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ASEAN Pharmaceutical Harmonization

(Product Registration)

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SCOPE

- Introduction
- Definition of Terms
- Content of ASEAN Common Technical Dossier
- Benefits of ASEAN Harmonized requirements

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Introduction

The availability of generic medication is an important issue in the ASEAN region. The regulatory requirements of various countries vary from each other. Therefore, it is a challenge for the companies to get the drug approved for marketing simultaneously in different countries.

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Philippine FDA

- **ACTD Full Implementation – July 2013**
- **Applicable for NCE, Biologics and Generic products**
- **Single and multi-component vitamin and mineral products, traditional medicines, OTC preparations, household remedies, medical gases and veterinary products are not covered by ACTD submission.**

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Definition of Terms

ACTD or ASEAN Common Technical Dossier – the part of marketing authorization application dossier that is common to all ASEAN member countries.

ACTR or ASEAN Common Technical Requirements – a set of written materials intended to guide applicants to prepare application dossiers in a way that is consistent with the expectations of all ASEAN Drug Regulatory Authorities (DRA).

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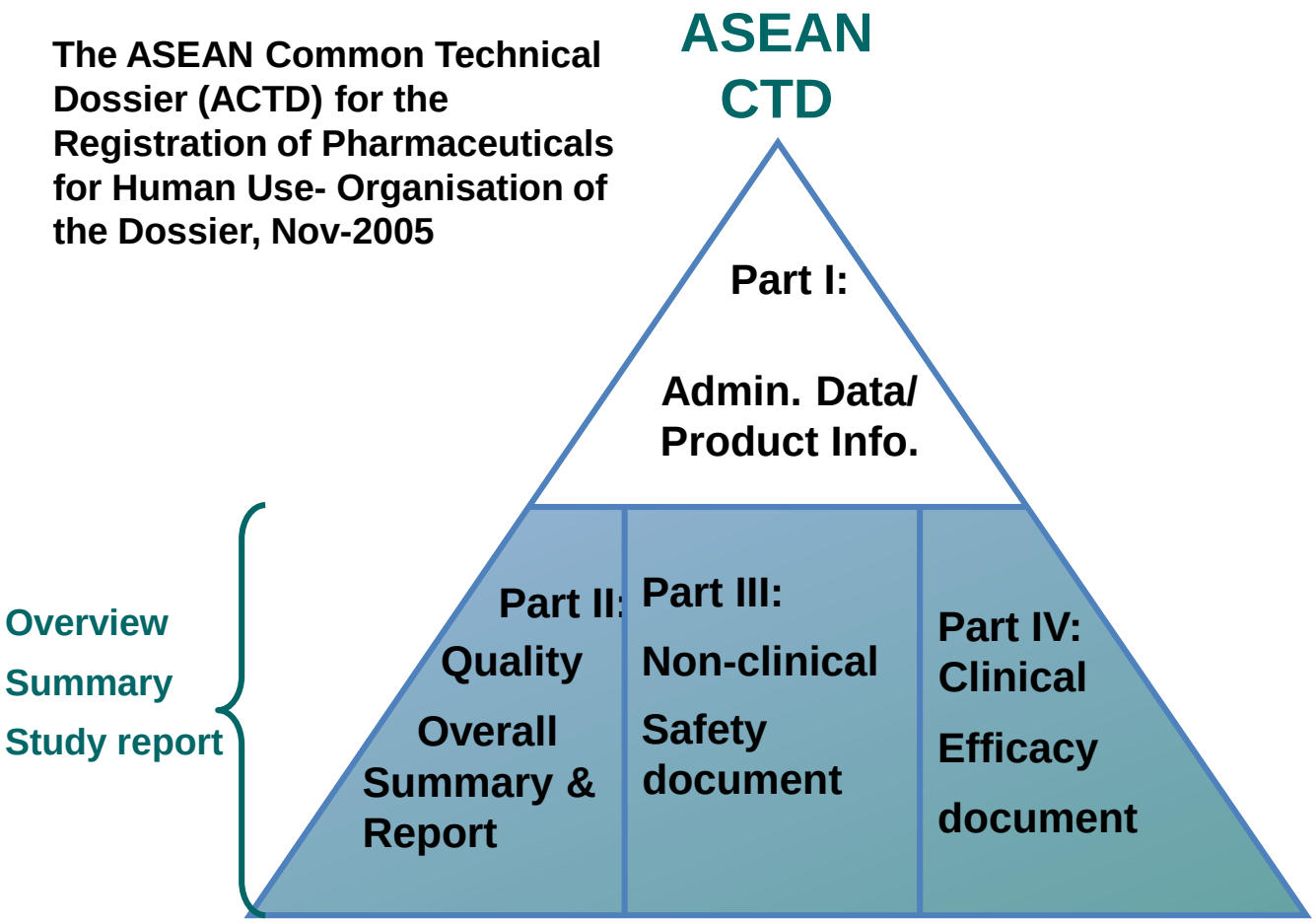
The ASEAN Common Technical Dossier (ACTD) for the Registration of Pharmaceuticals for Human Use- Organisation of the Dossier, Nov-2005



