

Method and duration of administration

The lyophilisate should be reconstituted immediately using the diluent supplied, and carefully agitated prior to injection. The reconstituted vaccine should be used immediately.

ChiroRab[®] must be given by intramuscular injection into the deltoid muscle (upper-arm muscle), or into the anterolateral region of the thigh in small children. The vaccine must not be given by intragluteal (in the gluteal muscle) injection.

The vaccine must not be administered by intravascular (in a blood vessel) injection!

Table 1: Appropriate rabies treatment based on different categories of exposure

Exposure category	Type of exposure		Treatment schedule
	Contact with a rabid or suspected rabid* wild or domestic animal	Contact with an inoculated animal carcass	
I	<ul style="list-style-type: none"> - Touching/feeding animals, but clearly no contact with their saliva; patient's skin undamaged prior to and during contact 	<ul style="list-style-type: none"> - Touching inoculated carcass; skin intact 	No treatment necessary. In cases of uncertainty, immunisation to be administered as per schedule B (Table 2)
II	<ul style="list-style-type: none"> - Animal has nibbled or licked exposed skin of the patient - Contact with saliva - Superficial, non-bleeding, scratches made by the animal, with the exception of scratches on the head, neck, shoulder region, arms and hands (see exposure grade III) 	<ul style="list-style-type: none"> - Touching inoculated carcass; skin damaged 	Immediate treatment as specified in schedule B. In cases of uncertainty, simultaneous administration of vaccine and immunoglobulin (active and passive immunisation) should be administered as specified in schedule C (Table 2). If the animal proves to be healthy after examination, it is advisable to continue treatment as in schedule A. Check patient's immunity against tetanus.
III	<ul style="list-style-type: none"> - All bites - Bleeding scratches - All scratches on the head, neck, shoulder region, arms, and hands - Contact of patient's mucous membrane with animal saliva (e.g. licking, spray) 	<ul style="list-style-type: none"> - Contact of inoculated carcass with mucous membrane or fresh skin wound 	Initiate immediate simultaneous administration of vaccine and immunoglobulin (active and passive immunization) as specified in schedule C (Table 2). If the animal proves to be healthy after examination, it is advisable to continue treatment as in schedule A. Check patient's immunity against tetanus.

(Based on the 1997 WHO guidelines)

* All animals exhibiting abnormal behaviour in an area which has been officially declared as rabies endemic area must be considered potentially rabid. The corpses of rabid animals can also transmit rabies.

Note: Where indicated, prophylactic immune treatment should be given as soon as possible

Table 2: Pre-exposure immunisation and post-exposure treatment of individuals with no or inadequate* immunity

Schedule A Immunisation prior to exposure	Schedule B Immunisation after exposure	Schedule C Simultaneous prophylaxis after exposure
One injection of ChiroRab® i.m. on days: 0, 7, and 21 or 28	One injection of ChiroRab® i.m. on days: 0, 3, 7, 14, 28 (5-dose schedule) Or One dose of ChiroRab□ to be given into the right deltoid muscle and one dose into the left deltoid muscle on day 0; and one dose to be applied into the deltoid muscle on days 7 and 21 (2-1-1 regimen). In small children the vaccine is to be given into the thighs.	Give ChiroRab® as in schedule B + 1 x 20 IU/kg BW human rabies immunoglobulin** or 40 IU/kg BW equine rabies immunoglobulin simultaneously with the first dose of ChiroRab□. If no rabies immunoglobulin is available at the time of the first vaccination, it must be administered no later than 7 days after the first vaccination.

*Persons who have received less than three immunisation doses, or a vaccine of doubtful potency or origin

** Observe manufacturer's instructions!

Additional Information

This vaccine conforms to the World Health Organisation (WHO) requirements and contains no preservative

The antibody concentration achieved by the immunisation falls gradually; booster doses are therefore required to maintain immunity.

All immunisations and all immunoglobulins administered should be entered by the doctor, with the name of the preparation (proprietary name) and Lot. No., in the international immunisation record.

Optimal immunity will only be conferred if the full immunisation schedule is completed.

