Australian Government
Department of Health
Therapeutic Goods Administration

# Australian Public Assessment Report for Rabies immunoglobulin

## Proprietary Product Name: KamRAB

## Sponsor: Link Medical Products Pty Ltd / Link Pharmaceuticals

**January 2022**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

# About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ABLV | Australian bat lyssavirus |
| ACM | Advisory Committee on Medicines |
| ARTG | Australian Register of Therapeutic Goods |
| ASA | Australian-specific annex |
| $AUC_{0\text{-}inf}$ | Area under the concentration versus time curve from dosing (time zero) extrapolated to infinity |
| $AUC_T$ | Area under the concentration versus time curve from dosing (time zero) to the end of the dosing period |
| CDNA | Communicable Diseases Network Australia |
| CI | Confidence interval |
| $C_{max}$ | Maximum concentration |
| CMI | Consumer Medicines Information |
| COR-B | Comparable Overseas Regulator approach B |
| CPD | Certified Product Details |
| DLP | Data lock point |
| FDA | Food and Drug Administration (United States of America) |
| GVP | Good Pharmacovigilance Practices |
| HRIG | Human rabies immunoglobulin |
| IgG | Immunoglobulin G |
| LS | Least squares |
| PEP | Post-exposure prophylaxis |
| PI | Product Information |
| PK | Pharmacokinetic(s) |
| PSUR | Periodic safety update reports |
| RFFIT | Rapid fluorescent foci inhibition test |
| RMP | Risk management plan |

| Abbreviation | Meaning |
|---|---|
| RVNA | Rabies virus neutralising antibody |
| SAS | Special Access Scheme |
| SD | Standard deviation |
| $t_{1/2}$ | Half life |
| $t_{max}$ | Time of maximum concentration |
| US(A) | United States (of America) |
| VNAb | Virus neutralising antibody |
| WHO | World Health Organization |

# I. Introduction to product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | New biological entity |
| *Product name:* | KamRAB |
| *Active ingredient:* | Rabies immunoglobulin |
| *Decision*: | Approved |
| *Date of decision:* | 11 August 2021 |
| *Date of entry onto ARTG:* | 16 August 2021 |
| *ARTG number:* | 336970 |
| , *Black Triangle Scheme:*[1] | Yes<br>This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia. |
| *Sponsor's name and address:* | Link Medical Products Pty Ltd T/A Link Pharmaceuticals<br>PO Box 718,<br>Mona Vale, NSW, 1660 |
| *Dose form:* | Solution for injection |
| *Strength:* | 150 IU/mL |
| *Container:* | Glass vial |
| *Pack sizes:* | Single-use packs containing one vial (2 mL or 10 mL). |
| *Approved therapeutic use:* | *KamRAB is rabies immunoglobulin indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KamRAB should be administered concurrently with a full course of rabies vaccine.*<br>• *Do not administer additional (repeat) doses of KamRAB once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine.*<br>• *Do not administer KamRAB to patients with a history of a complete pre-exposure or postexposure vaccination regimen and confirmed adequate rabies antibody titre.* |

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

| | |
|---|---|
| *Route of administration:* | Intramuscular |
| *Dosage:* | Post-exposure prophylaxis consists of a single dose of KamRAB and a full course of rabies vaccine. The recommended dose of KamRAB is 20 IU/kg body weight, given at the time of the first vaccine dose. KamRAB and the first dose of rabies vaccine should be given as soon as possible after exposure, and regardless of the time interval between exposure and initiation of post-exposure prophylaxis, as delays are potentially lethal. However, should a delay occur, KamRAB should be administered at any time up to and including seven days after the first dose of vaccine. The rabies vaccine should be given according to the manufacturer's instructions.<br><br>For further information regarding dosage, refer to the Product Information. |
| *Pregnancy category:* | B2<br><br>Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.<br><br>Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.<br><br>The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory. |

## Product background

This AusPAR describes the application by Link Medical Products Pty Ltd T/A Link Pharmaceuticals (the sponsor) to register KamRAB (rabies immunoglobulin) 150 IU/mL solution for injection, 2 mL and 10 mL vials for the following proposed indication:

> *KamRAB is a human rabies immunoglobulin (HRIG) indicated for passive, transient postexposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KamRAB should be administered concurrently with a full course of rabies vaccine.*
>
> > *Do not administer additional (repeat) doses of KamRAB once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine.*
> >
> > *Do not administer KamRAB to patients with a history of a complete pre-exposure or postexposure vaccination regimen and confirmed adequate rabies antibody titer.*

### Lyssaviruses in Australia

Rabies is a zoonotic disease caused by infection with rabies virus, or other lyssaviruses including Australian bat lyssavirus (ABLV). Aside from endemic lyssavirus, 2 imported human cases of rabies have been reported in Australia, in people from enzootic areas, that is, areas where the viruses that cause rabies are constantly present and regularly effect animals. Rabies lyssavirus is enzootic in Asia (including Southeast Asia where large numbers of Australians travel), Africa, North and South America and parts of Europe.

Clinical stages of rabies can progress from an incubation period (typically of 2 to 3 months in duration), to a prodromal state (between 0 and 10 days duration), evolving to an acute neurologic period (of 2 to 7 days duration), to coma (5 to 14 days duration), and in the worst scenario, culminating in death.

