Introducing...

World's First
novel cocktail RmAbs

TwinRab™

Novel Rabies Monoclonal Antibody cocktail containing Docaravimab and Miromavimab

DUAL PROTECTION AGAINST RABIES

Zydus Vaxxicare
LIFE IN GOOD HANDS

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Presenting...

Breakthrough innovation in **rabies** PEP

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DUAL PROTECTION AGAINST RABIES

Abridged Monograph

Abridged Monograph: TwinRab

Background on Rabies:

A recent World Health Organization publication estimated human mortality from endemic canine rabies to be 55,000 deaths/year with over 31,000 deaths in Asia alone. When the public health impact is quantified, rabies is ranked above such diseases as dengue. Around 6 million people undergo post-exposure prophylaxis (PEP) of rabies annually worldwide. Rabies is spread over 100 countries and territories. Highest burden of rabies is in Africa and Asia due to the epidemiological, cultural and socioeconomic factors (e.g. lack of rabies awareness, lack of access to affordable healthcare). Rabies death primarily occurs in those who cannot afford or access timely and effective post-exposure prophylaxis (PEP).

As per WHO, the global economic burden of rabies is estimated to be 8.6 billion USD per year. This includes economic burden due to premature death, direct cost of PEP, lost income while seeking PEP, livestock losses, dog vaccination, dog population management, and surveillance.

There is a widespread of rabies in all the parts of India except in the islands of Lakshadweep, Andaman and Nicobar. Around 25,000 to 30,000 deaths due to rabies are reported every year in India, with incidence of 1.7 per 100,000 population which accounts to 60% of the global report of 55,000 deaths. However, the actual number of deaths may be ten times more than that reported. Animal bite load every year is estimated to be 17.4 million and 46.9% take anti-rabies vaccination. Main biting animal is dog (91.5%). Population of dogs in India are estimated to be 25 million and most of them are not protected against rabies. Less than 50% cases of animal bites wash their wound with soap and water and around 20%-40% cases follow indigenous and religious remedies.

Rabies Post Exposure Prophylaxis:

A lethal disease in humans and other animals, rabies can be prevented, following rabies virus (RABV) exposure, by a combination of

- **Thorough wound washing**
- **Multiple-dose vaccine administration**
- **The local infiltration of rabies immune globulin (RIG)**

These are essential components of modern post-exposure prophylaxis (PEP). Although modern cell-culture-based rabies vaccines are increasingly used in many countries, RIG is much less available. Modern CCEEVs are mostly immunogenic and highly effective in preventing rabies. Animal models have been used to demonstrate the effectiveness of CCEEVs after experimental infection. All CCEEVs have shown to exhibit a high vaccine-induced neutralizing antibody (VNA) response to the G protein of RABV. The WHO suggests

a minimum serum antibody concentration of 0.5 IU/mL as a measure of adequate seroconversion after vaccination. This level is reached by day 7-14 of a PEP regimen in most individuals, irrespective of age or nutritional status.

Vaccines can be administered by either the ID or IM route for both PEP and PrEP. One ID dose is 0.1 mL of vaccine; one IM dose is 0.5 mL or 1.0 mL depending on the product, i.e. the entire content of the vial. Injection sites for ID administration are the deltoid region and either the anterolateral thigh or supra-scapular regions for all age groups. On the other hand for IM administration recommended site is the deltoid area of the arm for adults and children aged ≥2 years, and the anterolateral area of the thigh for children aged <2 years. WHO recommends that rabies vaccine should not be administered IM in the gluteal area.

Post-exposure prophylaxis (PEP) by category of exposure.

	Category I exposure	Category II exposure	Category III exposure
Immunologically naive individuals of all age groups	Washing of exposed skin surfaces	Wound washing and immediate vaccination	Wound washing and immediate vaccination
	No PEP required	2-sites ID on days 0, 3 and 7	2-sites ID on days 0, 3 and 7
		or	**or**
		1-site IM on days 0, 3, 7 and between day 14-28	1-site IM on days 0, 3, 7 and between day 14-28
		or	**or**
		2-sites IM on days 0 and 1-site IM on days 7, 21	2-sites IM on days 0 and 1- site IM on days 7, 21
		RIG/MAb is not indicated	RIG/MAb administration is recommended
Previously immunized individuals of all age groups	Washing of exposed skin surfaces	Wound washing and immediate vaccination	Wound washing and immediate vaccination
	No PEP required	1-sites ID on days 0, 3	1-sites ID on days 0, 3
		or	**or**
		At 4-sites ID on day 0	At 4-sites ID on day 0
		or	**or**
		At 1-site IM on days 0 and 3	At 1-site IM on days 0 and 3
		RIG/MAb is not indicated	RIG/MAb is not indicated

RIG should be administered only once, preferably at, or as soon as possible after, the initiation of PEP. RIG should not be given after day 7 following the first rabies vaccine dose.

