ChiroRab®

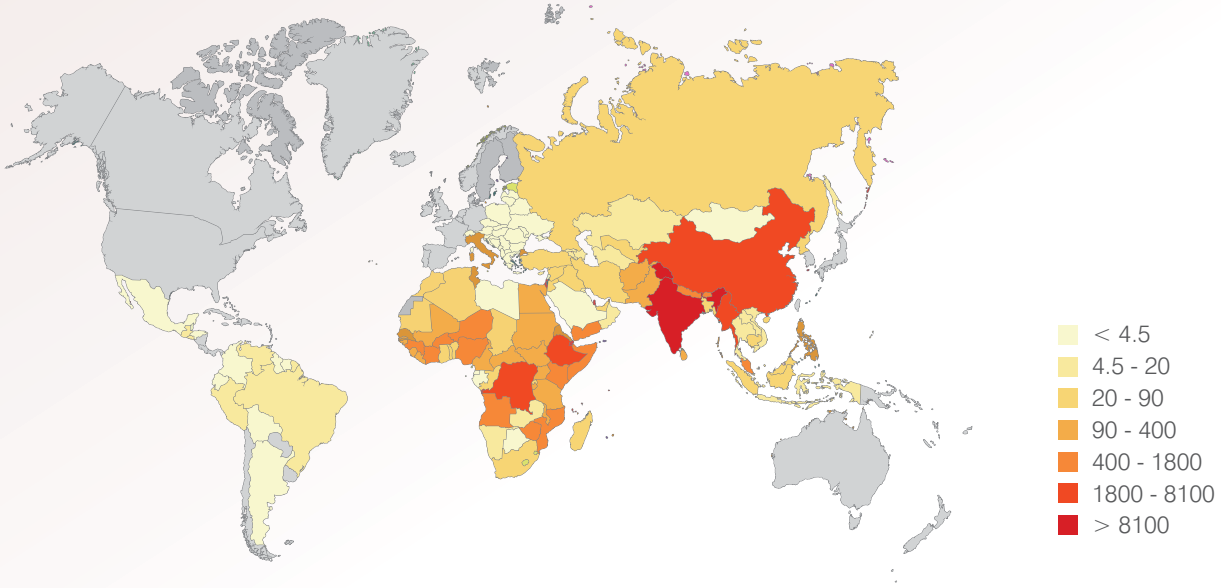
A LEGACY OF EXCELLENCE IN
PREVENTION OF **RABIES** CONTINUES...

CHIRON BEHRING®

Global Burden of Rabies Mortality

Rabies - A viral zoonotic disease (transmitted from animals to humans) that is prevalent worldwide. Domestic dogs are the most common reservoirs of the virus, with more than 99% of human deaths caused by dog-mediated rabies.[1]

Annual WHO estimates of human rabies deaths (2015)



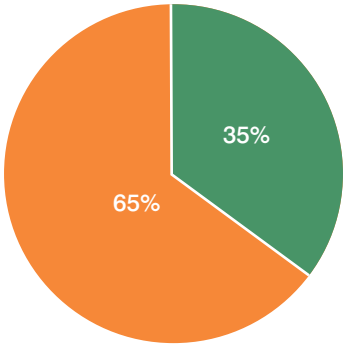
Rabies Global Statistics:

- Prevalent in >150 countries & territories
- >3.3 billion people at risk
- ~59,000 estimated deaths
- >95% of reported cases in Asia & Africa

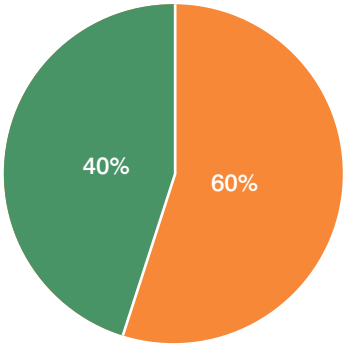
Rabies Mortality in India

Of ~59,000 global rabies mortality, 20,000 deaths i.e., nearly one-third are from India[1]

Global Mortality



Asian Mortality



Rabies - 100% vaccine preventable disease[1]