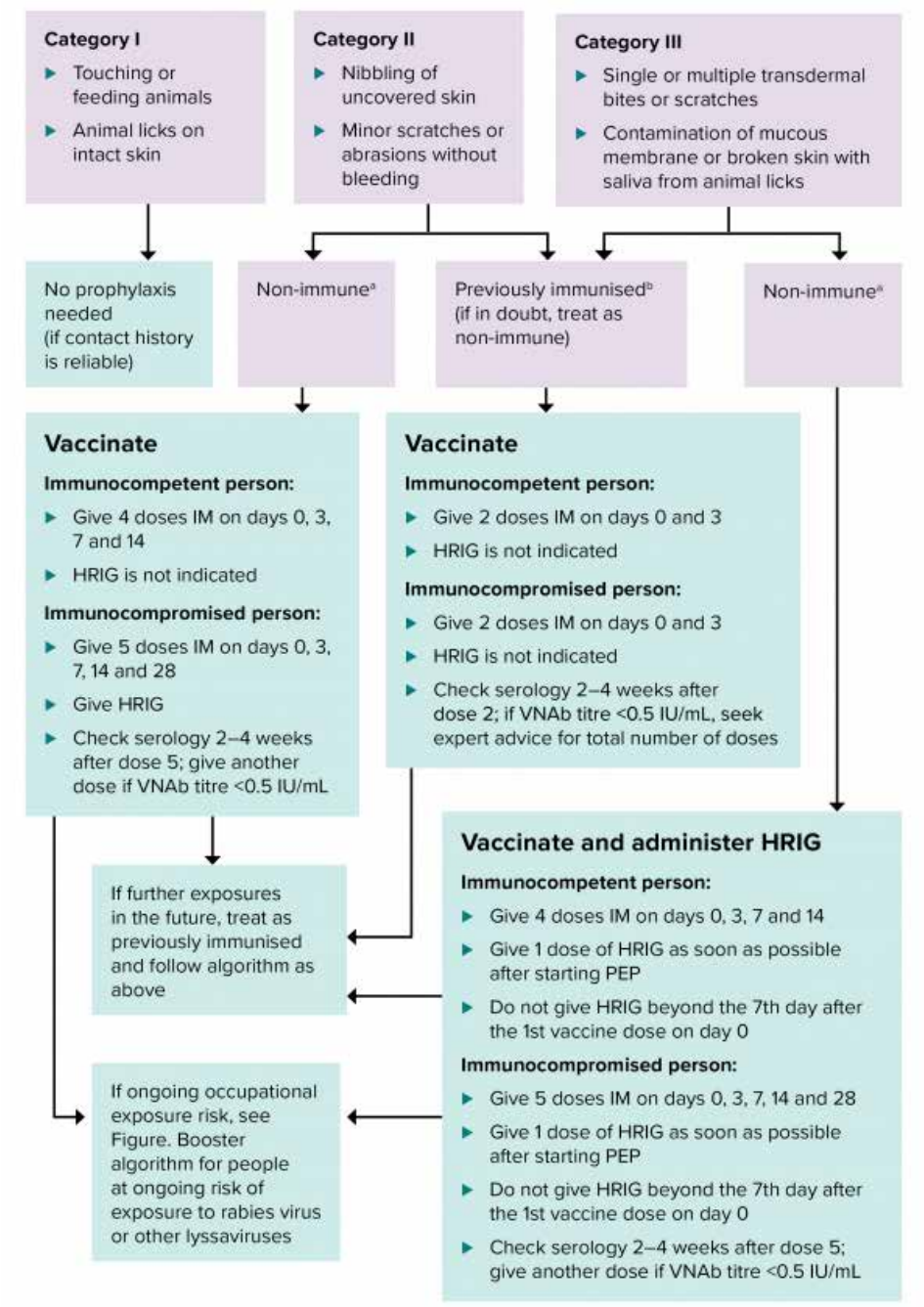
### Current treatment options

The Australian Immunisation Handbook (2018);[2] recommends post-exposure prophylaxis for rabies with wound management and rabies vaccine following potential exposures to rabies virus, with the addition of human rabies immunoglobulin in non-immune persons after potential Category III exposures to lyssaviruses from a terrestrial animal in a rabies-enzootic area, and Category II or III exposures to lyssavirus from bats in Australia or overseas.

Figure 1, shown below, is reproduced from the Australian Immunisation Handbook (2018) and provides an overview of the post-exposure prophylaxis algorithm for potential exposure to lyssaviruses from a terrestrial animal in a rabies-enzootic area. Note, this algorithm is also suitable for potential exposure to a terrestrial animal with a laboratoryconfirmed lyssavirus infection in an area where rabies is not enzootic, such as Australia.