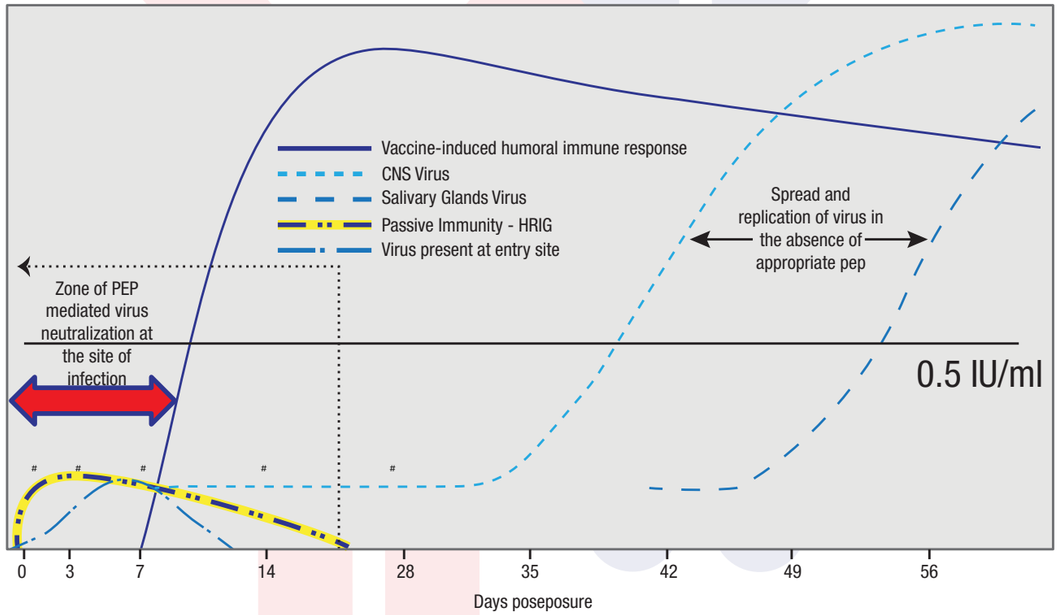
WHO recommends following categories for patients who should be given high priority to receive RIG: category III exposed patients with multiple bites ; those with deep wounds, or

bites to highly innervated parts of the body, such as the head, neck and hands; patients with severe immunodeficiency; and cases where the biting animal is a confirmed or probable rabies case, or where bites, scratches or exposure of a mucous membrane are caused by a bat.

The WHO recommends infiltration of RIG into and around the wound. However, if large volumes of RIG are injected into a small body area with limited tissue compartment syndrome can occur which is important to avoid. Therefore, maximal quantity that is anatomically feasible should be administered for small wounds. For large and multiple wounds, RIG can be diluted if necessary with physiological buffered saline to ensure the infiltration of all wounds. The WHO no longer recommends injecting the remainder of the calculated RIG dose IM at a distance from the wound. Unused fractionated doses and open vials of RIG should be discarded by the end of the day.

Contribution of passive immunity in Rabies PEP:

Figure 1: Schematic of dynamics of rabies virus pathogenesis*. In the presence and absence of PEP-mediated immune response@



* Rabies can progress though five stages: incubation period(5 days to >2 years : U.S median-35 days), prodrome state (0-10 days), acute neurological period (2-7 days), coma(5-14 days) and death.

@ Once in tissues at the entry sie, rabies virus can be neutralized by passively administered rabies immune globulin (RIG). Active immunization (vaccine) stimulates the host immune system and as a result, virus -neutralizing antibodies(VNA) are produced approximately 7-10 days after initiation of vaccination.By approxi mately day 14-28(after administration of 4 vaccine doses), VNAs peak in the absence of early and adequate. In the abesence of early and adequate PEP, virus enters host neurons , spreads to the central nervous system (CNS) and causes disease with inevitably fatal consequences.

