AUSTRALIAN PRODUCT INFORMATION – Hemlibra® (emicizumab)

WARNING: THROMBOTIC MICROANGIOPATHY AND THROMBOEMBOLISM

Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of > 100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving Hemlibra prophylaxis. Monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered. Discontinue aPCC and suspend dosing of Hemlibra if symptoms occur.

1. NAME OF THE MEDICINE

Emicizumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Hemlibra 30 mg/1 mL solution for injection

Each vial of 1 mL contains 30 mg of emicizumab at a concentration of 30 mg/mL.

Hemlibra 60 mg/0.4 mL solution for injection

Each vial of 0.4 mL contains 60 mg of emicizumab at a concentration of 150 mg/mL.

Hemlibra 105 mg/0.7 mL solution for injection

Each vial of 0.7 mL contains 105 mg of emicizumab at a concentration of 150 mg/mL.

Hemlibra 150 mg/1 mL solution for injection

Each vial of 1 mL contains 150 mg of emicizumab at a concentration of 150 mg/mL.

Emicizumab is a humanised monoclonal modified IgG4 antibody with a bispecific antibody structure bridging factor IXa and factor X produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for subcutaneous injection in single-use colourless glass vials.

Colourless to slightly yellow solution, adjusted to pH 6.0.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hemlibra is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adult and paediatric patients with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

4.2 DOSE AND METHOD OF ADMINISTRATION

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders.

Treatment with bypassing agents should be discontinued the day before starting Hemlibra therapy (see section 4.4). Factor VIII (FVIII) prophylaxis may be continued for the first 7 days of treatment with Hemlibra.

Dose

The recommended loading dose is 3 mg/kg administered as a subcutaneous injection once weekly for the first 4 weeks, followed by a maintenance dose from Week 5, administered subcutaneously either:

- 1.5 mg/kg once weekly, or
- 3 mg/kg every two weeks, or
- 6 mg/kg every four weeks.

The maintenance dose should be selected based on physician and patient/caregiver dosing regimen preference to support adherence.

Duration of treatment

Hemlibra is intended for long-term prophylactic treatment.

Dosage adjustments during treatment

No dosage adjustments of Hemlibra are recommended.

Delayed or missed doses

If a patient misses a scheduled subcutaneous injection of Hemlibra, the patient should be instructed to take the missed dose as soon as possible, before the day of the next scheduled dose. The patient should then administer the next dose on the usual scheduled dosing day. The patient should not take two doses on the same day to make up for a missed dose.

Special populations

Paediatric populations

No dose adjustments are recommended in paediatric patients. Currently available data are described in sections 5.1 and 5.2.

Elderly

No dose adjustments are recommended in patients ≥ 65 years of age (see sections 4.4 and 5.2).

Renal impairment

No dose adjustments are recommended in patients with renal impairment (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustments are recommended in patients with hepatic impairment (see sections 4.4 and 5.2).

Method of Administration

Hemlibra is a sterile, preservative-free, and ready to use solution that does not need to be diluted. Hemlibra is for subcutaneous use only.

The product is for single use in one patient only. Discard any residue. Once transferred from the vial to the syringe, the medicinal product should be used immediately since it does not contain any antimicrobial preservative.

Hemlibra should be administered using appropriate aseptic technique (see 'Instructions for handling'). The injection should be restricted to the recommended injection sites: the abdomen, the upper outer arms and the thighs (see section 5.2). No data are available on injection at other sites of the body. Administration of Hemlibra subcutaneous injection in the upper outer arm should be performed by a caregiver or healthcare professional.

Alternating the site of injection may help prevent or reduce injection site reactions (see section 4.8). Hemlibra subcutaneous injection should not be administered into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars.

During treatment with Hemlibra, other medicinal products for subcutaneous administration should, preferably, be injected at different anatomical sites.

<u>Administration by the patient and/or caregiver</u>

Hemlibra is intended for use under the guidance of a healthcare professional. After proper training in subcutaneous injection technique, a patient may self-inject Hemlibra, or the patient's caregiver may administer Hemlibra, if their physician determines that it is appropriate.

The physician and the caregiver should determine the appropriateness of a child self-injecting Hemlibra. However, self-administration is not recommended for children below 7 years of age.

<u>Instructions for handling</u>

Hemlibra is a colourless to slightly yellow solution. Hemlibra solution should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

Hemlibra solution should be discarded if particulate matter is visible or the product is discoloured.

A syringe, a transfer needle and an injection needle are needed to withdraw Hemlibra solution from the vial and inject it subcutaneously.

Please see below the selection criteria for the recommended device options.

A 1 mL syringe should be used for an injection up to 1 mL of Hemlibra solution. Administer doses of Hemlibra greater than 1 mL and up to 2 mL with a 2 mL to 3 mL syringe.

Refer to the Hemlibra 'Instructions for Use' for handling instructions when combining vials in a syringe. Do not combine different Hemlibra vial concentrations (30 mg/mL and 150 mg/mL) in a single injection to administer the prescribed dose.

Recommended criteria for syringes and needles are defined to ensure correct and safe administration of Hemlibra. These criteria are based on handling considerations (e.g., dosing accuracy, subcutaneous injection), Hemlibra characteristics (e.g., viscosity), and compatibility between Hemlibra and device materials.

1 mL syringe

Criteria: Transparent polypropylene or polycarbonate syringe with Luer-Lock tip (in case not locally available, a syringe with Luer Slip tip can be used), graduation 0.01 mL, sterile, for injection only, single-use, latex-free and non-pyrogenic.

2 to 3 mL syringe

Criteria: Transparent polypropylene or polycarbonate syringe with Luer-Lock tip (in case not locally available, a syringe with Luer Slip tip can be used), graduation 0.1 mL, sterile, for injection only, single-use, latex-free and non-pyrogenic.

Transfer needle with filter

Criteria: Stainless steel with Luer-Lock connection (in case not locally available, a syringe with Luer Slip connection can be used), sterile, gauge 18 G, length 25 to 40 mm, blunt or single-bevel (or semi-blunt tip), single-use, latex-free, containing a 5 micron filter and non-pyrogenic.

Injection needle

Criteria: Stainless steel with Luer-Lock connection (in case not locally available, a syringe with Luer Slip connection can be used), sterile, gauge 26 G (acceptable range: 25 G to 27 G), length preferably 9 mm or maximally 13 mm, single-use, latex-free and non-pyrogenic, preferably including needle safety feature.

The following procedures should be strictly adhered to regarding the use and disposal of syringes:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

4.3 CONTRAINDICATIONS

Hemlibra is contraindicated in patients with known hypersensitivity to emicizumab or to any of the excipients, or to patients with known hypersensitivity to hamster-derived proteins.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded in the patient's medical record. Advise patients/caregivers to record the batch number of the product whenever Hemlibra is administered outside of a healthcare setting.

Thrombotic microangiopathy associated with Hemlibra and aPCC

Cases of thrombotic microangiopathy (TMA) were reported from a clinical trial in patients receiving Hemlibra prophylaxis when on average a cumulative amount of > 100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more (see section 4.8). Treatment for the TMA events included supportive care with or without plasmapheresis and haemodialysis. Evidence of improvement was seen within one week following discontinuation of aPCC. This rapid clinical improvement is distinct from the usual clinical course observed in atypical haemolytic uremic syndrome and classic TMAs, such as thrombotic thrombocytopenic purpura (see section 4.8).

In case a bypassing agent is indicated in a patient receiving Hemlibra prophylaxis, see below for 'Guidance on the use of bypassing agents in patients receiving Hemlibra prophylaxis'.

Patients receiving Hemlibra prophylaxis should be monitored for the development of TMA when administering aPCC. The physician should immediately discontinue aPCC and interrupt Hemlibra therapy if clinical symptoms and/or laboratory findings consistent with TMA occur, and manage as clinically indicated. Physicians and patients/caregivers should weigh the benefits and risks of resuming Hemlibra prophylaxis following complete resolution of TMA on a case-by-case basis.

Thromboembolism associated with Hemlibra and aPCC

Thrombotic events were reported from a clinical trial in patients receiving Hemlibra prophylaxis when on average a cumulative amount of > 100 U/kg/24 hours of aPCC was administered for 24 hours or more. No cases required anticoagulation therapy, which is distinct from the usual treatment of thrombotic events. Evidence of improvement or resolution was seen after discontinuation of aPCC (see section 4.8).

In case a bypassing agent is indicated in a patient receiving Hemlibra prophylaxis, see below for 'Guidance on the use of bypassing agents in patients receiving Hemlibra prophylaxis'.

Patients receiving Hemlibra prophylaxis should be monitored for the development of thromboembolism (TE) when administering aPCC. The physician should immediately discontinue aPCC and interrupt Hemlibra therapy if clinical symptoms, imaging, and/or laboratory findings consistent with thrombotic events occur, and manage as clinically indicated. Physicians and patients/caregivers should weigh the benefits and risks of resuming Hemlibra prophylaxis following complete resolution of thrombotic events on a case-by-case basis.