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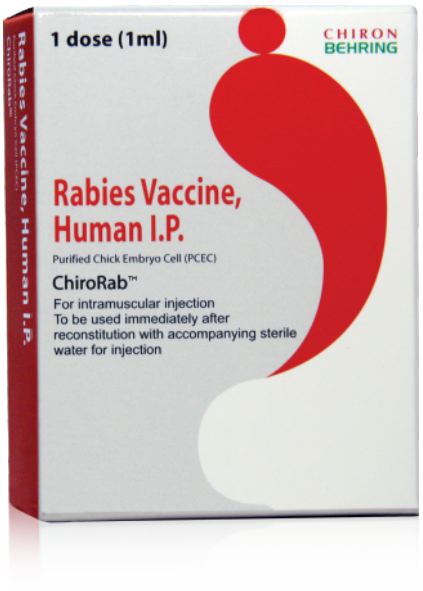
Presenting ChiroRab®



- WHO Prequalified, second-generation purified chick embryo cell (PCEC) rabies vaccine with high potency level per dose, recommended for all established WHO intramuscular (IM) and intradermal (ID) vaccination schedules.
- Contains inactivated rabies virus with a potency of ≥2.5 IU/dose and is suitable for both pre-exposure and post-exposure prophylaxis for all individuals at high-risk from Rabies infection.
- Contains no preservative.
- Conforms to the WHO requirements by inducing a rabies virus neutralizing antibodies (RVNA) concentration of ≥0.5 IU/mL which is regarded by the WHO as being an 'adequate' protective RVNA concentration, and is commonly used as a threshold in clinical trials.
- Most widely used chick embryo cell-culture rabies vaccine with over 80 million doses sold since its introduction into the world market.

ChiroRab® - The Journey

1985 - 2000

Hoechst India Limited » HMR & Chiron JV

- **1985:** Import from Germany.
- **1989:** Manufacturing at Ankleshwar, Gujarat.
- **1995:** Hoechst to Hoechst Marion Roussel (HMR).
- **1997:** Joint Venture (JV) between HMR & Chiron.
- **1999:** HMR & Rhône Poulenc merger to form Aventis.

2000 - 2010

HMR » Aventis » Sanofi Aventis » Novartis

- **2002:** Received WHO Prequalification certification for its vaccine production plants in Germany & India.
- **2004:** Sanofi acquired Aventis to form Sanofi-Aventis.
- **2006:** Chiron taken over by Novartis to form Novartis Sanofi-Aventis JV.
- **2010:** 100% Novartis (JV diluted).

2011 - 2019

Novartis » GSK » Chiron Behring

- **2015:** GlaxoSmithKline (GSK) acquired Novartis vaccines.
- **2019:** Chiron Behring Vaccines Pvt. Ltd., acquired GSK Ankleshwar facility.
  - With the acquisition, the rabies vaccine, **Rabipur is now renamed as ChiroRab®.**
  - There is no change in composition & manufacturing process of ChiroRab®.

Manufacturing of ChiroRab®

Highly immunogenic strain of rabies virus

- 'Flury-Low Egg Passage (LEP)-C 25' virus strain

Specific pathogen-free eggs (SPF) fibroblasts do not contain vertically transmitted pathogens, oncogenic DNA and laterally transmitted avian infections

- Propagation of virus in primary chick-embryo fibroblast cells
- Harvesting of virus in the tissue-culture fluid
- Inactivation of virus with beta-propiolactone

Purification step after inactivation to produce a highly purified vaccine, which greatly reduces the risk of hypersensitivity reactions

- Purification and concentration by continuous density-gradient centrifugation
- Addition of buffer and stabilizer
- Lyophilization

Posology & Administration of Rabies Vaccine

Pre-exposure Prophylaxis (PrEP)[2]		
Day of Administration	**IM (1 mL)**	**ID (0.1 mL)**
Day 0	1 dose	1 dose
Day 7	1 dose	1 dose
Day 21 or Day 28	1 dose	1 dose
-	-	-
-	-	-

Post-exposure Prophylaxis (PEP)[2]		
Day of Administration	**IM (1 mL) Essen Regimen**	**ID (0.1 mL) Modified Thai Red Cross Regimen**
Day 0	1 dose	2 doses*
Day 3	1 dose	2 doses*
Day 7	1 dose	2 doses*
Day 14	1 dose	-
Day 28	1 dose	2 doses*

*1 dose should be given on each arm/thigh.