^ Human rabies immune globulin

\# Day vaccine administered

Rabies immunoglobulin-polyclonal:

The polyclonal RIG is relatively easy to produce, possesses high potency, a broad spectrum of virus-neutralizing activity, poly-specificity that prevents the selection of neutralization escape mutants, and multiple effector functions, mediated by several isotypes, due to its heterogeneous nature.

The ERIG is a heterologous molecule and highly immunogenic in humans, resulting in induction of human antiequine antibody responses, leading to rapid clearance of ERIG, necessitating higher dosing and culminating in induction of severe type III hypersensitivity reactions and serum sickness, which is sometimes fatal. Consequently, often, physicians are hesitant to use ERIG, thus providing incomplete PEP, which may result in failures. Compared with HRIG, the less expensive nature of ERIG seems to be the primary reason for its continued use in developing countries. All licensed RIGs are expected to neutralize all known RABV variants, but no available product will neutralize all described lyssaviruses.

Modern HRIG is safe, non-immunogenic, and well tolerated by humans. The incidence of anaphylaxis or serum sickness is virtually unknown. However, as a human plasma product, it has the potential for transmission of blood-borne infectious agents, which can be mitigated by treatment with solvents or detergents or heat treatment. Such processes are expensive and not generally affordable in developing countries, where canine rabies remains the primary public health problem.

The worldwide inaccessibility of HRIG and its high cost of production place it out of reach of most patients in the developing world.

Regardless of the species of origin, polyclonal RIG in general has certain constraints, including the need for donor recruitment and immunization; multiple inoculations and bleeding procedures; donor retention; ethical problems; lower specific activity, which may necessitate the use of more protein, which may lead to higher viscosity and adverse events; variable batch-to-batch consistency; supply limitations from competing use of plasma products; and the potential risk of transmission of infectious agents. For such economic, supply, and safety reasons, replacement of HRIG and ERIG is advocated, and the World Health Organization strongly encourages development of alternative products.

Alternative to polyclonal immunoglobulins:

The invention of the concept of mAb technology by Kohler and Milstein in 1975 revolutionized biomedicine and has become a billion-dollar industry. New approaches, such as the use of hybridoma and humanization technologies, as well as use of single chain and VHH single domain antibodies, allow for cell culture or microbial expression systems production of monoclonal antibodies (mAbs), a promising alternative to polyclonal RIG with reduced risks for transmission of pathogens and large-scale production for a reduced cost.

The use of hybridomas in mAb production enables a sustained production of antibody and is not dependent on the life of the donor host as with polyclonal antibody production. The

rationale behind using mAbs for therapy is that they provide a more potent product with better activity than their polyclonal counterparts. Additionally, they do not seem to have the inherent variability with regards to epitope and isotype, and are homogeneous in nature and hence exhibit relatively low lot-to-lot variability. Significantly, the duration of action of mAbs is predictable and likely to be related to the biological half-life. High specific activity of mAbs essentially makes administration of a low amount of protein and volume possible, which per se avoids several adverse events, including the concern for compartment syndrome.

Although mAbs have significant promise as therapeutic agents, they are not without limitations: for example:

1. They may be expensive
2. By definition, they target a single epitope and hence provide one type of effector function corresponding to their isotype
3. Although the specificity of mAbs is a strength, a pathogen that possesses rapid antigenic variation poses a significant hurdle for broader mAb development
4. They may select for neutralization escape variants as a result of microbial mutation or microevolution

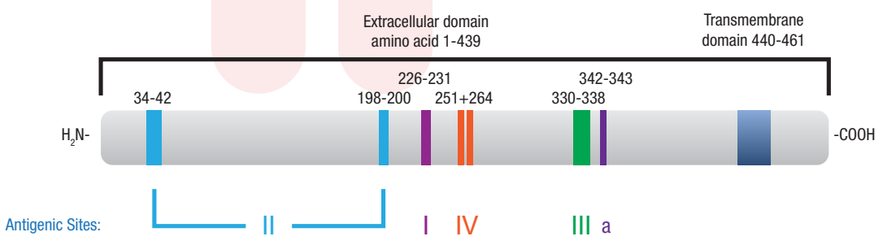
The use of mAbs that target conserved areas of viral particles, or a cocktail of mAbs that target various epitopes, can obviate this concern.

In fact, the World Health Organization has advocated the use of antirabies mAb cocktails for rabies PEP and does not recommend the use of single mAbs, due to the potential of viral escape. This concept of using a cocktail of at least two mAbs, which target distinct, non-overlapping epitopes and that do not compete for binding to the RABV glycoprotein, as a potential alternative to RIG in PEP, has been widely accepted by the scientific community and also endorsed by WHO.