Guidance on the use of bypassing agents in patients receiving Hemlibra prophylaxis

Treatment with bypassing agents should be discontinued the day before starting Hemlibra therapy.

Physicians should discuss with all patients and/or caregivers the exact dose and schedule of bypassing agents to use, if required while receiving Hemlibra prophylaxis.

Hemlibra increases the patient's coagulation potential. The bypassing agent dose required may therefore be lower than that used without Hemlibra prophylaxis. The dose and duration of treatment with bypassing agents will depend on the location and extent of bleeding and on the patient's clinical condition.

Avoid use of aPCC unless no other treatment options/alternatives are available. If aPCC is indicated in a patient receiving Hemlibra prophylaxis, the initial dose should not exceed 50 U/kg. If bleeding is not controlled with the initial dose of aPCC up to 50 U/kg, additional aPCC doses should be administered under medical guidance or supervision, and the total aPCC dose should not exceed 100 U/kg in the first 24 hours of treatment. Treating physicians must carefully weigh the risk of TMA and TE against the risk of bleeding when considering aPCC treatment beyond a maximum of 100 U/kg in the first 24 hours.

In pooled phase III clinical trials, there were 82 instances of aPCC treatment in patients receiving Hemlibra prophylaxis, of which eight instances (9.8%) consisted of on average a cumulative amount of > 100 U/kg/24 hours of aPCC for 24 hours or more. Two of the eight instances were associated with thrombotic events and three of the eight instances were associated with TMA (Table 1). No TMA or thrombotic events were associated with the remaining instances of aPCC treatment. Of all instances of aPCC treatment, 68% consisted of a single infusion ≤ 100 U/kg.

Table 1 Characterisation of aPCC treatment* in the pooled phase III clinical trials

Duration of aPCC treatment	Average cumulative amount of aPCC over 24 hours (U/kg/24 hours)		
	< 50	50 – 100	> 100
< 24 hours	9	47	13
24 – 48 hours	0	3	1[b]
> 48 hours	1	1	7[a,a,a,b]

* An instance of aPCC treatment is defined as all doses of aPCC received by a patient, for any reason, until there was a 36-hour treatment-free break

[a] Thrombotic microangiopathy

[b] Thrombotic event

In clinical trials, no cases of TMA or thrombotic events were observed with use of activated recombinant human factor VII (rFVIIa) alone in patients receiving Hemlibra prophylaxis.

Bypassing agent dosing guidance should be followed for at least 6 months following discontinuation of Hemlibra prophylaxis (see section 5.2).

Immunogenicity

Anti-emicizumab antibodies have been reported in a small number of patients treated with Hemlibra in clinical trials. Most patients found to have anti-emicizumab antibodies did not experience a change in emicizumab plasma concentrations or an increase in bleeding events; however, in uncommon (≥ 1/1,000 to < 1/100) cases, the presence of neutralizing anti-emicizumab antibodies with decreasing emicizumab concentration may be associated with loss of efficacy (see sections 4.8 and 5.1).

In case of clinical signs of loss of efficacy (e.g. increase in breakthrough bleeding events), prompt evaluation by a physician should be sought to assess the etiology and a possible change in treatment should be considered.

Use in hepatic impairment

The safety and efficacy of Hemlibra have not been specifically tested in patients with hepatic impairment. Patients with mild and moderate hepatic impairment were included in clinical trials. No data are available on the use of Hemlibra in patients with severe hepatic impairment. Hemlibra is a monoclonal antibody and is cleared via catabolism rather than by hepatic metabolism and a change in dose is not expected to be required for patients with hepatic impairment.

Use in renal impairment

The safety and efficacy of Hemlibra have not been specifically tested in patients with renal impairment. There are limited data available on the use of Hemlibra in patients with mild to moderate renal impairment. No data are available on the use of Hemlibra in patients with severe renal impairment (see section 5.2). Hemlibra is a monoclonal antibody and is cleared via catabolism rather than by renal excretion and a change in dose is not expected to be required for patients with renal impairment.

Use in the elderly

The safety and efficacy of Hemlibra have not been specifically tested in a geriatric population. Clinical studies of Hemlibra included 13 patients aged 65 and over. Relative bioavailability decreased with older age, but no clinically important differences were observed in the pharmacokinetics of emicizumab between patients < 65 years and patients ≥ 65 years (see section 5.2).

Paediatric use

The safety and efficacy of Hemlibra have been established in paediatric patients. Use of Hemlibra in paediatric patients with haemophilia A (with or without FVIII inhibitors) is supported by two randomised studies and two single-arm studies (see section 5.1).

All clinical trials included paediatric patients in the following age group: 47 adolescents (12 years to < 18 years). Only HAVEN 2 included paediatric patients in the following age groups: 55 children (2 years to < 12 years) and 5 infants and toddlers (14 months to < 2 years). Safety and efficacy results were consistent with those observed for adults (see sections 4.2 and 5.1).

The steady-state plasma trough concentrations of emicizumab were comparable in adult and paediatric patients older than 6 months at equivalent weight-based doses. Lower

concentrations of emicizumab were predicted in paediatric patients less than 6 months old (see section 5.2).

Effects on laboratory tests

Emicizumab restores the tenase cofactor activity of missing activated factor VIII (FVIIIa). Coagulation laboratory tests based on intrinsic clotting, including the activated clotting time (ACT), activated partial thromboplastin time (e.g. aPTT) and all assays based on aPTT, such as one-stage FVIII activity, measure the total clotting time including time needed for activation of FVIII to FVIIIa by thrombin. Such intrinsic pathway-based tests will yield overly shortened clotting times with Hemlibra, which does not require activation by thrombin. The overly shortened intrinsic clotting time will then disturb all single-factor assays based on aPTT, such as the one-stage FVIII activity assay (see Table 2 below). However, single-factor assays utilising chromogenic or immuno-based methods are unaffected by Hemlibra and may be used to monitor coagulation parameters during treatment, with specific considerations for FVIII chromogenic activity assays as described below.

Chromogenic FVIII activity tests may be manufactured with either human or bovine coagulation proteins. Assays containing human coagulation factors are responsive to Hemlibra but may overestimate the clinical haemostatic potential of Hemlibra. In contrast, assays containing bovine coagulation factors are insensitive to Hemlibra (no activity measured) and can be used to monitor endogenous or infused FVIII activity, or to measure anti-FVIII inhibitors.

Hemlibra remains active in the presence of inhibitors against FVIII and so will produce a false-negative result in clotting-based Bethesda assays for functional inhibition of FVIII. Instead, a chromogenic Bethesda assay utilising a bovine-based FVIII chromogenic test that is insensitive to Hemlibra may be used. Laboratory tests affected and unaffected by Hemlibra are shown in Table 2 below.

In summary, intrinsic pathway clotting-based laboratory test results in patients treated with Hemlibra should not be used to monitor Hemlibra activity, determine dosing for factor replacement or anti-coagulation, or measure FVIII inhibitor titres.

Due to the long half-life of Hemlibra, effects on coagulation assays may persist for up to 6 months after the last dose (see section 5.2).

Table 2 Coagulation test results affected and unaffected by Hemlibra

Results affected by Hemlibra	Results unaffected by Hemlibra
Activated partial thromboplastin time (aPTT) Bethesda assays (clotting-based) for FVIII inhibitor titres One-stage, aPTT–based, single-factor assays (e.g. FVIII activity) aPTT-based activated protein C resistance (APC-R) Activated clotting time (ACT)	Bethesda assays (bovine chromogenic) for FVIII inhibitor titres Thrombin time (TT) One-stage, prothrombin time (PT)-based, single-factor assays Chromogenic-based single-factor assays other than FVIII Immuno-based assays (e.g., ELISA, turbidimetric methods) Genetic tests of coagulation factors (e.g. Factor V Leiden, Prothrombin 20210)

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No adequate or well-controlled drug-drug interaction studies have been conducted with Hemlibra.

Clinical experience suggests that a drug interaction exists with Hemlibra and aPCC (see sections 4.4 and 4.8).

There is a possibility for hypercoagulability with rFVIIa or FVIII with Hemlibra based on preclinical experiments. Emicizumab increases coagulation potential, therefore the coagulation factor dose required to achieve haemostasis may be lower than when used without Hemlibra prophylaxis.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Conventional fertility studies have not been performed with emicizumab. In general toxicity studies, no changes in the reproductive organs of male or female cynomolgus monkeys to suggest adverse effects on fertility were observed with emicizumab at subcutaneous doses of up to 30 mg/kg/week (yielding 11 times the plasma AUC in patients at the maximum recommended human dose) and at intravenous doses of up to 100 mg/kg/week (20 times the maximum clinical systemic exposure).