[2] The Australian Immunisation Handbook is available at: https://immunisationhandbook.health.gov.au

**Figure 1: Post-exposure prophylaxis algorithm for potential exposure to lyssaviruses from a terrestrial animal in a rabies-enzootic area**



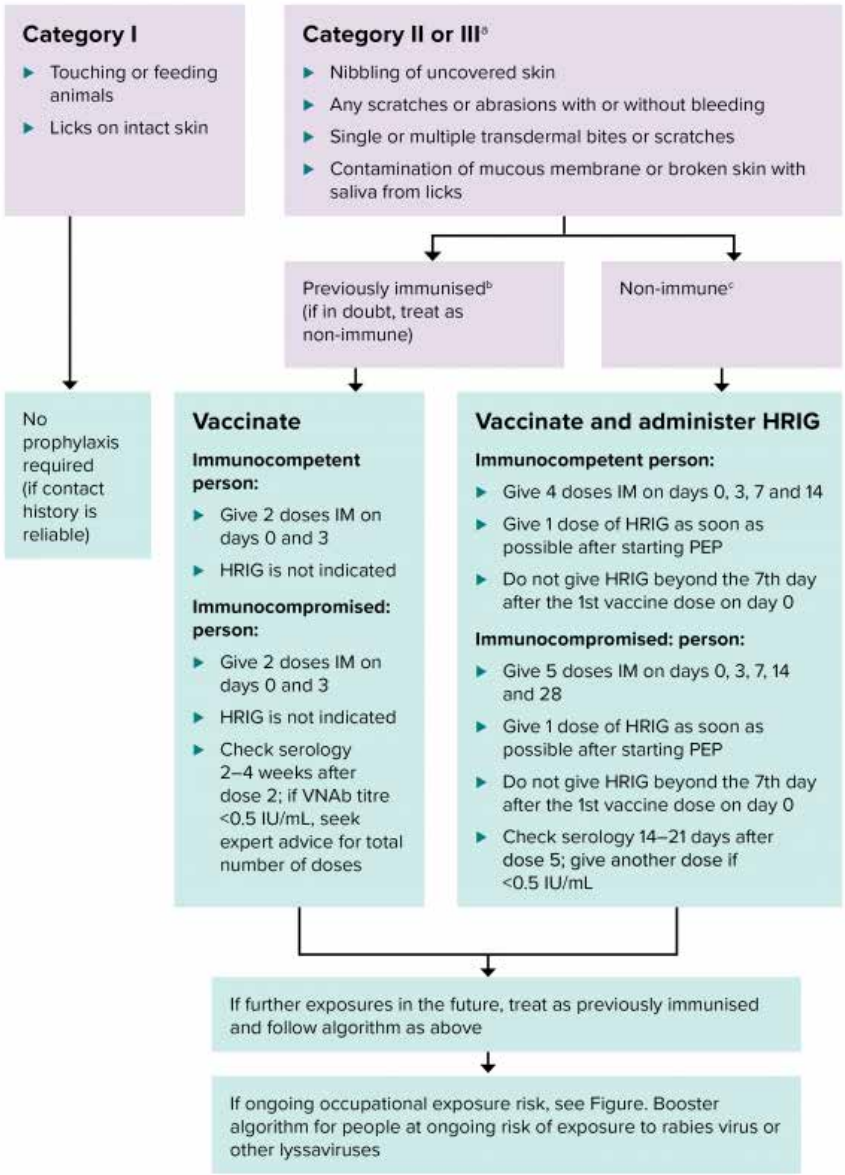

HRIG = human rabies immunoglobulin; IM = intramuscularly; PEP = post-exposure prophylaxis; VNAb = virus neutralising antibody

a) Non-immune: person who has never received pre- or post-exposure prophylaxis with rabies vaccine, or has had an incomplete or inadequate primary vaccination course; b) Previously immunised: documentation of a completed recommended pre- or post-exposure prophylaxis rabies vaccine regimen. This is regardless of the time since the last dose was given. It may be either a completed primary pre-exposure course or post-exposure course. It includes people who had subsequent boosters, or who have documented rabies VNAb titres ≥ 0.5 IU/mL.

Category II exposure is defined as nibbling of uncovered skin, minor scratches or abrasions without bleeding. Category III exposure is defined as single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, or exposure due to direct contact with bats.

Figure 2, below, is the algorithm (reproduced from the Australian Immunisation Handbook (2018)) for post-exposure prophylaxis for potential exposure to lyssaviruses from bats.

**Figure 2: Post-exposure prophylaxis algorithm for potential exposure to lyssaviruses from bats in Australia or overseas**




HRIG = human rabies immunoglobulin; IM = intramuscularly; PEP = post-exposure prophylaxis; VNAb = virus neutralising antibody

a) Includes situations where the exposure may be difficult to categorise, because a person does not know or cannot communicate if or how an exposure to a bat has occurred; b) Previously immunised: documentation of a completed recommended pre-exposure prophylaxis or PEP rabies vaccine regimen. This is regardless of the time since the last dose was given. It may be either a completed primary pre-exposure course or a post-exposure course, and includes people given subsequent boosters or whose documented rabies VNAb titres are ≥ 0.5 IU/mL; c) Non-immune: a person who has never received pre- or post-exposure rabies vaccine, or has had an incomplete or inadequate primary vaccination course.

Rabies vaccines available in Australia include Merieux Inactivated Rabies Vaccine;[3] and Rabipur Inactivated Rabies Virus Vaccine.[4] Imogam Rabies Pasteurised, as a rabies immunoglobulin, is registered in Australia for post-exposure prophylaxis.[5]

## Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

KamRAB was first supplied in Australia under the Special Access Scheme (SAS) from December 2013 to July 2016. A Section 19A application to supply Israeli registered KamRAB to address the anticipated shortage of Imogam (supply impact dates 1 November 2019 to 1 January 2021) was approved on 25 September 2019.[6]

At the time the TGA considered this application, similar applications had been approved in the countries listed in Table 1, below.