Pre-clinical Studies[3-9]

No attributable pathological findings

Well tolerated locally

No detectable antibodies against chicken fibroblasts

No anaphylactic reactions

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Clinical Trials - India

S. No.	Particulars	Country & Year	Prophylaxis/Route	Conclusion
Intramuscular Studies				
1.	Immunogenicity[10]	India 1989	PEP (HDCSV/PCECV)	PCECV is more cost- effective in developing countries.
2.	Phase 4 (M49P1) Immunogenicity and Safety/Non-inferiority[11]	India 2001	PEP ChiroRab®/Rabipur Essen Regimen	ChiroRab® and Rabipur induced similar immune response and comparable safety profile.
3.	Immunogenicity and Tolerability[12]	India 2004	PrEP PCECV (0.5 mL/1.0 mL of diluent)	A full antigenic dose of PCECV in a dilution of 0.5 mL WFI is as well tolerated locally and systemically as in a dilution of 1.0 mL.
4.	Immunogenicity (In malnourished Children)[13]	India 2005	PEP	Acceptable immune response despite severe degree of protein energy malnutrition.
5.	Immunogenicity and Safety[14]	India 2008	PrEP PCECV/PVRV	PCECV and PVRV are safe and immunogenic when administered intramuscularly for PrEP of rabies in children.
6.	Phase 4 (V49_25) Immunogenicity and Safety[15]	India 2015	PEP (Zagreb vs Essen Regimen)	Zagreb regimen was demonstrated to be immunologically non-inferior to the Essen regimen with similar safety profile.
Intradermal Studies				
7.	Efficacy[16]	India 2002	PEP (WHO recommended Multi-site ID regimen)	PCECV is efficacious in preventing rabies in people bitten by confirmed rabid dogs. Protective titers >0.5 mL up to the end of 3-year observation period.
8.	Immunogenicity[17]	India 2004	PEP (Modified TRC regimen (0.1 mL) PCECV/PVRV)	Adequate antibody response with reduced PCECV vaccine (0.2 to 0.1 mL).
9.	Feasibility, Immunogenicity and Safety[18]	India 2005	PrEP 2-site TRC regimen	Rabipur can be used for intradermal administration in India.
10.	Immunogenicity and Safety[19]	India 2005	PEP TRC Regimen PCECV/NTV	PCECV is highly immunogenic and safe.
11.	Immunogenicity and Tolerability[20]	India 2005	PEP (KIMS-ID/Essen Regimen)	PCECV administered using the KIMS-ID regimen was well tolerated and immunologically efficacious for 365 days.
12.	Efficacy, Immunogenicity and Tolerability[21]	India 2006	PEP (TRC regimen (0.1 mL) PCECV/PVRV)	PCECV is immunogenic, efficacious, and well tolerated when administered in the TRC regimen (0.1 mL). PCECV is also economical in developing countries.
13.	Phase 3 Immunogenicity and Safety[22]	India 2012	PEP (One week ID Regimen PCECV/PVRV)	One week ID regimen is immunogenic and safe for Rabies PEP.

HDCSV: human diploid-cell-strain vaccine; KIMS-ID: Kempegowda Institute of Medical Sciences- intradermal, 0.1 mL injected ID at 2 body sites on days 0, 3, 7, 14, and 28 (2-2-2-2-2); NTV: Nerve tissue vaccine (NTV) produced from rabies virus infected sheep brain tissue; One week Regimen: 4-4-4`; PCECV: purified chick-embryo cell culture vaccine; PVRV: purified vero cell rabies vaccine; TRC: Thai Red Cross; WFI: water for injection.

Note: All the above Clinical Trials and Publications were carried out with the Rabies vaccine manufactured under the brand name, "Rabipur", hereinafter referred to as "ChiroRab®". Except for the brand name change, the Manufacturing Process and Batch Release Specifications remain the same.