Use in pregnancy - Category B2

There are no clinical studies of Hemlibra use in pregnant women. Animal reproduction studies have not been conducted with emicizumab. It is not known whether Hemlibra can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. As an IgG antibody, placental transfer of emicizumab is expected, increasing as pregnancy progresses. Hemlibra should be used during pregnancy only if the potential benefit for the mother outweighs the potential risk to the fetus.

Labour and delivery

The safe use of Hemlibra during labour and delivery has not been established.

Use in lactation

It is not known whether emicizumab is excreted in human milk. No studies have been conducted to assess the impact of emicizumab on milk production or its presence in breast milk. Human IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Hemlibra and any potential adverse effects on the breastfed infant from Hemlibra or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no evidence that treatment with Hemlibra results in an increase in adverse reactions that might lead to the impairment of the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

The following adverse drug reactions (ADRs) are based on pooled data from four phase III clinical trials (three adult and adolescent studies [HAVEN 1, HAVEN 3 and HAVEN 4] and one paediatric study [HAVEN 2]). A total of 373 male patients with haemophilia A received at least one dose of Hemlibra as routine prophylaxis in these studies. Two hundred and sixty-six patients (71%) were adults (≥ 18 years), 47 (13%) were adolescents (≥ 12 to < 18 years), 55 (15%) were children (≥ 2 to < 12 years) and 5 (1%) were infants and toddlers (≥ 14 months to < 2 years). The median duration of exposure across the studies was 34.1 weeks (range: 0.1 to 94.3 weeks).

Three patients (0.8%) in the pooled phase III clinical trials receiving Hemlibra prophylaxis withdrew from treatment due to ADRs, which were thrombotic microangiopathy, skin necrosis contemporaneous with superficial thrombophlebitis, and headache.

Adverse drug reactions from the pooled phase III clinical trials in patients who received Hemlibra are listed by MedDRA system organ class (Table 3). The corresponding frequency categories for each ADR are based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1,000 to < 1/100).

Table 3 Summary of Adverse Drug Reactions from Pooled Clinical Trials with Hemlibra

System Organ Class ADR (preferred term MedDRA)	**Number of patients (n=373)**	**Percentage of patients**	**Frequency**
General disorders and administration site conditions			
Injection site reactions	77	21%	Very common
Pyrexia	22	6%	Common
Nervous system disorders			
Headache	52	14%	Very common
Gastrointestinal disorders			
Diarrhoea	19	5%	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	58	16%	Very common
Myalgia	13	4%	Common
Blood and lymphatic system disorders			
Thrombotic microangiopathy	3	< 1%	Uncommon
Infections and Infestations			
Cavernous sinus thrombosis	1	< 1%	Uncommon
Skin and subcutaneous tissue disorders			
Skin necrosis	1	< 1%	Uncommon

System Organ Class	Number of patients (n=373)	Percentage of patients	Frequency
ADR (preferred term MedDRA)			
Vascular disorders			
Thrombophlebitis superficial	1	< 1%	Uncommon

Description of selected adverse drug reactions

The most serious ADRs reported from the pooled phase III clinical trials with Hemlibra were thrombotic microangiopathy (TMA) and thrombotic events, including cavernous sinus thrombosis and superficial vein thrombosis contemporaneous with skin necrosis (see below and section 4.4).

Thrombotic microangiopathy

In the pooled phase III clinical trials, thrombotic microangiopathy events were reported in 3/373 patients (< 1%) and in 3/31 patients (9.7%) who received at least one dose of aPCC. Each patient was reported to have received on average a cumulative amount of > 100 U/kg/24 hours of aPCC for 24 hours or more while receiving Hemlibra prophylaxis prior to the development of TMA events (presenting with thrombocytopenia, microangiopathic haemolytic anaemia, and acute kidney injury, without severe deficiencies in ADAMTS13 activity) (see section 4.4). One patient resumed Hemlibra following resolution of TMA without recurrence.

Thrombotic events

In pooled phase III clinical trials, serious thrombotic events were reported in 2/373 patients (< 1%) and in 2/31 patients (6.5%) who received at least one dose of aPCC. Each patient was reported to have received on average a cumulative amount of > 100 U/kg/24 hours of aPCC for 24 hours or more while receiving Hemlibra prophylaxis, prior to the development of the thrombotic events (see section 4.4). One patient resumed Hemlibra following resolution of thrombotic event without recurrence.

Injection site reactions

Injection site reactions (ISRs) were reported very commonly (20%) from clinical trials. All ISRs observed in the Hemlibra clinical trials were reported as being non-serious and mild to moderate in intensity and 95% resolved without treatment. The commonly reported ISR symptoms were injection site erythema (11%), injection site pain (4%) and injection site pruritis (3%).

Immunogenicity

In the pooled phase III clinical trials with Hemlibra, development of neutralizing anti-emicizumab antibodies associated with decreasing emicizumab concentration was uncommon (0.6%) (see section 5.1). One patient, who developed neutralizing anti-emicizumab antibodies with decreasing emicizumab concentration, experienced loss of efficacy (manifest as breakthrough bleeding) after 5 weeks of treatment and later discontinued Hemlibra treatment (see sections 4.4 and 5.1). Overall, the safety profile of Hemlibra was similar between those

patients with anti-emicizumab antibodies (including neutralizing antibodies) and those without.

Post Marketing

The following adverse drug reactions have been identified from post marketing surveillance with Hemlibra (see Table 4). Adverse drug reactions from post marketing surveillance are listed by MedDRA system organ class.

Table 4 Adverse Drug Reactions from Post marketing Surveillance

System Organ Class	Frequency
ADR (preferred term MedDRA)	
Skin and subcutaneous tissue disorders	
Angioedema[a]	Uncommon
Urticaria[b]	Common
Rash[b]	Common
[a] Frequency estimated at the upper limit of the 95% confidence interval utilising the clinical trial safety population. [b] Frequency derived from clinical trial data.	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is limited experience with overdose of Hemlibra. Accidental overdose may result in hypercoagulability. Patients who receive an accidental overdose should immediately contact their physician and be monitored closely.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Emicizumab bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective haemostasis.

Emicizumab has no structural relationship or sequence homology to FVIII and, as such, does not induce or enhance the development of direct inhibitors to FVIII.

Pharmacodynamic effect

Haemophilia A is an X-linked hereditary disorder of blood coagulation due to a deficiency of functional FVIII and results in bleeding into joints, muscles or internal organs, either spontaneously or as result of accidental or surgical trauma. Prophylactic therapy with Hemlibra shortens the activated partial thromboplastin time (aPTT) and increases the reported FVIII activity (using a chromogenic assay with human coagulation factors). These two pharmacodynamic markers do not reflect the true haemostatic effect of emicizumab *in vivo* (aPTT is overly shortened and reported FVIII activity may be overestimated) but provide a relative indication of the pro-coagulant effect of emicizumab.

In an *in vitro* study of cytokine release that used the whole blood of healthy adults, the levels of cytokines induced by emicizumab were comparable to those induced by other antibodies known for their low cytokine-releasing potential.

Clinical trials

The efficacy of Hemlibra for routine prophylaxis in patients with haemophilia A with or without inhibitors was evaluated in four clinical trials (three adult and adolescent studies [HAVEN 3, HAVEN 1 and HAVEN 4] and a paediatric study [HAVEN 2]).

Clinical trials in adult and adolescent patients

HAVEN 3

The HAVEN 3 study was a randomised, multicentre, open-label, phase III clinical trial in 152 adult and adolescent males (aged ≥ 12 years and ≥ 40 kg) with haemophilia A without FVIII inhibitors who previously received either episodic ("on demand") or prophylactic treatment with FVIII. Patients received subcutaneous Hemlibra, 3 mg/kg once weekly for the first four weeks followed by either 1.5 mg/kg once weekly (Arms A and D), 3 mg/kg every two weeks (Arm B), or no prophylaxis (Arm C). Patients in Arm C could switch to Hemlibra (3 mg/kg once weekly for the first 4 weeks followed by 3 mg/kg every 2 weeks) after completing at least 24 weeks without prophylaxis. For Arms A and B dose up-titration to 3 mg/kg weekly was allowed after 24 weeks for patients who experienced two or more qualified bleeds (i.e., spontaneous and clinically significant bleeds occurring at steady state). Arm D patients could up-titrate after the second qualifying bleed. During the study, five patients underwent up-titration of their maintenance dose to 3 mg/kg once weekly.

Eighty-nine patients previously treated with episodic ("on demand") FVIII were randomised in a 2:2:1 ratio to receive Hemlibra either once weekly (Arm A; N=36), every two weeks (Arm B; N=35) or no prophylaxis (Arm C; N=18), with stratification by prior 24-week bleed rate (< 9 or ≥ 9). Sixty-three patients previously treated with prophylactic FVIII were enrolled into Arm D to receive Hemlibra (1.5 mg/kg once weekly).