Target for cocktail mAbs

During the last 3 decades, numerous murine mAbs against the RABV G that neutralize RABV and other lyssaviruses, both in vitro and in vivo, have been developed.

They are specific to one of five distinct antigenic sites on the RABV G (antigenic sites I, II, III, IV, and minor site a) with the vast majority of them recognizing either antigenic site II or III. Below is the figure of Rabies virus G protein:



Antigenic site II is discontinuous and conformation dependent, whereas antigenic site III is predicted to be continuous and conformation dependent. No single mAb will neutralize all known RABV variants, so mAbs can be broadly neutralizing only when used in combination, which is not the case when used alone, because the G is prone to a high level of diversity in nature. Cocktails of mouse mAbs have been envisioned to be less expensive alternatives to polyclonal RIG for PEP to prevent rabies in humans, because they performed as well as HRIG in animal models.

Difference between monoclonal antibodies and polyclonal antibodies:

Monoclonal antibodies	Polyclonal antibodies
Monoclonal antibodies refer to a homogenous population of antibodies that are produced by a single clone of plasma B cells	Polyclonal antibodies refer to a mixture of immunoglobulin molecules that are secreted against particular antigen
Produced by the clone of same plasma B cells	Produced by different clones of plasma B cells
Production requires hybridoma cell lines	Production does not require hybridoma cell lines
Interact with a particular epitope on an antigen	Interact with different epitopes on the same antigen
Production is expensive	Production is not expensive
Production takes some time	Production less time
Are highly specific	Possess comparatively high cross reactivity
Used as therapeutic drug	Used in general research applications
Advantages include immortal supply, high specificity and high reproducibility	Advantages include high affinity, tolerance of minor changes and more robust detection

Product Specification TwinRab

TwinRab is a cocktail of two anti-rabies monoclonal antibodies, docaravimab (62-71-3) and miromavimab (M777-16-3). The hybridomas used for the production of the monoclonal antibodies are sourced from the following WHO collaborating centres:

- mAb 62-71-3 from the Centres of the Disease Control and prevention (CDC), Atlanta, USA
- mAb M777-16-3 from the Animal Diseases Research Institute (ADRI), Nepean, Canada

TwinRab is a unique combination of two monoclonal antibodies that bind to two different epitopes on the G protein expressed on the surface of rabies virus. The two monoclonal antibodies bind to and neutralize both, rabies and rabies-like viruses, preventing their infection into the neighbouring cells. The individual monoclonal antibodies present in the TwinRab cocktail mixture were found to neutralize in vitro, various rabies and rabies related viruses such as (CVS 11, SAD B19, PV, Kelev, European Fox, Dog Turkey, Dog Ethiopia, Dog India, Dog Mexico, Wolf Sarajevo, Bobcat-USA, EBLV 1, EBLV 2, East European fox, Polar fox, Dog Azerbaijan, Dog Nepal). The cocktail of antibodies was also found to neutralize rabies virus strains isolated from Dog, Canine, Human, and Bovine sources from southern parts of India.

In various in vivo studies, the antibody cocktail was found to neutralize rabies virus isolates (CVS11, Mexican (2004), Thai (2006), Indian (2008) canine variants and Texas Fox 393 rabies virus). In still another in vivo study, the cocktail was also found to neutralize rabies virus isolates from Dog, Canine, Human, and Bovine sources isolated from southern parts of India.TwinRab is infiltrated (as much of the dose as possible) into and around the exposure site/s (if visible) and the remainder administered intramuscularly at site/s distant from the site of vaccination. It is administered as a part of anti-rabies Post Exposure Prophylaxis into previously unvaccinated persons to provide immediate passive rabies virus neutralizing antibody protection until the patient's immune system esponds to vaccination by actively producing antibodies.