Clinical Trials – Global

S. No.	Particulars	Country & Year	Prophylaxis/Route	Conclusion
Intramuscular Studies				
1.	Phase 2 (M49P2) Immunogenicity & Safety Booster response[23]	Thailand 2009	PrEP (IM/ID)	Immune responses were greater with intramuscular schedules.
2.	Phase 3 (M49P8) Schedule evaluation/ Non-inferiority study Immunogenicity & Safety[24]	China 2014	PEP (IM)	Zagreb & Essen regimens are safe and immunogenic for PEP against Rabies.
3.	Phase 3 (M49P8E1) Immunogenicity persistence[24]	China 2014	PEP (IM)	
4.	Phase 3b (V49_24) Schedule evaluation Non-inferiority study Immunogenicity & Safety[25]	China 2015	PEP (IM: Zagreb/Essen)	Zagreb regimen, immunologically non-inferior to the Essen regimen in both children and adults.
5.	Phase 4 (V49_24E1) Immunogenicity persistence[25]	China 2015	PEP (IM: Zagreb/Essen)	
Intradermal Studies				
6.	Phase 4 (M49P3) Non-inferiority study, Immunogenicity & Safety[26]	Srilanka 2004	PEP (ID: TRC)	ChiroRab® is non-inferior to Verorab.
7.	Phase 4 (M49P4) Efficacy Immunogenicity & safety[27]	Philippines 2005	PEP (ID: TRC)	ChiroRab® demonstrated 100% efficacy as evaluated by survival of all 113 subjects.
8.	Phase 3 (V49_30) Schedule evaluation Non-inferiority study Immunogenicity & safety[28]	Thailand & Philippines 2018	PEP (ID: 4-site/2-site TRC)	ChiroRab®, 4-site/1-week ID regimen was non-inferior to that of 2-site/TRC ID regimen.

Adapted from Alexandra Giesen, et al. *Expert Rev. Vaccines.* 14(3), 351–367 (2015).

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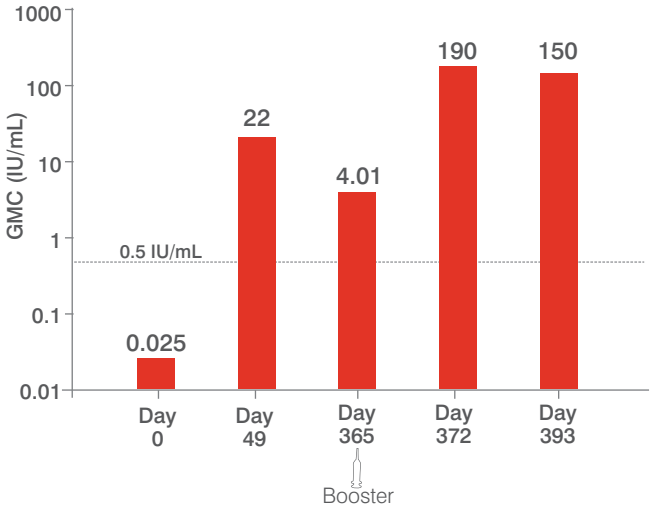
I. Intramuscular Route of Administration

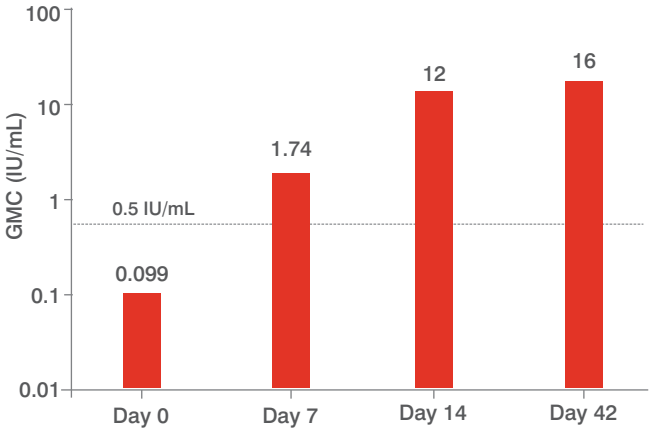
1. Pre-exposure Prophylaxis (M49P2)[23]