Intradermal schedule

The WHO recognises the effectiveness of modern tissue culture rabies vaccines when given by the intradermal route (i.d.) for post-exposure immunisation. The WHO recommends the use of 0.1 ml ChiroRab® for intradermal use for the Thai Red Cross (TRC) 2-2-2-0-1-1 regimen⁽¹⁻⁴⁾. The intradermal use of 0.1 ml ChiroRab® has been proven to be well tolerated, immunogenic and efficacious⁽⁴⁻⁶⁾. Furthermore, the WHO has recently updated the recommendations for the TRC regimen to be used also in a 2-2-2-0-2 schedule². If ChiroRab® is to be administered by the intradermal route, the following instructions and warnings must be strictly adhered to:

Dosage and administration (post-exposure):

One i.d. dose comprised of 0.1 ml of the total reconstituted vaccine, is to be administered in the upper arm, over the deltoid.

Non-vaccinated individuals:

The 2-site intradermal method (2-2-2-0-1-1), also known as the TRC schedule is recommended:

- one i.d. injection of 0.1 ml over each left and right deltoid on days 0, 3, 7
- one i.d. injection of 0.1 ml at a single site on upper arm (deltoid) on day 28 (or 30) and day 90
(Alternatively, the i.d. injection for day 90 can be administered as a second dose on day 28 (or 30)). This schedule is the updated TRC regimen (2-2-2-0-2).

Fully vaccinated individuals (see above definition):

immediate booster injection of a single dose of 0.1 ml on days 0, 3.

4.3 Contraindication**a.) Immunisation prior to exposure**

It is advisable to avoid pre-exposure (prophylactic) immunisation in individuals with acute disorders requiring treatment.

If complications arise after vaccination, this should be considered a contraindication for further administration of the same vaccine, until the causes of the complications have been clarified.

In individuals with known allergy to one of the constituents of ChiroRab® use of this vaccine is contraindicated.

b.) Treatment after exposure

In view of the fact that rabies is a fatal disease, there are no contraindications to immunisation after suspected exposure (see section "Special precautions for use").

4.4 Special warnings and precautions for use

There is not, as a rule, an increased risk during immunisation with ChiroRab® in subjects who state that they are "allergic to chicken protein" or who exhibit a positive reaction in the chicken protein skin test.

In the extremely rare cases in which subjects have reacted with clinical symptoms such as urticaria (nettle rash), lip and epiglottis oedema (inflammatory swelling of the lips and larynx region), laryngo- or bronchospasm (spasm of the glottis or bronchial muscles), a fall in blood pressure, or shock after eating chicken protein, the immunisation should be conducted only under close clinical monitoring, and with the appropriate facilities for emergency treatment available.

ChiroRab® contains polygeline and may contain residual amounts of the antibiotics amphotericin B, chlortetracycline, neomycin and this could potentially cause allergic reactions.

In patients with known hypersensitivity to constituents of the vaccine receiving post-exposure treatment, appropriate medical treatment addressing anaphylactic shock should always be on-hand during vaccination, or alternatively another equivalent modern cell culture rabies vaccine should be used.

Minor infections (even with subfebrile temperatures ($\leq 38.5^{\circ}\text{C}$)) are not a contraindication, nor is possible contact with individuals suffering from infectious diseases.

Do not administer by intravascular injection!

If the vaccine is inadvertently administered intravascularly (in a blood vessel), there is a risk of adverse reactions, with shock potentially occurring in extreme cases. Appropriate emergency measures to prevent shock must be taken immediately.

Do not mix vaccine with rabies immunoglobulin in the same syringe.

After contact with animals which are suspected carriers of rabies, it is essential to observe the following procedures

Immediate wound treatment

First aid: In order to remove as much of the rabies virus as possible, immediately cleanse the wound with soap and flush thoroughly with water.

Then treat with alcohol (70 %) or an iodine tincture.

Where possible, wounds should not be closed with a suture, or only sutured to secure apposition. Prophylaxis against tetanus should be administered when necessary!

In cases in which simultaneous administration of vaccine and immunoglobulin is indicated, as much of the recommended dose of human rabies immunoglobulin as is anatomically feasible should be applied as deeply as possible in and around the wound. Any remaining immunoglobulin should be injected intramuscularly at a site distant from the site of vaccine administration, preferably intragluteally (in the gluteal muscle).

Special precautions for the intradermal route:

It is essential that intradermal administration of vaccine be administered only by medical staff trained in the i.d. technique in order to ensure that the vaccine is delivered intradermally and not subcutaneously. For the intradermal route, a sterile syringe with fixed needle (insulin type) is preferred. A separate sterile needle and syringe must be used for each patient. Correct intradermal injection should result in a raised papule with an orange peel appearance. If the vaccine has been injected too deeply and a papule is not observed, the needle should be withdrawn and vaccine re-administered nearby. WHO recommendations for the use of rabies immunoglobulin after exposure to rabies virus should be carefully followed.