Highlights of TwinRab:

- TwinRab has also received orphan designation from US FDA.
- Two murine neutralizing monoclonal antibodies binding to two distinct viral epitopes on the G-protein of virus membrane.
- TwinRab has been tested for neutralization of viruses isolated from domestic and wild animals from a variety of countries (Dogs from India, Turkey, Ethiopia, Mexico, Nepal etc.; Fox from Europe, Easter Europe, Polar fox; Wolf from Sarajevo; Bat from Europe; variety of animals from US; etc.)
- Hybridomas have been sourced from WHO collaborating centres. Extensive in vitro and in vivo virus neutraliza tion studies conducted at WHO collaborating laboratories –
    - o FLI, Germany
    - o CDC Atlanta, USA
    - o Wusterheusen, Canada
    - o NIMHANS, Bangalore, India
- Highly purified and can be produced in large quantities. Well characterized cell banks.
- Standard quality and greater effectiveness. Twice the potency of HRIG ensures more pro tective titer is available at site of bite.
- Elimination of use of animals, no risk of zoonotic infections. No risk of blood/plasma/serum borne diseases (HIV, HBV, HCV etc.)
- Reduced amount of proteins in the drug and high purity ensures less adverse reactions

Composition, dosage and Indication:

TwinRab is a sterile preservative free clear colourless liquid solution for infiltration. TwinRab is available in four different strengths viz.

- 10 mL vial containing 3000 IU (300 IU/mL) of TwinRab,
- 5 mL vial containing 3000 IU (600 IU/mL) of TwinRab,
- 2.5 mL vial containing 1500 IU (600 IU/mL) of TwinRab and
- 1 mL vial containing 600 IU (600 IU/mL) of TwinRab.

The recommended dose of TwinRab is 40 IU/kg of body weight.

TwinRab is indicated for post exposure prophylaxis in individuals with suspected rabies exposure. TwinRab must always be used in combination with Rabies vaccine as part of post-exposure prophylaxis in line with the recommendation of World Health Organization (WHO).The table below comprises of qualitative and quantitative composition of TwinRab Drug Product.

Strengths	**3000 IU in 10 mL**	**3000 IU in 5 mL**	**1500 IU in 2.5 mL**	**600 IU in 1 mL**
Name of the Ingredients	**Quantity per mL**			
Active Ingredients				
Docaravimab	150 IU	300 IU	300 IU	300 IU
Miromavimab	150 IU	300 IU	300 IU	300 IU
Inactive Ingredients				
T ri-sodium citrate dihydrate (IP/USP)	5.12 mg	5.12 mg	5.12 mg	5.12 mg
Citrate acid (IP/USP)	0.5 mg	0.5 mg	0.5 mg	0.5 mg
Sodium chloride (IP/USP)	5.84 mg	5.84 mg	5.84 mg	5.84 mg
Polysorbate (IP/NF)	0.1 mg	0.1 mg	0.1 mg	0.1 mg
Sodium hydroxide (IP/NF) or Hydrochloric acid (IP/EP/USP)	q.s. to adjust pH 6.0	q.s. to adjust pH 6.0	q.s. to adjust pH 6.0	q.s. to adjust pH 6.0
Water for Injection (IP/USP)	q.s.	q.s.	q.s.	q.s.
Each strenght of drug product preparation is prepared with equipotent amounts of Docaravimab and Miromavimab monoclonal antibodies.				

For further details, please refer to the prescribing information of TwinRab.

Frequently asked queries

Q.1. What are the major differences between RIGs *vs.* TwinRab?

♦ Major differences between RIgs and TwinRab are outlined in below table:

S.No.	Rabies Immunoglobulins (RIG)	TwinRab
1.	RIGs are available in limited quantities and in most situations is inaccessible to those that need it most	No Such concerns TwinRab is manufactured using hybridoma technology, no animal rearing is required for manufacturing TwinRab. TwinRab can be manufactured in bulk quantities and made available in all quantities
	More and more international manufacturers are discontinuing RIG production	
	Animal protection groups that are becoming more and more influential in developing countries, condemn animal rearing for serum production	
2.	RIGs may or may not be target oriented in binding to G protein of rabies virus	Two monoclonal antibodies present in TwinRab effectively binds to 2 different epitopes of g protein of rabies virus
3.	RIGs may interfere with rabies vaccine activity	TwinRab (cocktail of two monoclonal antibodies) is shown to be not interfering with the rabies vaccine activity in the clinical studies
4.	Serum sickness can occur 1 week after administration of highly purified equine rabies immunoglobulin in < 1–3% of recipients	No Such concerns with TwinRab
5.	Risk of allergic reaction	No such cases of allergic reaction reported in clinical studies conducted with TwinRab

Q.2. Why it is called Monoclonal Antibody and why not Polyclonal Antibody as it has two Mabs?