PreP regimen (1.0 mL) (1-1-1)
Days 0, 7, and 28

- *All children achieved RVNA Geometric mean concentration (GMC) of ≥0.5 IU/mL with ChiroRab® by Day 49.*
- *After booster dose, RVNA concentrations rapidly increased within 7 days.*

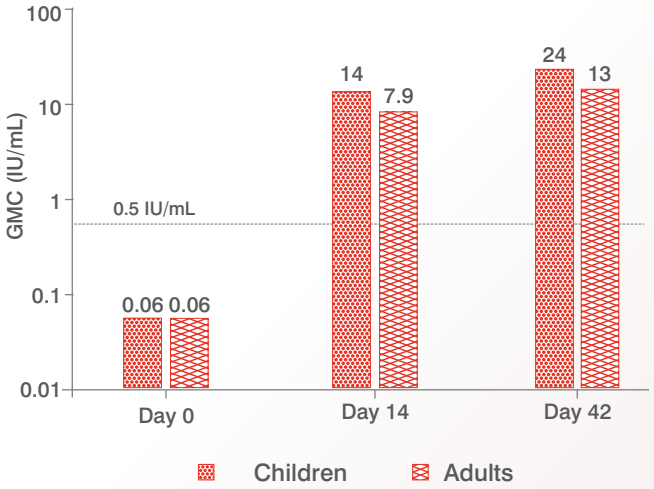
2. Post-exposure Prophylaxis (V49_25)[15]



Essen regimen (1–1–1–1–1)
Days 0, 3, 7, 14, and 28

ChiroRab® achieved a strong immune response by Day 7.

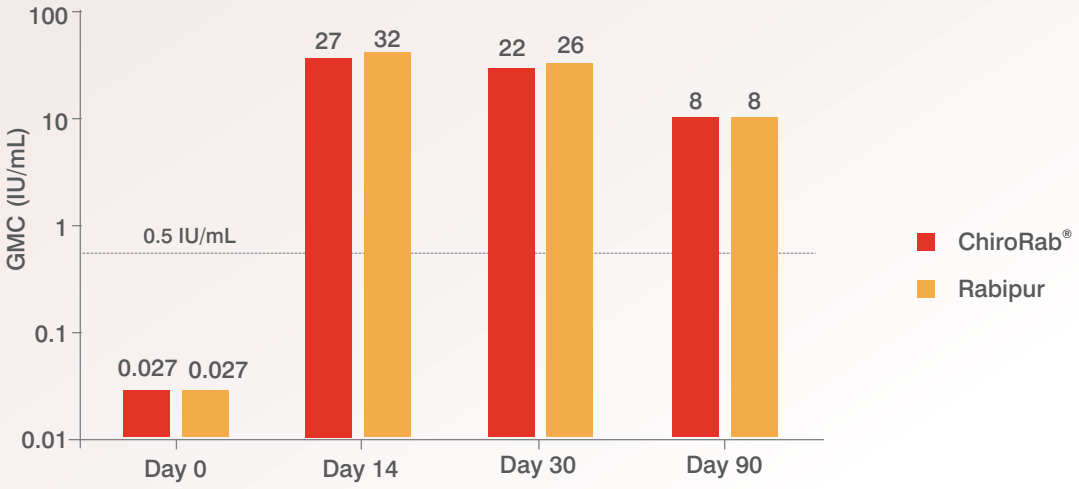
3. Post-exposure Prophylaxis (V49_24)[25]



Essen regimen (1–1–1–1–1)
Days 0, 3, 7, 14, and 28

ChiroRab® induced a strong immune response at Day 14 in children (6-17 years) and adults (≥51 years).