This vaccine does not contain a preservative, therefore, great care must be taken to avoid contamination of the reconstituted vaccine.

Any reconstituted vaccine should be used as soon as possible. It must be stored in a refrigerator at +2 to +8 °C and used within 6 to 8 hours of reconstitution. If not maintained at +2 to +8 °C, the vaccine must be immediately discarded.

The i.d. route must not be used in the following instances:

- individuals receiving long term corticosteroid or other immunosuppressive therapy or chloroquine.
- immunocompromised individuals.

This vaccine is of sufficient potency to allow its safe use in one of the WHO recommended intradermal post-exposure regimens in countries where relevant national authorities have approved the use of the intradermal route for rabies post-exposure prophylaxis.

4.5 Interaction with other medical products and forms of interaction

In patients receiving immunosuppressive therapy (treatment which reduces the defence system of the body), or with congenital or acquired immunodeficiency, the response to the vaccination may be reduced or uncertain (see also “Dosage and administration”).

Administration of immunosuppressive medication and antimalarial compounds during treatment after exposure should be avoided.

Rabies immunoglobulins should only be administered at the recommended dose. The immunoglobulins should neither be given at higher nor lower doses than those recommended, nor should they be repeatedly administered, as this may reduce the effects of rabies vaccine given at the same time.

Time intervals to be observed before other vaccinations are given

It is not necessary to observe an interval with regard to other vaccinations.

4.6 Pregnancy and lactation

No cases of harm attributable to use of this vaccine during pregnancy have been observed to date in mothers or children.

It is not known whether ChiroRab® passes into breast milk.

No risk to the breast-feeding infant has been described to date.

It is advisable to carefully weigh expected benefits against potential risks prior to pre-exposure (prophylactic) immunisation with ChiroRab® during pregnancy and breast-feeding.

4.7 Effects on the ability to drive and use machines

Not Applicable

4.8 Undesirable effects

If you develop side effects, especially side effects which are not mentioned in this package leaflet, please inform your doctor or pharmacist.

Mild reactions at the injection site, such as pain, redness, swelling or induration are possible. More marked local reactions, fever, headache, myalgia, lymph node swelling, fatigue, arthritis, and gastrointestinal disorders may occasionally occur. Rare are circulatory reactions, sweating, chills, paraesthesias and allergic reactions; these require treatment only in exceptional cases (see section “Special precautions for use”).

There have been isolated reports of inflammatory and demyelinating neurological disorders, such as progressive ascending paralysis (Guillain-Barré syndrome) or optic neuritis in individual cases. On the basis of currently available data, the possibility cannot be completely excluded that in rare cases immunisation may induce an acute episode in patients with an autoimmune disorder (such as multiple sclerosis) or with an appropriate genetic predisposition. However, there is no evidence of an increased frequency of autoimmune disorders after immunisation.

4.9 Overdose

Not Applicable

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Not Applicable

5.2 Pharmacokinetic properties

Not Applicable

5.3 Preclinical safety data

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TRIS-(hydroxymethyl)-aminomethane, sodium chloride, EDTA (Titriplex III), potassium-L-glutamate, polygeline, saccharose, water for injections

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

ChiroRab® should be stored at +2 to +8°C.

Store out of reach of children!

6.5 Nature and contents of container

Single dose pack contains:

- 1 Vial of lyophilised powder
- 1 Ampoule with 1 ml sterile water for injections B.P.
- 1 disposal syringe with needle

4 Doses pack contains:

- 4 Vials of lyophilised powder
- 4 Ampoules, each with 1 ml sterile water for injections B.P.

5 Doses pack contains:

- 5 Vials of lyophilised powder
- 5 Ampoules, each with 1 ml sterile water for injections B.P.

6.6 Special precautions for disposal and other handling

Not Applicable

7. MARKETING AUTHORISATION HOLDER

Biogenetech Co., Ltd.

18 Soi Udomsuk 37, Sukhumvit 103 Rd., Bangjak, Prakanong, Bangkok, 10260
THAILAND

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

January 13, 2020

10. DATE OF REVISION OF THE TEXT

February 12, 2020