The primary objective of the study was to evaluate efficacy, based on number of bleeds requiring treatment with coagulation factors, of prophylactic Hemlibra administered weekly (Arm A) or every two weeks (Arm B) compared to no prophylaxis (Arm C) in patients previously treated with episodic FVIII (Table 5). Other objectives of the study included evaluation of the randomised comparison of Arms A or B and Arm C for the efficacy of Hemlibra prophylaxis in reducing the number of all bleeds, spontaneous bleeds, joint bleeds,

and target joint bleeds (Table 6). Patient treatment preference was also assessed using a preference survey.

The efficacy of Hemlibra prophylaxis was also compared with previous prophylactic FVIII treatment (Arm D) in patients who had participated in a non-interventional study (NIS) prior to enrolment (Table 7). Only patients from the NIS were included in this comparison, because bleed and treatment data were collected with the same level of granularity as used in HAVEN 3.

HAVEN 1

The HAVEN 1 study was a randomised, multicentre, open-label clinical trial in 109 adolescent and adult males (aged ≥ 12 years old and ≥ 40 kg) with haemophilia A with FVIII inhibitors who had previously received either episodic ("on demand") or prophylactic treatment with bypassing agents. In the study, patients received weekly Hemlibra prophylaxis (Arms A, C, and D) — 3 mg/kg once weekly for 4 weeks followed by 1.5 mg/kg once weekly thereafter — or no prophylaxis (Arm B). Patients randomised to Arm B could switch to Hemlibra prophylaxis after completing at least 24 weeks without prophylaxis. Dose up-titration to 3 mg/kg once weekly was allowed after 24 weeks on Hemlibra prophylaxis for patients who experienced two or more qualified bleeds (i.e., spontaneous and clinically significant bleeds occurring at steady state). During the study, two patients underwent up-titration of their maintenance dose to 3 mg/kg once weekly.

Fifty-three patients previously treated with episodic ("on demand") bypassing agents were randomised in a 2:1 ratio to receive Hemlibra prophylaxis (Arm A) or no prophylaxis (Arm B), with stratification by prior 24-week bleed rate (< 9 or ≥ 9).

Forty-nine patients previously treated with prophylactic bypassing agents were enrolled in Arm C to receive Hemlibra prophylaxis. Seven patients previously treated with episodic ("on demand") bypassing agents who had participated in the NIS prior to enrolment but were unable to enrol in HAVEN 1 prior to the closure of Arms A and B were enrolled in Arm D to receive Hemlibra prophylaxis.

The primary objective of the study was to evaluate among patients previously treated with episodic ("on demand") bypassing agents the treatment effect of weekly Hemlibra prophylaxis compared with no prophylaxis (Arm A vs. Arm B) on the number of bleeds requiring treatment with coagulation factors over time (minimum of 24 weeks or date of discontinuation) (Table 5). Other secondary objectives of the randomised comparison of Arms A and B were the efficacy of weekly Hemlibra prophylaxis in reducing the number of all bleeds, spontaneous bleeds, joint bleeds and target joint bleeds (see Table 8), as well as assessing patient reported health-related quality of life (HRQoL) and health status (Tables 12 and 13).

The efficacy of weekly Hemlibra prophylaxis compared with previous prophylactic bypassing agents was also evaluated in patients who had participated in the NIS prior to enrolment (Arm C) (Table 9). Only patients from the NIS were included in this comparison, because bleed and treatment data were collected with the same level of granularity as that used in HAVEN 1.

HAVEN 4

Hemlibra was investigated in a single arm, multicentre, phase III clinical trial in 41 adult and adolescent males (aged ≥ 12 years and ≥ 40 kg) with haemophilia A with or without FVIII

inhibitors who had previously received either episodic ("on demand") or prophylactic treatment with FVIII or bypassing agents. Patients received Hemlibra prophylaxis – 3 mg/kg once weekly for four weeks followed by 6 mg/kg every four weeks thereafter.

The primary objective of the study was to evaluate the efficacy, based on treated bleeds, of Hemlibra prophylaxis administered every four weeks in maintaining adequate bleed control (Table 5). Other objectives were to evaluate the clinical efficacy of Hemlibra prophylaxis on all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds (Table 11). Patient treatment preference was also assessed using a preference survey.

Efficacy results in adult and adolescent studies

The efficacy results of Hemlibra prophylaxis with respect to rate of treated bleeds (primary endpoint) in HAVEN 3, HAVEN 1 and HAVEN 4 are shown in Table 5.

Table 5 HAVEN 3, HAVEN 1 and HAVEN 4: Annualised Bleed Rate (Treated Bleeds – Primary Endpoint) with Hemlibra Prophylaxis in Patients ≥ 12 Years of Age with or without FVIII Inhibitors

Endpoint	**HAVEN 3**			**HAVEN 1**		**HAVEN 4**
	Arm C: No Prophylaxis (N=18)	**Arm A: Hemlibra 1.5 mg/kg weekly[a] (N=36)**	**Arm B: Hemlibra 3.0 mg/kg every 2 weeks[a] (N=35)**	**Arm B: No Prophylaxis (N=18)**	**Arm A: Hemlibra 1.5 mg/kg weekly[a] (N=35)**	**Hemlibra 6 mg/kg every 4 weeks[a] (N=41)**
Median Efficacy Period (weeks)	24.0	29.6	31.3	24.0	29.3	25.6
Treated Bleeds						
ABR (95% CI)[b]	38.2 (22.9; 63.8)	1.5 (0.9; 2.5)	1.3 (0.8; 2.3)	23.3 (12.3; 43.9)	2.9 (1.7; 5)	2.4 (1.4; 4.3)
% reduction vs episodic treatment (95% CI), p-value	NA	96% (92.5%; 98.0%), < 0.0001	97% (93.4%; 98.3%), < 0.0001	NA	87% (72.3%; 94.3%), < 0.0001	NA
% patients with 0 bleeds (95% CI)	0.0 (0.0; 18.5)	55.6 (38.1; 72.1)	60.0 (42.1; 76.1)	5.6 (0.1; 27.3)	62.9 (44.9; 78.5)	56.1 (39.7; 71.5)
% patients with 0-3 bleeds (95% CI)	5.6 (0.1; 27.3)	91.7 (77.5; 98.2)	94.3 (80.8; 99.3)	11.1 (1.4; 34.7)	85.7 (69.7; 95.2)	90.2 (76.9; 97.3)
Median ABR (IQR)	40.4 (25.3; 56.7)	0 (0; 2.5)	0 (0; 1.9)	18.8 (13.0; 35.1)	0 (0; 3.7)	0 (0; 2.1)

ABR = Annualised Bleed Rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile; NA = not applicable

[a] Patients exposed to Hemlibra started with a loading dose of 3 mg/kg/week for 4 weeks.

[b] Based on negative binomial regression model.

HAVEN 3

The efficacy results of Hemlibra prophylaxis compared with no prophylaxis with respect to rate of treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds are shown in Table 6.

Table 6 HAVEN 3: Annualised Bleed Rate with Hemlibra Prophylaxis Arm versus No Prophylaxis Arm in Patients ≥ 12 Years of Age without FVIII Inhibitors

Endpoint	**Arm C: No Prophylaxis (N=18)**	**Arm A: Hemlibra 1.5 mg/kg weekly[a] (N=36)**	**Arm B: Hemlibra 3 mg/kg every 2 weeks[a] (N=35)**
Treated Bleeds			
ABR (95% CI)[b]	38.2 (22.9; 63.8)	1.5 (0.9; 2.5)	1.3 (0.8; 2.3)
% reduction (95% CI), p-value	NA	96% (92.5%; 98.0%), <0.0001	97% (93.4%; 98.3%), <0.0001
% patients with 0 bleeds (95% CI)	0.0 (0.0; 18.5)	55.6 (38.1; 72.1)	60.0 (42.1; 76.1)
Median ABR (IQR)	40.4 (25.3; 56.7)	0 (0; 2.5)	0 (0; 1.9)
All Bleeds			
ABR (95% CI)[b]	47.6 (28.5; 79.6)	2.5 (1.6; 3.9)	2.6 (1.6; 4.3)
% reduction (95% CI), p-value	NA	95% (90.1%; 97%), <0.0001	94% (89.7%; 97%), <0.0001
% patients with 0 bleeds (95% CI)	0 (0.0; 18.5)	50 (32.9; 67.1)	40 (23.9; 57.9)
Median ABR (IQR)	46.9 (26.1; 73.9)	0.6 (0; 3.9)	1.6 (0; 4.0)
Treated Spontaneous Bleeds			
ABR (95% CI)[b]	15.6 (7.6; 31.9)	1.0 (0.5; 1.9)	0.3 (0.1; 0.8)
% reduction (95% CI), p-value	NA	94% (84.9%; 97.5%), <0.0001	98% (94.4%; 99.4%), <0.0001
% patients with 0 bleeds (95% CI)	22.2 (6.4; 47.6)	66.7 (49.0; 81.4)	88.6 (73.3; 96.8)
Median ABR (IQR)	10.8 (2.1; 26.0)	0 (0; 1.3)	0 (0; 0)
Treated Joint Bleeds			
ABR (95% CI)[b]	26.5 (14.67; 47.79)	1.1 (0.59; 1.89)	0.9 (0.44; 1.67)
% reduction (95% CI), p-value	NA	96% (91.5%; 98.1%), <0.0001	97% (93%; 98.5%), <0.0001
% patients with 0 bleeds (95% CI)	0 (0; 18.5)	58.3 (40.8; 74.5)	74.3 (56.7; 87.5)
Median ABR (IQR)	21.3 (14.5; 41.3)	0 (0; 1.9)	0 (0; 1.3)
Treated Target Joint Bleeds			
ABR (95% CI)[b]	13.0 (5.2; 32.3)	0.6 (0.3; 1.4)	0.7 (0.3; 1.6)
% reduction (95% CI), p-value	NA	95% (85.7%; 98.4%), <0.0001	95% (85.3%; 98.2%), <0.0001
% patients with 0 bleeds (95% CI)	27.8 (9.7; 53.5)	69.4 (51.9; 83.7)	77.1 (59.9; 89.6)