4. Post-exposure Prophylaxis (M49P1)[11]

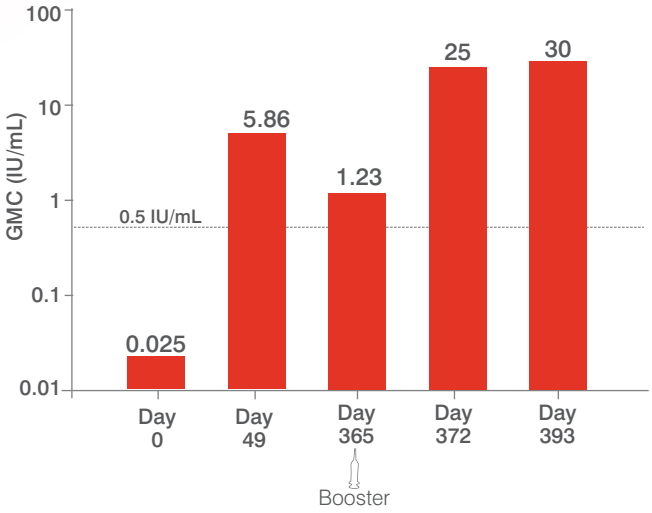


Essen regimen (1–1–1–1–1)
Days 0, 3, 7, 14, and 30

Comparable Immunogenicity and Lot-to-lot consistency between ChiroRab® and Rabipur.

II. Intradermal Route of Administration

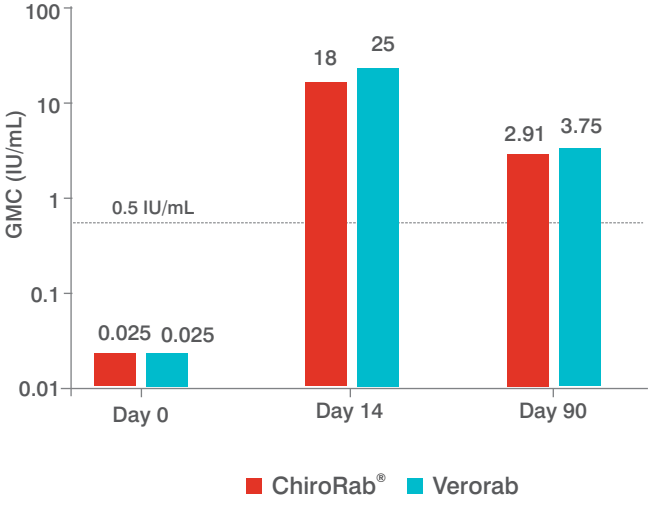
1. Pre-exposure Prophylaxis (M49P2)[23]



PreP regimen (0.1 mL) (1-1-1)
Days 0, 7, and 28

- *All children achieved RVNA concentrations of ≥0.5 IU/mL with ChiroRab® by Day 49.*
- *After booster dose, RVNA concentrations rapidly increased within 7 days.*

2. Post-exposure Prophylaxis (M49P3)[26]



TRC regimen (2-2-2-0-1-1)
Days 0, 3, 7, 30, and 90

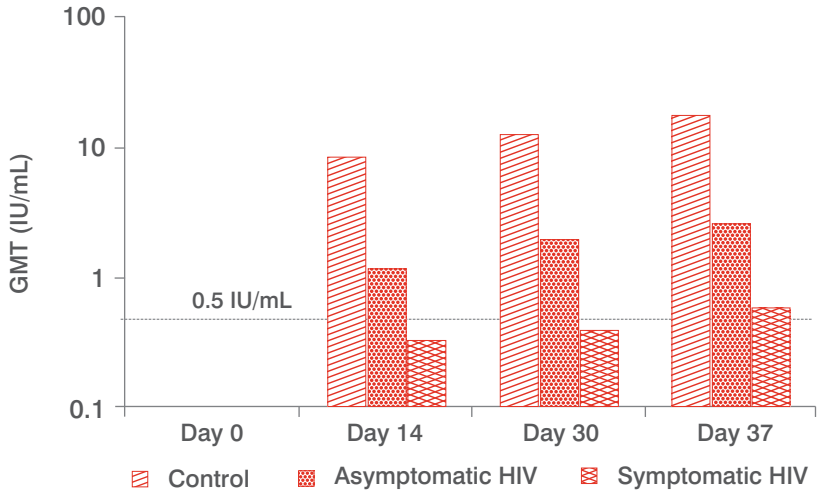
ChiroRab® administered in a dose of 0.1 mL according to the Thai Red Cross ID PEP regimen is safe, immunogenic and non-inferior to Verorab.