**Table 1: International regulatory status**

| Region | Submission date | Status | Approved indications |
|---|---|---|---|
| United States of America | 29 August 2016 | 23 August 2017 | *Passive, transient post-exposure prophylaxis (PEP) of rabies infection to persons of all ages when given immediately after contact with a rabid or possibly rabid animal* |
| Canada | 22 November 2017 | 7 November 2018 | *Passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal* |

[3] Merieux inactivated rabies vaccine 2.5 IU powder for injection vial with diluent syringe. ARTG number: 26675 Date of first approval: 21 October 1991

[4] Rabipur rabies virus vaccine (Inactivated) 2.5 IU powder for injection vial with diluent pre-filled syringe. ARTG number: 298194. Date of first approval: 25 July 2005.

[5] Imogam rabies pasteurized, human rabies immunoglobulin 150 IU/mL injection vial. ARTG number: 72931. Date of first approval: 23 July 2007.

[6] Section 19A approvals are granted for a specified period, which usually coincides with the period that the medicine on the ARTG is unavailable or in short supply. However, approval may lapse early if:
- a decision has been made about whether or not to register the medicine in Australia
- any of the specific criteria for approval no longer apply (for example, the registered medicine is no longer in short supply)
- a condition of approval has been breached.

Section 19A approvals are subject to a number of conditions specified by the TGA including the following (though additional conditions can be imposed where the circumstances warrant it):
- the approval applies only to the medicine specified in the approval
- the approval is only for importation into and supply within Australia
- the medicine is sourced from manufacturers with acceptable evidence of Good Manufacturing Practice (GMP)
- a letter to health professionals who will be prescribing the medicine is usually required
- the goods must be labelled with the name and address of the approval holder to ensure that adverse events can be reported.

| Region | Submission date | Status | Approved indications |
|---|---|---|---|
| Israel | 14 January 2008 | 9 July 2008 | *Passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately to individuals in cases of contact with a rabid or possibly rabid animal* |

### Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

**Table 2: Timeline for Submission PM-2020-02488-1-2**

| Description | Date |
|---|---|
| Submission dossier accepted and first round evaluation commenced | 30 June 2020 |
| First round evaluation completed | 30 November 2020 |
| Sponsor provides responses on questions raised in first round evaluation | 25 February 2021 |
| Second round evaluation completed | 31 March 2021 |
| Delegate's Overall benefit-risk assessment | 9 July 2021 |
| Registration decision (Outcome) | 11 August 2021 |
| Completion of administrative activities and registration on the ARTG | 16 August 2021 |
| Number of working days from submission dossier acceptance to registration decision | 181 |

*Statutory timeframe for standard applications is 255 working days.

## III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

This section is a TGA summary of wording used in the TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

## Quality

### Pharmaceutical particulars

KamRAB (rabies immunoglobulin) is supplied as solution for injection (sterile) in single-use Type I clear glass vials in two pack sizes; one vial containing 2 mL, and one vial containing 10 mL of solution. One mL of solution contains 150 IU rabies immunoglobulin (from human plasma), corresponding with 300 IU in 2 mL or 1,500 IU in 10 mL.

In appearance, KamRAB solution is a clear to slightly opalescent, colourless to pale yellow. The solution may contain some protein particles.

KamRAB is formulated with the following excipients: glycine, water for injection, and sodium hydroxide (for pH adjustment).

KamRAB should be stored (refrigerated) at 2°C to 8°C. KamRAB should not be frozen.

When refrigerated, KamRAB has a maximum shelf life of 30 months. The exact expiry date is stated on the product packaging.

KamRAB may be stored at room temperatures not exceeding 25 °C for up to one month. The vial should be used within one month after removal from refrigeration; do not return to refrigeration.

### Summary and conclusion

There are no objections on quality grounds to the approval of KamRAB rabies immunoglobulin.

KamRAB is a human rabies immunoglobulin isolated from healthy human plasma immunised with rabies vaccine to achieve high titres of anti-rabies antibodies. The human plasma is collected from donors in the USA. The sponsor demonstrated overall compliance with relevant international and Australia regulatory requirements for collection of plasma for fractionation. There are no objections to the registration of this product from sterility, endotoxin, container safety and viral safety related aspects.

Overall, sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality have been controlled to an acceptable level.

The PI, Consumer Medicines Information (CMI) and labels are acceptable with respect to quality matters.

### Quality-related proposed conditions of registration

The following are proposed quality-related conditions of registration.

Laboratory testing and compliance with Certified Product Details (CPD):

1. All batches of KamRAB rabies immunoglobulin supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
2. When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are

published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

## Nonclinical

One single dose toxicity study in rats with KamRAB was conducted with no evidence of significant toxicity at 120 IU/kg (6 x clinical dose). The efficacy and safety of KamRAB and similar products are well established. It is expected to be administered once in a lifetime.

The proposed limits for residual chemicals tri-(*n*-butyl) phosphate (TnBP) and octoxinol 9 (Triton X-100) in the drug product were comparable with the levels of these residues in TGA approved similar products.