Endpoint	Arm C: No Prophylaxis (N=18)	Arm A: Hemlibra 1.5 mg/kg weekly[a] (N=36)	Arm B: Hemlibra 3 mg/kg every 2 weeks[a] (N=35)
Median ABR (IQR)	12.8 (0; 39.1)	0 (0; 1.4)	0 (0; 0)

ABR = Annualised Bleed Rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile; NA = not applicable

[a] Patients exposed to Hemlibra started with a loading dose of 3 mg/kg/week for 4 weeks.

[b] Based on negative binomial regression model.

In the HAVEN 3 clinical trial intra-patient analysis, Hemlibra prophylaxis resulted in a statistically significant (p<0.0001) reduction (68%) in bleed rate for treated bleeds compared with previous FVIII prophylaxis collected in the NIS prior to enrolment (Table 7).

Table 7 HAVEN 3: Intra-Patient Comparison of Annualised Bleed Rate (Treated Bleeds) with Hemlibra Prophylaxis versus Previous FVIII Prophylaxis

Endpoint	Arm D_{NIS}: Previous FVIII Prophylaxis (N=48)	Arm D: Hemlibra 1.5 mg/kg weekly[a] (N=48)
Median Efficacy Period (weeks)	30.1	33.7
Treated Bleeds		
ABR (95% CI)[b]	4.8 (3.2; 7.1)	1.5 (1; 2.3)
% reduction (95% CI), p-value	68% (48.6%; 80.5%), <0.0001	
% patients with zero bleeds (95% CI)	39.6 (25.8; 54.7)	54.2 (39.2; 68.6)
Median ABR (IQR)	1.8 (0; 7.6)	0 (0; 2.1)

ABR = Annualised Bleed Rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

[a] Patients exposed to Hemlibra started with a loading dose of 3 mg/kg/week for 4 weeks.

[b] Based on negative binomial regression model.

HAVEN 1

The efficacy results of Hemlibra prophylaxis compared with no prophylaxis with respect to rate of treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds are shown in Table 8.

Table 8 HAVEN 1: Annualised Bleed Rate with Hemlibra Prophylaxis Arm versus No Prophylaxis Arm in Patients ≥ 12 Years of Age with FVIII Inhibitors

Endpoint[a]	Arm B: No Prophylaxis[b] (N=18)	Arm A: Hemlibra 1.5 mg/kg weekly[c] (N=35)
Treated Bleeds[d]		
ABR (95% CI)	23.3 (12.33; 43.89)	2.9 (1.69; 5.02)
% reduction (95% CI), p-value	87% (72.3%, 94.3%), <0.0001	
% patients with 0 bleeds (95% CI)	5.6 (0.1; 27.3)	62.9 (44.9; 78.5)
Median ABR (IQR)	18.8 (12.97; 35.08)	0 (0; 3.73)

Endpoint[a]	Arm B: No Prophylaxis[b] (N=18)	Arm A: Hemlibra 1.5 mg/kg weekly[c] (N=35)
All Bleeds[e]		
ABR (95% CI)	28.3 (16.79; 47.76)	5.5 (3.58; 8.60)
% reduction (95% CI), p-value	80% (62.5%; 89.8%), <0.0001	
% patients with 0 bleeds (95% CI)	5.6 (0.1; 27.3)	37.1 (21.5; 55.1)
Median ABR (IQR)	30.2 (18.3; 39.4)	2 (0; 9.9)
Treated Spontaneous Bleeds		
ABR (95% CI)	16.8 (9.94; 28.30)	1.3 (0.73; 2.19)
% reduction (95% CI), p-value	92% (84.6%; 96.3%), <0.0001	
% patients with 0 bleeds (95% CI)	11.1 (1.4; 34.7)	68.6 (50.7; 83.1)
Median ABR (IQR)	15.2 (6.6; 30.4)	0 (0; 3.3)
Treated Joint Bleeds		
ABR (95% CI)	6.7 (1.99; 22.42)	0.8 (0.26; 2.20)
% reduction (95% CI), p-value	89% (48%; 97.5%), 0.0050	
% patients with 0 bleeds (95% CI)	50.0 (26.0; 74.0)	85.7 (69.7; 95.2)
Median ABR (IQR)	1 (0; 14.4)	0 (0; 0)
Treated Target Joint Bleeds		
ABR (95% CI)	3.0 (0.96; 9.13)	0.1 (0.03; 0.58)
% reduction (95% CI), p-value	95% (77.3%; 99.1%), 0.0002	
% patients with 0 bleeds (95% CI)	50.0 (26.0; 74.0)	94.3 (80.8; 99.3)
Median ABR (IQR)	1 (0; 6.5)	0 (0; 0)

ABR = Annualised Bleed Rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

[a] Bleed definitions adapted based on ISTH criteria. CI comes from Negative Binomial Regression model and p-value from Stratified Wald test, comparing bleed rate between specified arms.

[b] Arm B: includes no prophylaxis period only.

[c] Patients exposed to Hemlibra started with a loading dose of 3 mg/kg/week for 4 weeks. Includes data before up-titration only, for patients whose dose was up-titrated.

[d] Treated bleeds = bleeds treated with bypassing agents.

[e] All bleeds = bleeds treated and not treated with bypassing agents.

Additional analyses for HAVEN 1 to assess long term control of bleeds with Hemlibra prophylaxis were conducted using 12-week treatment intervals up to week 72. When Annualised Bleed Rate (ABR) for treated bleeds was assessed over 12-week intervals the mean ABRs decreased over time and the improvement was sustained up to week 72, while the median remained consistently at zero (Table 9). These data demonstrate the long term efficacy of Hemlibra prophylaxis. The mean and median calculated ABRs for treated bleeds are shown in Table 9.

Table 9 HAVEN 1: Annualised Bleed Rate with Hemlibra Prophylaxis per 12-Week Intervals in Patients ≥ 12 Years of Age with FVIII Inhibitors

	Time interval from start of Hemlibra treatment (weeks)					
	1 – 12 (N=109)	**13 – 24 (N=108)**	**25 – 36 (N=93)**	**37 – 48 (N=93)**	**49 – 60 (N=57)**	**61 – 72 (N=42)**
Treated Bleeds						
Mean ABR (95% CI)	3.9 (1.1; 10.2)	2.2 (0; 7.6)	0.9 (0; 5.5)	0.4 (0; 4.4)	0.5 (0; 4.7)	0.6 (0; 4.9)
Median ABR (IQR)	0 (0; 4.4)	0 (0; 0)	0 (0; 0)	0 (0; 0)	0 (0; 0)	0 (0; 0)

ABR = Annualised Bleed Rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

In the HAVEN 1 clinical trial intra-patient analysis, Hemlibra prophylaxis resulted in a statistically significant (p=0.0003) reduction (79%) in bleed rate for treated bleeds compared with previous bypassing agent prophylaxis collected in the NIS prior to enrolment (Table 10).

Table 10 HAVEN 1: Intra-Patient Comparison of Annualised Bleed Rate (Treated Bleeds) with Hemlibra Prophylaxis versus Previous Bypassing Agent Prophylaxis*

Endpoint[a]	**Arm C_{NIS}: previous bypassing agent prophylaxis N=24**	**Arm C: Hemlibra 1.5 mg/kg weekly[b] N=24**
Median Efficacy Period (weeks)	32.1	30.1
Treated Bleeds[c]		
ABR (95% CI)	15.7 (11.08; 22.29)	3.3 (1.33; 8.08)
% reduction (95% CI), p-value	79% (51.4%; 91.1%), 0.0003	
% patients with 0 bleeds (95% CI)	12.5 (2.7; 32.4)	70.8 (48.9; 87.4)
Median ABR (IQR)	12.0 (5.73; 24.22)	0.0 (0.00; 2.23)

ABR = Annualised Bleed Rate; CI = confidence interval; IQR=interquartile range, 25th percentile to 75th percentile

* Intra-patient comparator data from non-interventional study (NIS). Only patients who participated in the NIS and in HAVEN 1 are included.