III. Special Populations

1. Post-exposure Prophylaxis in Pregnant Women[29]

- Essen regimen (1–1–1–1–1) was used for the subjects involved, one dose was administered at Days 0, 3, 7, 14, and 28.
- ChiroRab® is safe for pregnant women and did not interfere with the development of the fetuses or infants.
- All of the infants exhibited normal development.
- No miscarriages, stillbirths, or fetal malformations were reported.
- No rabies cases were reported for any of the subjects or babies.

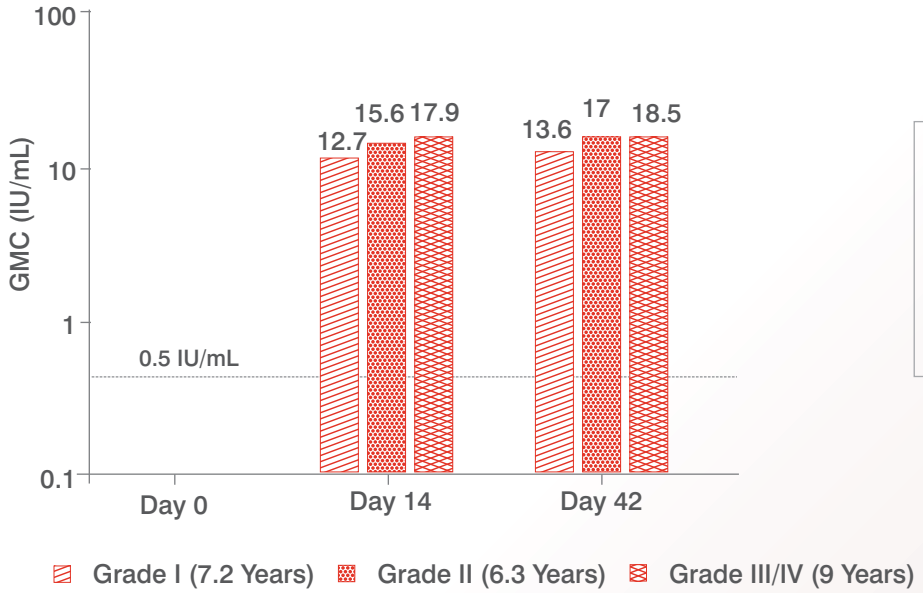
2. Immunogenicity of ChiroRab® in Immunocompromised Individuals[30]



Essen regimen (1–1–1–1–1)
Days 0, 3, 7, 14, and 30

- *57% of individuals in the symptomatic HIV-infected group had RVNA titers >0.5 IU/mL by Day 37 (0.6 IU/mL).*
- *Due to the possibility of a lower antibody response in individuals who are HIV-positive, it is important to note that when PEP is administered to HIV-positive individuals following exposure to rabies, the WHO recommends the administration of RIG in all cases.*

3. Post-exposure Prophylaxis in Malnourished Children[31]



Essen regimen (1–1–1–1–1)
Days 0, 3, 7, 14, and 28.

All children diagnosed with various degrees of malnutrition responded immunologically to ChiroRab® by producing RVNA titers well above the acceptable level of 0.5 IU/mL by Day 14.

Protein energy malnutrition (PEM) as defined by the Indian Academy of Pediatrics:

- Grade I: Children between 71 and 80% of the normal percent of standard weight for age.
- Grade II: Children between 61 and 70% of the normal percent of standard weight for age.
- Grade III: Children between 51 and 60% of the normal percent of standard weight for age.
- Grade IV: Children below 50% of the normal percent of standard weight for age.