There are no non clinical objections to the registration of KamRAB.

The draft Product Information is acceptable with respect to nonclinical matters.

## Clinical

KamRAB was developed in line with established monographs;[7,8] on a non-inferior basis to an established comparator product.

### Pharmacology

#### *Pharmacokinetics*

The pharmacokinetics (PK) of KamRAB were assessed in Study 23630, and Study 24061. These two Phase I studies include safety information and measured the levels of rabies virus neutralising antibody in clinical study plasma samples.

*Rabies virus neutralising antibody (RVNA) levels*: The RVNA level of 500 IU/L has been defined by the WHO (World Health Organization) as the protective level that prevents development of rabies infection. The WHO standard for RVNA level of 500 IU/L that is, > 0.5 IU/mL) on Day 14. Day 14 is most commonly cited in the literature as the day by which protective target antibody levels should have been reached for those receiving post-exposure prophylaxis even though the antibody measured on that day is a mixture of both passive and active antibodies.

Studies 24061 and 23630 were analysed at a site in Israel. Study 003 analysed at a site in the USA. A later accuracy qualification study was performed. Quantitatively similar plasma RVNA titres were observed at Day 7 and earlier time points in each of the 3 studies, which suggests assay reliability for determination of RVNA titres across studies.

#### *Study 23630*

Study 23630 was a Phase I, randomised, single dose, double blind, two-period crossover study in healthy adult volunteers conducted at a single centre in Israel in 2004.

Study treatments were:

1. Injection KamRAB 20 IU/kg IM (Kamada, Israel; Test); and
2. Injection BayRab 20 IU/kg (Talercris Biotherapeutics, USA, Reference);

[7] United States Pharmacopeia; (BBBBP05) Biologics and Biotechnology – Blood and Blood Products (expert committee): Rabies Immune Globulin; USP29-NF24, page 1887.
[8] Ph. Eur., Monograph 0338 Human Normal, Immunoglobulin for Intramuscular Administration

This was a crossover study with passive vaccine administered on Days 1, single dose, intramuscularly to the gluteus.

Study visits were at screening, and at Days 3, 7, 14, 18, 35 and 42 post-dose.

A total of 26 subjects were enrolled and randomised, of these, 23 completed both doses of the study. The mean age was 27.0 years, a mean weight of 66.9 kg and a mean height of 1.73 metres.

**Table 3: Study 23630 Mean (standard deviation) of main anti-rabies antibody titre pharmacokinetic findings for each dose administered**

| Treatment | $C_{max}$ (IU/mL) | $t_{max}$ (Day) | $AUC_T$ | $AUC_I$ | $t_{1/2}$ (Day) |
|---|---|---|---|---|---|
| KamRAB | 0.249 (SD 0.063) | 7.000 (3-14) | 5.222 (SD 1.297) | 6.734 (SD 1.274) | 17.87 (SD 6.370) |
| BayRab | 0.302 (SD 0.068) | 3.000 (3-14) | 6.266 (SD 1.236) | 7.972 (SD 1.362) | 17.79 (SD 6.741) |

$t_{max}$ is expressed as days not as hours as stated in protocol

Median (range) expressed for $t_{max}$ values

A statistical bioequivalence analysis was performed for selected PK parameters such as $C_{max}$, $t_{max}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, or $t_{1/2}$ for KamRAB-human rabies immunoglobulin relative to comparator human rabies immunoglobulin. The point estimates for the geometric least squares (LS) mean ratios were within the 80 to 125% bioequivalence range.

In Study 23630, RVNA PK parameters were quantitatively similar following treatment with KamRAB-human rabies immunoglobulin (test) or BayRab human rabies immunoglobulin (reference). Point estimates of ratios of test to reference geometric LS means for $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were within the 80 to 125% range:

- The point estimate for the ratio of anti-rabies antibody titre maximum concentration ($C_{max}$) values of the test formulation and reference formulation was 81.71 (90% confidence interval (CI), 75.34% to 88.62%).
- The point estimate for the ratio of anti-rabies antibody titre area under the concentration versus time curve from dosing (time zero) to the end of the dosing period ($AUC_T$) values of the test formulation and reference formulation was 82.35 (90% CI, 77.39% to 87.63%).
- The point estimate for the ratio of anti-rabies antibody titre area under the concentration versus time curve from dosing (time zero) extrapolated to infinity ($AUC_{0\text{-inf}}$) values of the test formulation and reference formulation was 84.44 (90% CI, 78.63% to 90.68%).
- There was no statistically significant difference (p = 0.4491) in anti-rabies antibody titre time to maximum concentration ($t_{max}$) between the test formulation and reference formulation.
- There is a marginally statistically significant sequence effect seen in $C_{max}$ (p = 0.0415) and $AUC_T$ (p = 0.0329). This is effectively a treatment by period interaction.

### *Study 24061*

Study 24061 was a Phase I, randomised, single dose KamRAB with three doses of rabies vaccine (Rabipur), double blind, one-period, parallel study in healthy adult volunteers conducted at a single centre in Israel in 2004.

Study treatments were KamRAB 20 IU/kg (0.133ml/kg) or sodium chloride (NaCl) 0.9% 0.133ml/kg (placebo) injected intramuscularly to the gluteus, and 3 x intramuscular injections of Rabipur rabies vaccine 1.0 mL (≥ 2.5 IU/mL), at Days 0, 7, 28.