[a] Bleed definitions adapted based on ISTH criteria. CI comes from Negative Binomial Regression model and p-value from Stratified Wald test, comparing bleed rate between specified arms.

[b] Patients exposed to Hemlibra started with a loading dose of 3 mg/kg/week for 4 weeks. Includes data before up-titration only, for patients whose dose was up-titrated.

[c] Treated bleeds: bleeds treated with bypassing agents.

HAVEN 4

Efficacy results for the HAVEN 4 clinical study are summarised below. Forty-one patients ≥ 12 years old were evaluated for efficacy with a median observation time of 25.6 weeks (range 24.1 – 29.4 weeks). The efficacy results of Hemlibra prophylaxis every four weeks with respect to rate of treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds are shown in Table 11.

Table 11 HAVEN 4: Annualised Bleed Rate with Hemlibra Prophylaxis in Patients ≥ 12 Years of Age with or without FVIII Inhibitors

	Hemlibra 6 mg/kg Q4W[a]		
Endpoints[b]	**ABR (95% CI)[c]**	**Median ABR (IQR)[d]**	**% Zero Bleeds (95% CI)**
	N=41	N=41	N=41
Treated Bleeds	2.4 (1.4; 4.3)	0 (0; 2.1)	56.1 (39.7; 71.5)
All Bleeds	4.5 (3.1; 6.6)	2.1 (0; 5.9)	29.3 (16.1; 45.5)
Treated Spontaneous Bleeds	0.6 (0.3; 1.5)	0 (0; 0)	82.9 (67.9; 92.8)
Treated Joint Bleeds	1.7 (0.8; 3.7)	0 (0; 1.9)	70.7 (54.5; 83.9)
Treated Target Joint Bleeds	1.0 (0.3; 3.3)	0 (0; 0)	85.4 (70.8; 94.4)

ABR = Annualised Bleed Rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile; Q4W = once every four week prophylaxis

[a] Patients exposed to Hemlibra started with a loading dose of 3 mg/kg/week for 4 weeks.

[b] Bleed definitions adapted based on ISTH criteria. Treated bleeds = bleeds treated with FVIII or rFVIIa. All bleeds = bleeds treated and not treated with FVIII or rFVIIa.

[c] Calculated with negative binomial regression (NBR) model.

[d] Calculated ABR.

Patient-Reported Outcomes in adult and adolescent studies

The HAVEN adult and adolescent clinical studies evaluated patient-reported outcomes with several measures. The Haemophilia-Specific Quality of Life (Haem-A-QoL) questionnaire for adults (≥ 18 years) and its adolescent version (Haemo-QoL-SF, for 8 to < 18 years) assessed haemophilia-related quality of life in patients. For the Haem-A-QoL and Haemo-QoL-SF, the Physical Health Score (i.e., painful swellings, presence of joint pain, pain with movement, difficulty walking far and needing more time to get ready) and Total Score (summary of all scores) were protocol-defined endpoints of interest. To measure change in health status, the Index Utility Score (IUS) and the Visual Analog Scale (VAS) from the EuroQoL Five-Dimension-Five Levels Questionnaire (EQ-5D-5L) were examined.

In HAVEN 3 and HAVEN 4, an assessment of patient preference for treatment, the Emicizumab Preference Survey (EmiPref), was used.

HAVEN 1

In HAVEN 1, HRQoL for patients aged ≥ 18 years was evaluated at week 25 based on the Haem-A-QoL questionnaire for adults (Table 13). The Haem-A-QoL is a valid and reliable measure of HRQoL. The Haem-A-QoL is a valid and reliable measure of HRQoL.

Table 12 HAVEN 1: Change in Haem-A-QoL Physical Health Score with Hemlibra Prophylaxis versus No Prophylaxis in Patients (≥ 18 Years of Age) with FVIII Inhibitors at 25 Weeks*

Haem-A-QoL Scores at week 25[a]	Arm B: No Prophylaxis[b] (N=16)	Arm A: Hemlibra 1.5 mg/kg weekly[c] (N=31)
Total Score (range 0 – 100)		
n	14	25
Adjusted mean	43.21	29.2
Difference in adjusted means (95% CI)	14.01 (5.56; 22.45)	
p-value	0.0019	
Physical Health		
n	14	25
Adjusted mean	54.17	32.61
Difference in adjusted means (95% CI)	21.55 (7.89; 35.22)	
p-value	0.0029	

* Only patients ≥ 18 years completed the Haem-A-QoL questionnaire.

[a] Lower scores are reflective of better HRQoL. Clinically meaningful difference: Total Score: 7 points; Physical Health: 10 points.

[b] Arm B: includes no prophylaxis period only.

[c] Patients exposed to Hemlibra started with a loading dose of 3 mg/kg/week for 4 weeks. Includes data before up-titration only, for patients whose dose was up-titrated.

In HAVEN 1, patients' health status was assessed according to the EQ-5D-5L (Table 13). EQ-5D-5L is a valid and reliable measure of health status.

Table 13 HAVEN 1: EQ-5D-5L Scores at Week 25

EQ-5D-5L Scores at week 25[a]	Arm B: No prophylaxis[b] (N=18)	Arm A: Hemlibra 1.5 mg/kg weekly[c] (N=35)
Visual Analogue Scale (VAS)		
n	16	29
Adjusted mean	74.36	84.08
Difference in adjusted means (95% CI)	-9.72 (-17.62; -1.82)	
p-value	0.0171	
Index Utility Score		
n	16	29
Adjusted mean	0.65	0.81
Difference in adjusted means (95% CI)	-0.16 (-0.25; -0.07)	
p-value	0.0014	

[a] Higher scores indicate better quality of life. Clinically meaningful difference: VAS: 7 points; Index Utility Score: 0.07 points

[b] Arm B: includes no prophylaxis period only.

[c] Patients exposed to Hemlibra started with a loading dose of 3 mg/kg/week for 4 weeks. Includes data before up-titration only, for patients whose dose was up-titrated.

HAVEN 3 and HAVEN 4 patient preference

In HAVEN 3 and HAVEN 4, patients who received Hemlibra (once weekly, every two weeks or every four weeks) reported whether they preferred subcutaneous Hemlibra, their prior intravenous (IV) treatment or had no preference at week 17. Of the patients in HAVEN 3 who responded to the preference questionnaire, 89 of 95 patients (93.7%) reported preferring Hemlibra to their prior IV treatment, and specifically 45 of 46 patients (97.8%) preferred Hemlibra to their prior prophylactic FVIII treatment. In HAVEN 4, all 41 patients (100%) responded to the preference questionnaire and reported preferring Hemlibra to their prior IV treatment.

In HAVEN 3 and HAVEN 4, the two reasons most frequently ranked by patients as the most important for their preference for Hemlibra were that the route of administration was easier and the frequency of treatments was lower.

Clinical trial in paediatric patients (HAVEN 2)

In HAVEN 2, Hemlibra weekly prophylaxis was evaluated in a single-arm, multicentre, open-label clinical trial in paediatric patients (age < 12 years old, or 12 to 17 years old weighing < 40 kg) with haemophilia A with FVIII inhibitors. Patients received Hemlibra prophylaxis at 3 mg/kg once weekly for the first four weeks followed by 1.5 mg/kg once weekly thereafter.

The study evaluated the pharmacokinetics, safety and efficacy, including the efficacy of weekly Hemlibra prophylaxis compared with previous episodic and prophylactic bypassing agent treatment in patients who had participated in the NIS prior to enrolment (intra-patient comparison).

HAVEN 2 efficacy results (interim analysis)

At the time of the interim analysis, efficacy was evaluated in 59 paediatric patients who were < 12 years old and had been receiving weekly Hemlibra prophylaxis for at least 12 weeks, including 38 patients aged 6 to < 12 years, 17 patients aged 2 to < 6 years and 4 patients aged 14 months to < 2 years.

Annualised bleed rate and percent of patients with zero bleeds were calculated for 59 patients (Table 14). The median observation time for these patients was 29.6 weeks (range: 18.2 - 63 weeks).

Table 14 HAVEN 2: Annualised Bleed Rate with Hemlibra Prophylaxis in Paediatric Patients < 12 Years of Age (Interim Analysis)

	Hemlibra 1.5 mg/kg weekly[a]		
Endpoint[b]	**ABR[c] (95% CI)**	**Median ABR[d] (IQR)**	**% Zero Bleeds (95% CI)**
N[e]	**59**	**59**	**59**
Treated Bleeds	0.3 (0.1; 0.5)	0.0 (0; 0)	86.4 (75; 94)
All Bleeds	3.8 (2.2; 6.5)	0 (0; 3.4)	55.9 (42.4; 68.8)
Treated Spontaneous Bleeds	0 (0; 0.2)	0.0 (0; 0)	98.3 (90.9; 100)
Treated Joint Bleeds	0.2 (0.1; 0.4)	0.0 (0; 0)	89.8 (79.2; 96.2)
Treated Target Joint Bleeds	0.1 (0; 0.7)	0.0 (0; 0)	96.6 (88.3; 99.6)

ABR = Annualised Bleed Rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

[a] Patients exposed to Hemlibra started with a loading dose of 3 mg/kg/week for 4 weeks.