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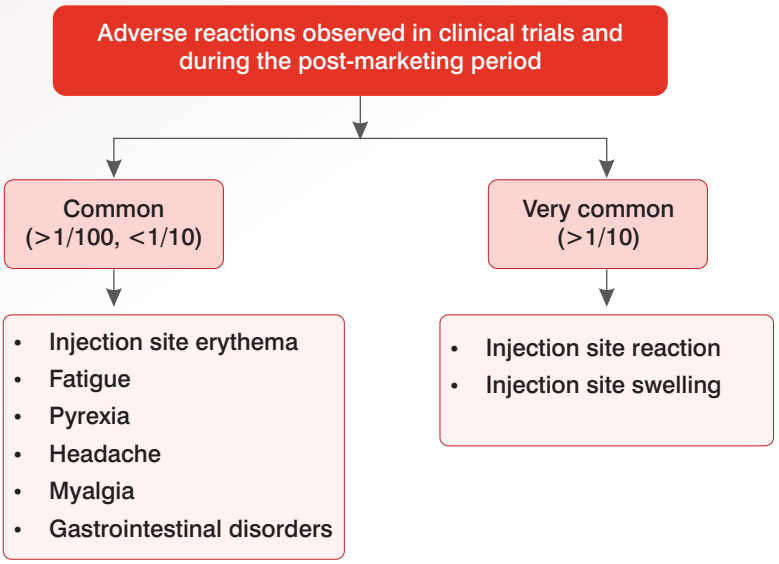
IV. Efficacy of ChiroRab®

Phase IV study to evaluate the efficacy in terms of 1 year survival with ChiroRab® administered intradermally in subjects exposed to laboratory confirmed rabid animals has shown that 12 months after exposure, all 113 patients were alive and no patient had succumbed to rabies or died of other causes.[27]

V. Safety of ChiroRab®

- ChiroRab® has an excellent safety and tolerability profile. Safety of ChiroRab® has been established in more than 20 clinical trials worldwide in both children, adults and post-marketing reports.
- In clinical trials, ChiroRab® has been associated with local reactions, such as injection site pain (30–85%) and induration (15–35%).
- Most of the side-effects in clinical studies were minor, self-limiting and required no treatment.
- ChiroRab® is safe to administer in pregnant and immunocompromised individuals.



Key Features of ChiroRab®

- ChiroRab® is approved for active immunization against rabies, both PrEP and PEP.
- ChiroRab® can be given either as IM or ID using various schedules for PrEP and PEP and as booster vaccinations in all age groups.
- ChiroRab® PEP demonstrated 100% efficacy with favourable tolerability and safety profile.
- No risk to the breast-feeding infants due to ChiroRab® vaccination.
- Pregnancy is not a contraindication to Rabies PEP with ChiroRab®.
- To be stored at +2°C to +8°C during shelf life.
- Confirms its immunogenicity and tolerability for both pre- and post-exposure vaccination regimens among diverse populations.
- ChiroRab® is a global product registered in more than 30 countries.
- ChiroRab® is a well-established vaccine with more than 25 years' post-marketing experience.

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ChiroRab®

Abridged Prescribing Information

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. **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. **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 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. **Dosage and Administration:** Prior to exposure, immunisation- One vaccination (1 ml) on days 0, 7 and 21 or 28. After exposure, begin with the course of immunisation immediately with one single dose of vaccine on days 0, 3, 7, 14, 28 (5-dose schedule) + 1 x 20 IU/kg bodyweight human rabies immunoglobulin or 40 IU/kg bodyweight equine rabies immunoglobulin simultaneously with the first dose of ChiroRab®. **Precautions:** In extreme rare cases in which subjects have reacted with clinical symptoms such as urticaria (nettle rash), lip and epiglottis oedema, laryngo- or bronchospasm, 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. 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. Do not mix vaccine with rabies immunoglobulin in the same syringe. **Adverse Events:** 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. There have been isolated reports of inflammatory and demyelinating neurological disorders, such as progressive ascending paralysis 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. **Storage and Stability:** ChiroRab® should be stored at +2°C to +8°C. ChiroRab® should not be used after the expiry date printed on the pack and container. ChiroRab® is a highly purified, highly immunogenic modern cell-culture PCECV from Chiron Behring Vaccines Pvt. Ltd. with a high potency level per dose.

CHIRON BEHRING

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