Study visits were screening, and Days 3, 7, 14, 18, 35 and 42 post-dose.

In total, 16 subjects enrolled; 15 successfully completed the whole study. One subject was discontinued because of a positive urine analysis for cannabinoids on Day 7 of the study. The subjects had a mean age of 27.3 years, a mean weight of 69.7 kg and a mean height of 1.71 metres.

**Table 4: Study 24061 mean of main anti-rabies antibody titre pharmacokinetic findings for each dose administered**

| Treatment | Cmax (IU/ml) | Tmax* (Day) | $AUC_T$ (Day*IU/mL) |
|---|---|---|---|
| IM Inj. KamRAB 20 IU/kg | 9.36 (SD 10.72) | 42 (42-42) | 85.17 (SD 92.16) |
| IM Inj. NaCl 0.9% 0.133ml/kg (Placebo) | 23.98 (SD 21.11) | 42 (14-42) | 276.3 (SD 204.7) |

* Median and (range) from nominal sampling times

Protection was zero for the placebo group and positive for the KamRAB group starting at Day 3. The first positive antibody titre was observed on Day 7 for the placebo group.

The statistical analysis of the PK data shows that the $C_{max}$ for the test formulation appears to be substantially lower than the $C_{max}$ for the placebo formulation (42.93%). The mean $AUC_T$ for the test formulation is statistically significantly lower than mean $AUC_T$ for the placebo formulation as illustrated by the 95% CI values (10.14 to 100.42).

KamRAB showed detectable rabies antibodies at earlier times compared to placebo. There is some blunting of the immune response to the rabies vaccine as expected, but the levels achieved are still considered protective.

## Efficacy

### *Study 003*

Study 003 is a randomised, double-blind, Phase II/III study of KamRAB human rabies immunoglobulin compared with comparator human rabies immunoglobulin when co-administered with active rabies vaccine in healthy male and female adult volunteers. The study was conducted at one site in the USA between April 2013 and August 2014.

The primary endpoint was anti-rabies immunoglobulin subtype G (IgG) concentration on Day 14. The primary hypothesis is that the proportion of KamRAB plus vaccine recipients with anti-rabies concentration ≥ 0.5 IU/mL on Day 14 will not be less than the corresponding proportion of human rabies immunoglobulin comparator subjects by as much as 0.1. The RFFIT test[9] specified in the protocol determined RVNA titres rather than IgG concentrations and was prespecified for evaluation of the primary endpoint.

Inclusion criteria were healthy male or female subjects of age 18 to 75 years who have no previous exposure to rabies, the rabies vaccine or rabies immune globulin.

Subjects were randomised to receive a single dose of KamRAB HRIG (20 IU/kg) or HRIG Comparator (HyperRAB, 20 IU/kg) and the first dose of the rabies vaccine (RabAvert, 1 mL of ≥ 2.5 IU/mL) on Day 0. Subjects subsequently received 4 more doses of rabies vaccine

[9] **RFFIT** stands for **rapid fluorescent foci inhibition test**. It is a serum neutralisation (inhibition) test, which means it measures the ability of rabies specific antibodies to neutralise rabies virus and prevent the virus from infecting cells. These antibodies are called rabies virus neutralising antibodies (RVNA).

during the treatment period at Visit 3 (Day 3), Visit 4 (Day 7), Visit 5 (Day 14), and Visit 6 (Day 28).

In total, 118 subjects were included in the safety population; 115 of these subjects (97.5%) were included in the 'as-treated' population. Three subjects (2.5%) were excluded from the as-treated population, which was defined as all randomised subjects who received at least 3 vaccine doses (until Day 14 before the serum sample was taken) and one dose of HRIG. The PK population comprised 117 of the 118 subjects.

Subjects were predominately female (63.6%), white (93.2%), were not of Hispanic or Latino ethnicity (97.5%), and had a median age of 47.5 years. The median BMI was 26.32 $kg/m^2$.

*Results for the primary efficacy outcome*

Overall, 55 of 56 subjects (98.2%) in the KamRAB group and all in the HRIG comparator group had an anti-rabies IgG antibody titre ≥ 0.5 IU/mL on Day 14. The difference between the proportion of subjects with an anti-rabies IgG antibody titre ≥ 0.5 IU/mL on Day 14 in the KamRAB and HRIG comparator groups was -1.8% (90% CI: -8.2, 3.1). The lower limit of the 90% CI was greater than the pre-specified non-inferiority margin of -10%, demonstrating KamRAB was non-inferior to HRIG comparator for the primary endpoint.

Pharmacokinetic parameters ($C_{max}$, $t_{max}$, $AUC_T$, $AUC_I$, and $t_{1/2}$ of anti-rabies IgG antibody concentrations) were analysed as secondary endpoints. The plasma HRIG concentration-time profiles following intramuscular injection of KamRAB or HRIG comparator appeared to be similar. Only the plasma HRIG concentrations on Visit 3 (Day 3) were statistically different for the KamRAB treatment group relative to the HRIG comparator treatment group. No statistically significant differences in plasma HRIG PK parameters ($C_{max}$, $t_{max}$, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf,}$ or $t_{1/2}$) were detected between the KamRAB and HRIG comparator treatment groups.