[b] Bleed definitions adapted based on ISTH criteria. Treated bleeds = bleeds treated with bypassing agents. All bleeds = bleeds treated and not treated with bypassing agents.

[c] Calculated with negative binomial regression (NBR) model.

[d] Calculated ABR

[e] Efficacy data from treated patients aged < 12 years who had been on HAVEN 2 for at least 12 weeks (n=59), as the study aimed to primarily investigate treatment effect based on age.

In the intra-patient interim analysis, weekly Hemlibra prophylaxis resulted in a clinically meaningful (98%) reduction in bleed rate for treated bleeds in 18 paediatric patients who had at least 12 weeks of Hemlibra prophylaxis compared to their bleed rate collected in the NIS prior to enrolment (Table 15).

Table 15 HAVEN 2: Intra-Patient Comparison of Annualised Bleed Rate (Treated Bleeds) with Hemlibra Prophylaxis versus Previous Bypassing Agent Prophylaxis*

Endpoint[a]	**Previous treatment with bypassing agents (N=18)**	**Hemlibra 1.5 mg/kg weekly (N=18)**
Treated Bleeds[b]		
ABR (95% CI)	19.8 (15.3; 25.7)	0.4 (0.15; 0.88)
% reduction (95% CI)	98% (95.7%; 99.2%)	
% patients with 0 bleeds (95% CI)	5.6 (0.1; 27.3)	77.8 (52.4; 93.6)
Median ABR (IQR)	16.2 (11.49; 25.78)	0.0 (0.00; 0.00)

ABR = Annualised Bleed Rate; CI = confidence interval; RR = rate ratio

* Intra-patient comparator data from non-interventional study (NIS). Only patients < 12 years old who participated in the NIS and in HAVEN 2 for at least 12 weeks are included. Note: 15 of the 18 patients received prior bypassing agent prophylaxis; 3 patients received prior episodic bypassing agents.

[a] Bleed definitions adapted based on ISTH criteria. CI comes from negative binomial regression (NBR) model.

[b] Treated bleeds: bleeds treated with bypassing agents.

HAVEN 2 Patient-Reported Outcomes

In HAVEN 2, HRQoL for patients aged ≥ 8 to < 12 years was evaluated at week 25 based on the Haemo-QoL-SF questionnaire for children. The Haemo-QoL-SF is a valid and reliable measure of HRQoL (see Table 16).

Table 16 HAVEN 2: Change from Baseline to Week 25 in Haemo-QoL-SF in the Physical Health Score of Patients (≥ 8 to < 12 Years of Age) following Treatment with Hemlibra Prophylaxis

	Haemo-QoL-SF[a]
Physical Health Score (Score range 0 to 100)	
Mean Baseline score (95%CI) (N=18)	29.51 (16.38; 42.65)
Mean change from baseline (95% CI) (N=15)	-21.67 (-37.08; -6.25)

[a] Lower scores (negative change scores) are reflective of better functioning.

In HAVEN 2, HRQoL for patients ages < 12 years was also evaluated at week 25 based on the Adapted InhibQoL with Aspects of Caregiver Burden questionnaire completed by caregivers. The Adapted InhibQoL is a valid and reliable measure of HRQoL (see Table 17).

Table 17 HAVEN 2: Change from Baseline to Week 25 in the Caregiver-reported Physical Health Score of Patients (< 12 Years of Age) following Treatment with Hemlibra Prophylaxis

	Adapted InhibQoL with Aspects of Caregiver Burden[a]
Physical Health Score (range 0 to 100)	
Mean Baseline score (95% CI) (N=54)	37.2 (31.5; 42.8)
Mean change from baseline (95% CI) (N=43)	-32.4 (-38.6; -26.2)
Dealing with Inhibitor Score (range 0 to 100)	
Mean baseline score (95% CI) (N=54)	57.7 (53.3; 62.1)
Mean change from baseline (95% CI) (N=43)	-24.6 (-30.1; -19.1)
Perceived Treatment Score (range 0 to 100)	
Mean baseline score (95% CI) (N=54)	44.5 (40.4; 48.6)
Mean change from baseline (95% CI) (N=43)	-16.9 (-23.1; -10.6)

[a] Lower scores (negative change scores) are reflective of better functioning.

Surgeries and procedures in the HAVEN clinical trials

There is limited experience with bypassing agent or FVIII use during surgeries and procedures in patients receiving Hemlibra prophylaxis. Bypassing agent or FVIII use during surgeries and procedures was determined by the investigator.

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with Hemlibra. A total of 668 patients were tested for anti-emicizumab antibodies in the pooled phase III clinical trials, of which 5.1% of patients (34/668) tested positive for anti-emicizumab antibodies. Anti-emicizumab antibodies were neutralizing *in vitro* in 2.7% of patients (18/668). Of these, the neutralizing anti-emicizumab antibodies did not appear to have a clinically meaningful impact on the pharmacokinetics or efficacy of Hemlibra in 14 patients, while decreased emicizumab plasma concentrations were observed in 4 patients (0.6%). One patient (0.2%) from the HAVEN 2 clinical trial with neutralizing anti-emicizumab antibodies and decreased emicizumab plasma concentrations experienced loss of efficacy after 5 weeks of treatment and discontinued Hemlibra. Overall, the safety profile of Hemlibra was similar between those patients with anti-emicizumab antibodies (including neutralizing antibodies) and those without (see sections 4.4 and 4.8). There was no clinically apparent impact of the presence of anti-emicizumab antibodies on safety.

The data reflects the number of patients whose test results were considered positive for antibodies to emicizumab using an enzyme-linked immunosorbent assay (ELISA) and/or for neutralizing anti-emicizumab antibodies using a FVIII chromogenic assay. Immunogenicity assay results may be influenced by several factors including assay sensitivity and specificity, sample handling, timing of sample collection, concomitant medicinal products and underlying disease. For these reasons, comparison of incidence of antibodies to emicizumab with the incidence of antibodies to other products may be misleading.

5.2 PHARMACOKINETIC PROPERTIES

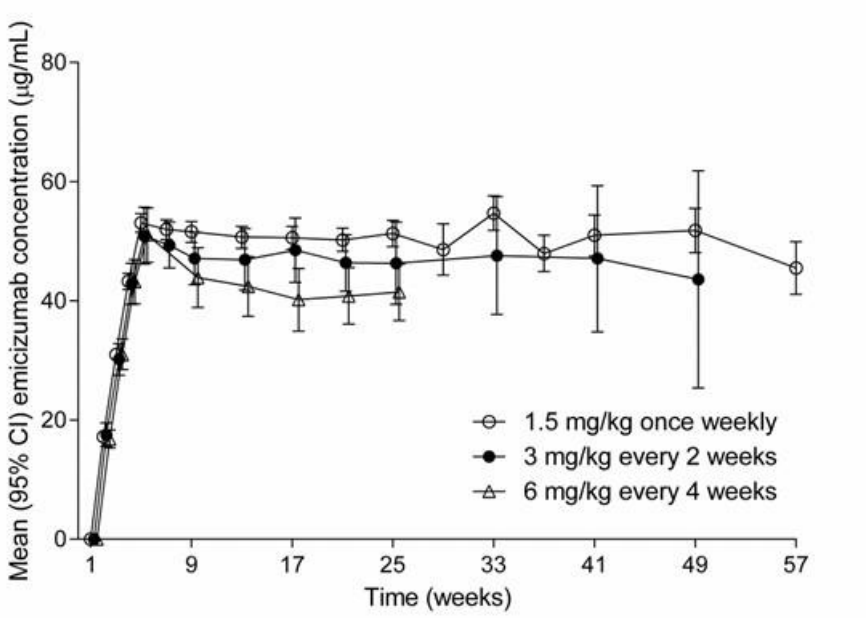
The pharmacokinetics of emicizumab were determined via a non-compartmental analysis in healthy subjects and using a population pharmacokinetic analysis on a database composed of 389 patients with haemophilia A.

Absorption

Following subcutaneous administration in haemophilia A patients, the absorption half-life was 1.6 days.

Following multiple subcutaneous administrations of 3 mg/kg once weekly for the first 4 weeks in haemophilia A patients, mean trough plasma concentrations of emicizumab achieved 52.6 ± 13.6 microgram/mL at week 5. Sustained mean predicted trough plasma concentrations of emicizumab at steady-state were 51.1, 46.7 and 38.3 microgram/mL with the recommended maintenance doses of 1.5 mg/kg once weekly, 3 mg/kg every two weeks or 6 mg/kg every four weeks, respectively (Figure 1, Table 18).