♦ Antibodies are a type of globular proteins produced by the plasma B cells in response to a specific antigen. An antigen can be a foreign molecule that interacts with the cells of the immune system, triggering an immune response. The molecules on the antigens to which the antibodies attach themselves are called epitopes. The region of the antibody which binds to the epitope is called a paratope. Monoclonal antibodies and polyclonal antibodies are the two varieties of antibodies, which are used in therapeutics applications. Both monoclonal and polyclonal antibodies interact with the same antigen. The main difference between monoclonal and polyclonal antibodies is that monoclonal antibodies are produced by the same clone of plasma B cells, and they bind to a unique epitope whereas polyclonal antibodies are produced by different clones of plasma B cells, and they bind to the different epitopes in the same antigen. In case of TwinRab, it consists of two individual monoclonal antibodies derived from two different clones. The two monoclonal antibodies binds specifically to two different epitopes of G protein of rabies virus. Hence, TwinRab provides more effective rabies binding as compared to any other polyclonal antibody. Also, because polyclonal antibodies are composed of a mixture of antibodies, they are prone to a higher risk of batch-to-batch variability than monoclonal antibodies. Because monoclonal antibodies specifically detect a particular epitope on the antigen, they are less likely than polyclonal antibodies to cross-react with other proteins.

Q.3. Could TwinRab be administered alone or along with Rabies Vaccine only?

♦ TwinRab should always be administered along with rabies vaccine.

Q.4. What would be the effect if it's administered alone or without Antirabies vaccine?

♦ If TwinRab is administered alone then it will neutralize the rabies virus at the site of wound and drug titers will be maintained till 7 days of exposure. In such a case when there is no vaccine administration, post 7 days of exposure the drug titers will start to deplete and therefore complete window of protection against the rabies virus will not be provided.

Q.5. Is TwinRab an adjuvant therapy or 1st line drug?

♦ Anti-rabies antibodies are key to protection against lethal rabies. Anti-rabies antibodies are used as passive immunization against rabies virus. TwinRab, neutralizes the rabies virus by localizing the rabies virus at the site of exposure before patients start producing their own antibodies as a result of vaccination.

Q.6. How dose can be calculated for TwinRab? Is it as per subject's body weight or standard dosing?

♦ Dose can be calculated on subject body weight. TwinRab should be dosed at 40 IU/kg body weight.

Q.7. All Rabies vaccine will be given till 90 days period along with Equine Ig or Human Ig, How about TwinRab is to be positioned?

♦ Response: Same procedure is recommended to be followed for TwinRab also.

Q.8. Whether any test dose is required?

♦ No test dose required for TwinRab.

Q.9. Any relapse with TwinRab, any relapse rate will be occurred if subjects withheld or withdraw the therapy?

♦ No relapse rate is expected with TwinRab administration.

Q.10. What is the ideal temperature to store TwinRab?

♦ Ideal storage condition is between 2°C and 8°C.

Q.11. How TwinRab is to be re-constituted if it is supplied in powdered form?

♦ Response: TwinRab is available in liquid solution for injection. No lyophilized powder form is available, hence no re-constitution is required.

Q.12. Is there any cross sensitivity with other mABs/IGs/Vaccines/Drugs?

♦ Response: TwinRab is not sensitive or does not affect the activity of vaccine. Cross reactivity of TwinRab with other mAbs or IGs or drugs have not been studied.

Q.13. Why TwinRab and not Rabishield which is human mAB?

♦ Response: TwinRab is a cocktail of two monoclonal antibodies having equipotent mixture of two monoclonal antibodies. Rabishield consists of single monoclonal antibody binding to antigenic site III of G protein of rabies virus. Whereas TwinRab being an cocktail of two monoclonal antibodies provides additional safety by binding to site III / I and also site II of G protein of rabies virus.

Q.14. Mention the merits of TwinRab & Demerits of Other Ig with Rabies Vaccine.

Merits of TwinRab are as under:-

> TwinRab is cocktail of two monoclonal antibodies and binds to two sites of G protein of rabies virus. Thus provides better immunity against rabies virus.
> Both the monoclonal antibodies act in a complementary manner and binds to some of the escape mutants also.
> TwinRab can be manufactured in bulk quantities, therefore there is no availability constrains with TwinRab.
> The dosage of TwinRab is 40 IU/kg, therefore it provides maximum amount of drug at the site of exposure.
> Extensive in vitro and in vivo studies conducted with TwinRab have proved that TwinRab is effec tive against a wide variety of rabies and rabies related viruses.
> Various clinical studies conducted with TwinRab proved that the product safe and effective at its prescribed dosing and capable of providing the unbroken window of immunization against rabies virus when administered along with rabies vaccine.

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