## Safety

Safety was assessed in Study 003 and the two Phase I PK studies. In the three studies, 91 subjects were exposed to KamRAB-HRIG with 67 exposed to KamRAB-HRIG with rabies vaccine and 24 subjects were exposed to KamRAB-HRIG without rabies vaccine. A total of 84 subjects were exposed to comparator HRIG, with 59 subjects exposed to comparator HRIG with rabies vaccine, and 25 subjects exposed to comparator HRIG without rabies vaccine.

A similar proportion in the all KamRAB-HRIG population and all comparator-HRIG population groups had related adverse events, injection site adverse events, related injection site adverse events, adverse events occurring within 72 hours of administration, and related adverse events occurring within 72 hours of administration. The proportion of subjects in the all KamRAB-HRIG and all comparator-HRIG groups with mild adverse events was similar, while the percent of subjects with moderate adverse events was lower in the all KamRAB-HRIG group. In the placebo group, a lower proportion of subjects, compared with the other treatment groups, had adverse events, related adverse events, injection site adverse events, adverse events occurring within 72 hours of administration, related adverse events occurring within 72 hours of administration, and moderate adverse events. The proportion of subjects in the placebo group with related injection site adverse events and mild adverse events were similar to those in the all KamRAB-HRIG and all comparator HRIG groups. The proportion of subjects with adverse events were higher in Study 003 than the other studies.

In the all studies pooling, common adverse events by preferred term were injection site pain (33% in the all KamRAB-HRIG, 31% in the all comparator-HRIG, and 25% in the saline placebo with vaccine groups, respectively), headache (15%, 13%, and 38%,

respectively), myalgia (9%, 7%, and 0%, respectively), arthralgia (6%, 0%, and 13%, respectively) and upper respiratory tract infection (9%, 10%, and 0%, respectively).

In the related adverse events that occurred in at least one subject category in the KamRAB-HRIG with vaccine group, test article or comparator with vaccine pooling, common adverse events were injection site pain (37.3% in the all KamRAB-HRIG, 28.8% in the all comparator HRIG, and 25.0% in the saline placebo with vaccine groups, respectively), abdominal pain (3%,0%,0%, respectively), headache (3%, 5.1%,12.5%, respectively), musculoskeletal stiffness (3%, 0%,0%, respectively), nausea (3%, 0%,0%, respectively) and presyncope (3%, 1.7%, 0%, respectively).

No deaths were reported in Studies 23630, 24061 and 003. The one subject with a serious adverse event (intraductal proliferative breast lesion) and the one subject with a severe adverse event occurring in the clinical studies were both in the all KamRAB-HRIG group; neither of these events was assessed by the investigator as study treatment related. Nine subjects were withdrawn from the 3 studies. For five of these subjects, the reason for withdrawal was an adverse event. In 2 the adverse event was haematuria, considered possibly related.

### Post-marketing experience

This product was first marketed in Israel in 2008 and used safely in other markets in over 200,000 individuals, including Australian patients.

Periodic safety update reports for 2016-2017, 2017-2018, and 2018-2019 were provided in this submission and were reviewed. No new significant safety issues were identified during the reporting periods. The benefit-risk balance remains the same and comparable to that of currently marketed HRIG products.

### Clinical evaluator's recommendation

KamRAB was non-inferior to the HRIG Comparator for the primary efficacy endpoint of the proportion of subjects with an anti-rabies IgG antibody titre ≥ 0.5 IU/mL on Day 14. This result indicated that KamRAB, when given in conjunction with rabies vaccine, provides a level of protection of anti-rabies antibodies that is sufficient and comparable with that of the HRIG-comparator, when also given in conjunction with the rabies vaccine.

KamRAB was very well tolerated and had a comparable safety profile to the HRIG comparator, which was also very well tolerated. There were no clinically meaningful differences between KamRAB and the HRIG-Comparator with regard to treatment emergent adverse events, laboratory values, vital signs, and ECGs (electrocardiograms). There were no haemolysis or thrombotic events.

KamRAB was not infiltrated around an imaginary wound, as it would be in the treatment schedule in the clinical setting. Instead the entire dose was given intramuscularly either in one site, or across two sites if the volume was too large for a single intramuscularly injection.

The clinical evaluator concludes the small studies presented in this submission taken together with the huge body of efficacy and safety data amassed for KamRAB-HRIG for post-exposure prophylaxis in the countries were licensed provide overwhelming evidence of benefit.

The clinical studies were conducted in healthy volunteers and excluded populations such as children. The clinical evaluator notes that patients of diverse age groups, races, ethnicities, and health status have all received KamRAB-HRIG for post-exposure prophylaxis against rabies infection, with no safety signals identified amongst certain groups.