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Content of ACTD

Part I: Table of Contents, Administrative Data & Product Information

Section A: Introduction
Section B: Overall ACTD – Table of Contents
Section C: Documents Required for Registration
- Application Form
- Letter of Authorization
- Certification
- Labeling
- Product Information

Part II : Quality Document

Section A: Table of Contents
Section B: Quality Overall Summary (QOS)
Section C: Body of Data

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Content of ACTD

ACTD- *Quality*

Drug Substance

S1- General information
S2- Manufacture
S3- Characterization
S4- Control of drug substance
S5- Reference standard or materials
S6- Container closure system
S7- Stability

Drug Product

P1- Description and composition
P2- Pharmaceutical development
P3- Manufacture
P4- Control of excipients
P5- Control of finished product
P6- Reference standard or materials
P7- Container closure system
P8- Stability
P9- Product interchangeability/ equivalence evidence

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GMP Certificate

CONSULATE GENERAL OF THE PHILIPPINES
CONSULAR SECTION
MUMBAI, INDIA
} s.s.

CERTIFICATE OF AUTHENTICATION

I, (Mrs.)Rajashree Birla, Consul General a.h., of the Republic of the Philippines duly commissioned and qualified do hereby certify that Mr. S. D. Perke was, at the time he signed and affixed his official seal to the document hereto annexed, Section Officer, Home Department, Govt. of Maharashtra, Mumbai authorized to authenticate legal documents and verily believe that his signature affixed there to is genuine.

The Consulate General Republic of the Philippines, Mumbai, India, assumes no responsibility whatsoever with regard to the contents of the instrument referred to above.

THE WITNESS WHEREOF, I have hereunto set my hand and affixed the seal of the Consulate General of the Philippines, Mumbai, India this 14th October, 2013.

Rajashree Birla

Rajashree Birla
Consul General ad honorem
Annexed documents were submitted by M/s. Chiron Behring Vaccines Private Limited, Mumbai, India.

PHILIPPINE CONSULATE GENERAL MUMBAI

Fee:- Rs.1,600/- + Rs.1,600/- for 1 extra copy
Service No:- 8705/MISC/2013
O.R. No:- 6211227-FA
Date:- 14 OCT 2013