Figure 1 Mean (± 95%CI) Emicizumab Trough Concentrations for Maintenance Doses (microgram/mL)



Based on population PK simulations, the predicted mean (± SD) C_{trough}, C_{max} and ratios of C_{max}/C_{trough} at steady state for the recommended maintenance doses of 1.5 mg/kg once weekly, 3 mg/kg every two weeks or 6 mg/kg every four weeks are shown in Table 18.

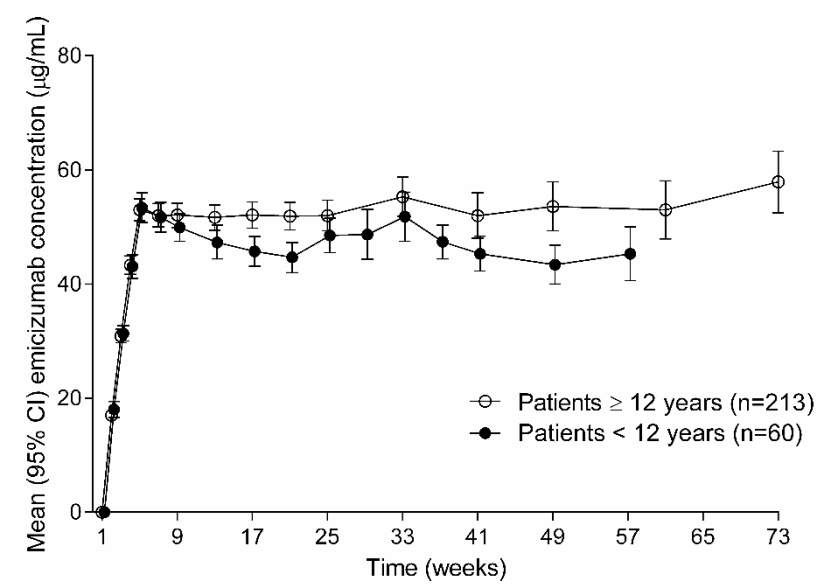
Table 18 Mean (± SD) Steady State Emicizumab Concentrations

	Maintenance Dose		
Parameters	1.5 mg/kg QW	3 mg/kg Q2W	6 mg/kg Q4W
$C_{max, ss}$ (µg/mL)	54.9 ± 15.9	58.1 ± 16.5	67.0 ± 17.7
$C_{avg, ss}$ (µg/mL)	53.5 ± 15.7	53.5 ± 15.7	53.7 ± 15.6
$C_{trough, ss}$ (µg/mL)	51.1 ± 15.3	46.7 ± 16.9	38.5 ± 14.2
C_{max}/C_{trough} ratio	1.08 ± 0.03	1.26 ± 0.12	1.85 ± 0.47

$C_{max, ss}$ = maximum plasma concentration at steady state; $C_{avg, ss}$ = average concentration at steady state; $C_{trough, ss}$ = trough concentration at steady state; QW = once weekly; Q2W = every two weeks; Q4W = every four weeks. Pharmacokinetic parameters derived from the population pharmacokinetic model.

Similar pharmacokinetic (PK) profiles were observed following once weekly dosing (3 mg/kg/week for 4 weeks followed by 1.5 mg/kg/week) in adults/adolescents (≥ 12 years) and children (< 12 years) (see Figure 2).

Figure 2 Mean Plasma Emicizumab Concentration vs Time Profiles for Patients ≥ 12 Years (HAVEN 1, HAVEN 3) Compared with Patients < 12 Years (HAVEN 2)



In healthy subjects, the absolute bioavailability following subcutaneous administration of 1 mg/kg was between 80.4% (upper arm) and 93.1% (thigh) depending on the injection site. Similar pharmacokinetic profiles were observed following subcutaneous administration in the abdomen, upper arm, and thigh. Emicizumab can be administered interchangeably at these anatomical sites (see section 4.2).

Distribution

The apparent volume of distribution (V/F), estimated from the population PK analysis, in haemophilia A patients following multiple subcutaneous doses of emicizumab was 10.4 L.

Metabolism

The metabolism of emicizumab has not been studied. IgG antibodies are mainly catabolised by lysosomal proteolysis and then eliminated from or reused by the body.

Excretion

Following intravenous administration of 0.25 mg/kg in healthy subjects, the total clearance of emicizumab was 3.26 mL/kg/day (i.e. 0.228 L/day for a 70 kg adult) and the mean terminal half-life was 26.7 days.

Following single subcutaneous injection in healthy subjects, the elimination half-life was approximately 4 to 5 weeks.

Following multiple subcutaneous injections in haemophilia A patients, the apparent clearance was 0.272 L/day and the elimination apparent half-life was 26.8 days.

Emicizumab exhibited dose-proportional pharmacokinetics in patients with haemophilia A over a dose range from 0.3 to 6 mg/kg once weekly following subcutaneous administration.

Pharmacokinetics in special populations

Paediatrics

The effect of age on the pharmacokinetics of emicizumab was assessed in a population pharmacokinetic analysis which included 5 infants and toddlers (14 months to < 2 years), 55 children (2 years to < 12 years) and 50 adolescents (12 to < 18 years) with haemophilia A. Age did not affect the pharmacokinetics of emicizumab in paediatric patients older than 6 months at equivalent weight-based doses (see section 4.2). In paediatric patients less than 6 months old, the predicted concentrations of emicizumab were 19% to 33% lower than the older patients, especially with maintenance doses of 3 mg/kg once every two weeks or 6 mg/kg once every four weeks.

Elderly

The effect of age on the pharmacokinetics of emicizumab was assessed in a population pharmacokinetic analysis which included 13 patients aged 65 years and older (no patients were older than 75 years of age). Relative bioavailability decreased with older age, but no clinically important differences were observed in the pharmacokinetics of emicizumab between patients < 65 years and patients ≥ 65 years.

Renal impairment

No dedicated studies on the effect of renal impairment on the pharmacokinetics of emicizumab have been conducted. Most of the patients with haemophilia A in the population pharmacokinetic analysis had normal renal function (N=332; creatinine clearance [CLcr] ≥ 90 mL/min) or mild renal impairment (N=27; CLcr of 60-89 mL/min). Only 2 patients had moderate renal impairment (CLcr of 30-59 mL/min). No patients had severe renal impairment. Mild or moderate renal impairment did not appear to have an impact on the pharmacokinetics of emicizumab (see Section 4.2).

Hepatic impairment

No dedicated studies on the effect of hepatic impairment on the pharmacokinetics of emicizumab have been conducted. Most of the patients with haemophilia A in the population pharmacokinetic analysis had normal hepatic function (bilirubin and AST ≤ ULN, N=300) or mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 times ULN and any AST, N=51). Only 6 patients had moderate hepatic impairment (bilirubin > 1.5 to 3 times ULN and any AST). Mild or moderate hepatic impairment did not affect the pharmacokinetics of emicizumab (see section 4.2). Hepatic impairment was defined by the National Cancer Institute (NCI) criteria for hepatic dysfunction.

Race

Population pharmacokinetic analyses in patients with haemophilia A showed that race did not affect the pharmacokinetics of emicizumab.

Factor VIII inhibitor status

Population pharmacokinetic analyses in patients with haemophilia A showed that FVIII inhibitor status did not affect the pharmacokinetics of emicizumab.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been performed with emicizumab. As a monoclonal antibody, emicizumab is not expected to interact with DNA or other chromosomal material.

Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of emicizumab.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Arginine
Histidine
Poloxamer
Aspartic acid
Water for injections.

6.2 INCOMPATIBILITIES

No incompatibilities between Hemlibra and the recommended syringes and needles have been observed.

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Keep the vial in the outer carton in order to protect from light. Do not shake.

Once removed from the refrigerator, unopened vials can be kept at room temperature (below 30°C) for up to 7 days. After storage at room temperature, unopened vials may be returned to the refrigerator. Cumulative storage time at room temperature should not exceed 7 days.

Hemlibra should not be used after the expiry date (EXP) shown on the pack.

6.5 NATURE AND CONTENTS OF CONTAINER

Hemlibra is supplied in single-use glass vials containing 30 mg/mL or 150 mg/mL emicizumab for subcutaneous injection:

- 30 mg/1 mL (30 mg/mL), 1 vial
- 60 mg/0.4 mL (150 mg/mL), 1 vial
- 105 mg/0.7 mL (150 mg/mL), 1 vial
- 150 mg/1 mL (150 mg/mL), 1 vial

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Hemlibra (emicizumab) is a recombinant humanised monoclonal modified immunoglobulin G4 (IgG4) antibody. Emicizumab has an approximate molecular weight of 145.6 kDa.
CAS Registry Number: 1610943-06-0.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30-34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

23 February 2018

10. DATE OF REVISION

29 November 2023

Summary table of changes

Section Changed	Summary of new information
	Removal of the black triangle