## Risk management plan

With this submission the sponsor submitted the Canadian risk management plan (RMP) Version 1.0 with a data lock point (DLP) October 2017; and an Australian-specific annex (ASA) version 0.2 dated January 2021.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 5: Summary of safety concerns.[10]

**Table 5: Summary of safety concerns**

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|---|---|---|---|---|---|
| | | Routine | Additional | Routine | Additional |
| **Important identified risks** | None | – | – | – | – |
| **Important potential risks** | Thromosis[1] | ü | – | – | – |
| | Haemolysis[1] | ü | – | – | – |
| | Hypersensitivity reactions | ü | – | ü | – |
| | Interaction with concomitant vaccine administration | ü | – | ü | – |
| | Transmission of infectious agents | ü | – | ü | – |
| **Missing information** | Exposure during pregnancy | ü | – | ü | – |
| | Exposure during breast-feeding | ü | – | ü | – |
| | Paediatric exposure | ü | ü | ü | – |
| | Geriatric exposure | ü | – | ü | – |
| | Use in patients with important concomitant medical conditions | ü | – | ü | – |

1) Thrombosis and Haemolysis are to be removed from the Canadian RMP and Product Monograph and in the Global RMP and ASA to be submitted in November 2021; and that the potential risks for thrombosis and haemolysis are to be removed in the post approval condition to update the RMP to the Global version within 3 months of approval.

2) Missing Information (Paediatric data) will be deleted in the post-approval condition to update the RMP to the Global version within 3 months of approval.

[10] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
*Routine pharmacovigilance* practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The summary of safety concerns is acceptable from an RMP perspective. Routine pharmacovigilance activities will be conducted to monitor all potential risks and missing information. The safety concerns associated with this product are expected to be adequately managed through routine risk minimisation measures.

KamRAB is a new biological entity, and as such meets the inclusion criteria for the Black Triangle Scheme.[1]

### Recommendations regarding conditions of registration

The RMP evaluator recommended the following wording as conditions of registration.

> The KamRAB Canadian Risk Management Plan (RMP) (version 1.0 (date not provided; data lock point (DLP) October 2017), with Australia-Specific Annex (ASA; version 0.2, January 2021), included with submission PM-2020-02488-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
>
> The sponsor should provide a global or core RMP with an Australia-Specific Annex, or an Australia-specific RMP to replace the Canadian RMP, within 3 months of approval of this product. If an EU RMP become available within the next 3 months, the EU RMP and an ASA should be provided.
>
> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.
>
> If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
>
> KamRAB (rabies immunoglobulin) is to be included in the Black Triangle Scheme. The PI and CMI for KamRAB must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

## Risk-benefit analysis

### Delegate's considerations

The conclusions of the clinical evaluation on the benefit risk balance of KamRAB are accepted by the Delegate. The three small clinical studies presented in the submission are taken together with efficacy and safety data available for KamRAB-HRIG for post-exposure prophylaxis in the countries were licensed, or used on compassionate grounds (including Australia), and provide adequate support for registration.

The post marketing safety data provides reassurance about deficiencies in the clinical study program concerning specific populations such as children and lack of information on 'wound' infiltration with rabies immunoglobulin.

### Proposed action

The Delegate proposes to approve KamRAB (human rabies immunoglobulin) for the indications proposed in Australia.

### Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Does the Canadian Monograph and US Product Information, currently include potential risks for haemolysis and thrombosis?***

The current US Product Information does not include potential risks for haemolysis and thrombosis.

These warnings were previously included in the US product Information and were removed in a recent submission to the US FDA (Food and Drug Administration) following their approval (PI approved in May 2021).

The current Canadian Monograph includes these potential risks. The sponsor intends to submit a Canadian Monograph update to remove these potential risks in [redacted]..

Please note, further justification for the omission of these potential risks was included in the cover of registration application

2. ***The PSURs submitted with the submission and RMP evaluation report mention an ongoing paediatric clinical study. The sponsor is requested to provide an update on the status of this study and any expected date for completion and availability of a clinical study report.***

The paediatric clinical study ended successfully in 2020. The clinical study report of this study, as well as evaluation report from the FDA are enclosed herein [not included in this AusPAR].

### Advisory Committee considerations[11]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

[11] The ACM provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre market and post-market functions for medicines. Further information can be found here: https://www.tga.gov.au/committee/advisory-committee-medicines-acm.

## Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of KamRAB (rabies immunoglobulin) 150 IU/mL, solution for injection, vial indicated for following indication:

> *KamRAB is rabies immunoglobulin indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KamRAB should be administered concurrently with a full course of rabies vaccine.*
>
> *• Do not administer additional (repeat) doses of KamRAB once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine.*
>
> *• Do not administer KamRAB to patients with a history of a complete pre-exposure or postexposure vaccination regimen and confirmed adequate rabies antibody titre.*

### Specific conditions of registration applying to these goods

- KamRAB (rabies immunoglobulin) is to be included in the Black Triangle Scheme.

  The PI and CMI for KamRAB must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

- The KamRAB Canadian Risk Management Plan (RMP) (version 1.0 (date not provided; DLP October 2017), with Australia-Specific Annex (version 0.2, January 2021), included with submission PM-2020-02488-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  The sponsor should provide a global or core RMP with an Australia-Specific Annex, or an Australia-specific RMP to replace the Canadian RMP, within 3 months of approval of his product. If an EU RMP become available within the next 3 months, the EU RMP and an ASA should be provided.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to be at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- Laboratory testing & compliance with Certified Product Details (CPD)

a. All batches of KamRAB rabies immunoglobulin supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

b. When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

- For all injectable products the Product Information must be included with the product as a package insert.

# Attachment 1. Product Information

The PI for KamRAB approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
**https://www.tga.gov.au**