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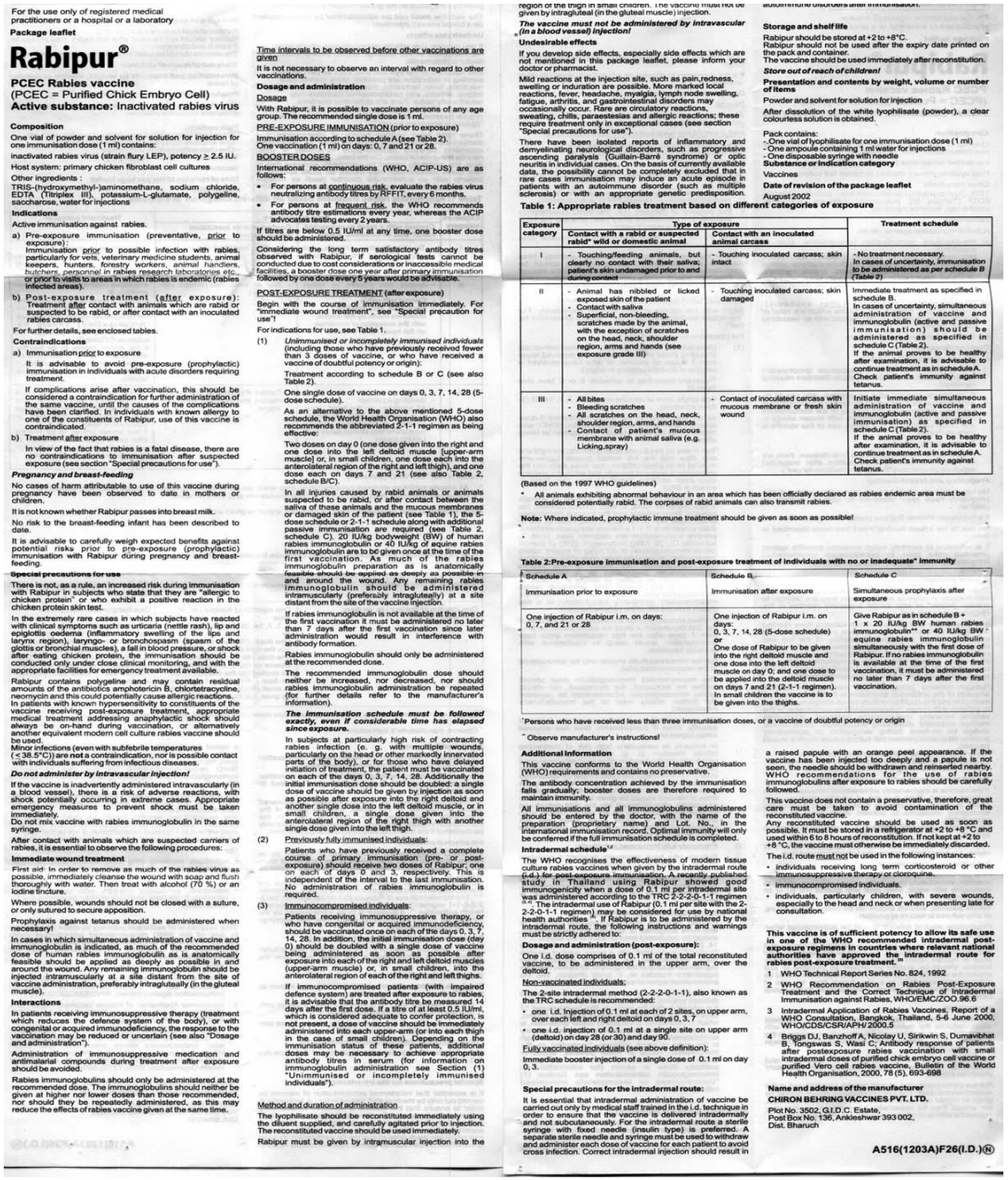
Product Insert



For the use only of registered medical practitioners or at a hospital or a laboratory

Package leaflet

Rabipur®

PCEC Rabies vaccine
(PCEC = Purified Chick Embryo Cell)
Active substance: Inactivated rabies virus

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

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

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 visits 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.

For further details, see enclosed tables.

Contraindications

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 Rabipur, 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").

Pregnancy and breast-feeding

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 Rabipur 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 Rabipur during pregnancy and breast-feeding.

Special precautions for use

There is not, as a rule, an increased risk during immunisation with Rabipur 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.

Rabipur 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 (< 38.5°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).

Interactions

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.

Dosage and administration

Dosage

With Rabipur, 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 Rabipur, 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 indications 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/C).

In all injuries caused by rabid animals or animals suspected to be rabid, or after contact between the saliva of those 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 Rabipur, 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 on each of both sides 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.

Rabipur must be given by intramuscular injection into the 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!

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, paraestesias 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.

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	- Touching/feeding animals, but clearly no contact with their saliva; patient's skin undamaged prior to and during contact	- Touching inoculated carcass; skin intact	- No treatment necessary. In cases of uncertainty, immunisation to be administered as per schedule B (Table 2)
II	- 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)	- 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	- 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)	- Contact of inoculated carcass with mucous membrane or fresh skin wound	Initiate immediate simultaneous administration of vaccine and immunoglobulin (active and passive immunisation) 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	Schedule B	Schedule C
Immunisation prior to exposure	Immunisation after exposure	Simultaneous prophylaxis after exposure
One injection of Rabipur i.m. on days: 0, 7, and 21 or 28	One injection of Rabipur i.m. on days:- 0, 3, 7, 14, 28 (5-dose schedule) or One dose of Rabipur to be given into the right deltoid muscle and one dose into the left deltoid muscle or in children 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 Rabipur 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 Rabipur. 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[1,2]

The WHO recognises the effectiveness of modern tissue culture rabies vaccines when given by the intradermal route (i.d.) for post-exposure immunisation. A recently published study in Thailand using Rabipur showed good immunogenicity when a dose of 0.1 ml per intradermal site was administered according to the TRC 2-2-2-0-1-1 regimen [3, 4]. The intradermal use of Rabipur (0.1 ml per site with the 2-2-2-0-1-1 regimen) may be considered for use by national health authorities [4]. If Rabipur 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 comprises of 0.1 ml of the total reconstituted vaccine, 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 at each of 2 sites, on upper arm, 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.

Fully vaccinated individuals (see above definition):

Immediate booster injection of a single dose of 0.1 ml on day 0, 3.

Special precautions for the intradermal route:

It is essential that intradermal administration of vaccine be carried out 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 to withdraw and administer each dose of vaccine for each patient to avoid cross infection. 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 seen, the needle should be withdrawn and reinserted nearby. WHO recommendations for the use of rabies immunoglobulins after exposure to rabies 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 kept at +2 to +8 °C, the vaccine must otherwise 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 clorquine.
- immunocompromised individuals.
- individuals, particularly children, with severe wounds, especially to the head and neck or when presenting late for consultation.

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 intradermal route for rabies post-exposure treatment. "

1 WHO Technical Report Series No. 824, 1992

2 WHO Recommendation on Rabies Post-Exposure Treatment and the Correct Technique of Intradermal Immunisation against Rabies, WHO/EMC/ZOO.96.6

3 Intradermal Application of Rabies Vaccines, Report of a WHO Consultation, Bangkok, Thailand, 5-6 June 2000, WHO/CDS/CSR/APH/ 2000.5

4 Briggs DJ, Banzhoff A, Nicolay U, Sirikwin S, Dumavibhat B, Tongwas S, Wasi C: Antibody response of patients after postexposure rabies vaccination with small intradermal doses of purified chick embryo cell vaccine or purified Vero cell rabies vaccine, Bulletin of the World Health Organisation, 2000, 78 (5), 693-698

Name and address of the manufacturer

CHIRON BEHRING VACCINES PVT. LTD.

Plot No. 3502, G.I.D.C. Estate,
Post Box No. 136, Ankleshwar 393 002,
Dist. Bharuch

A516(1203A)F26(I.D.)®

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Content of ACTD

Part III: Non-Clinical Document

Section A: Table of Contents

Section B: Non-Clinical Overview

Section C: Non-Clinical Written and Tabulated Result

- Pharmacology
- Pharmacokinetics
- Toxicology

Section D: Non-Clinical Study Reports

- Pharmacology
- Pharmacokinetics
- Toxicology
  - Genotoxicity
  - Carcinogenicity
  - Reproductive and Developmental Toxicity
  - Local Tolerance
  - Other Toxicity Studies (if available)

Section E: List if Key Literature References

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Content of ACTD

Part IV: Clinical Document

Section A: Table of Contents

Section B: Clinical Overview

Section C: Clinical Summary

Section D: Tabular Listing of All Clinical Studies

Section E: Clinical Study Reports

- Report of Biopharmaceutic Studies
- Reports of Studies Pertinent to Pharmacokinetic Using Human Biomaterials
- Report of Human Pharmacokinetic (PK) Studies
- Reports of Human Pharmacodynamic (PD) Studies
- Reports of Efficacy and Safety Studies
- Reports of Post-Marketing Experience Local Tolerance

Section F: List if Key Literature References

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Country specific requirements

- **Application Form**
- **Labeling**
- **Stability**

Even though ACTD format is mandatory, the member countries have their own requirements for registration process.

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Benefits of ASEAN Harmonized requirements

- ❑ Save time, resources & costs for regulators & industry.
- ❑ Facilitate trade in medicinal products across ASEAN
- ❑ Quicker access of medicinal products hence benefit patients & consumers
- ❑ Elimination of technical barriers to trade

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Thank you!