▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ADZYNMA® (APADAMTASE ALFA/CINAXADAMTASE ALFA [rADAMTS13]) POWDER AND SOLVENT FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT

apadamtase alfa/cinaxadamtase alfa [rADAMTS13]

(recombinant "A disintegrin and metalloproteinase with thrombospondin motifs 13" [rADAMTS13])

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADZYNMA 500 IU powder for injection with solvent vial

Each vial of powder contains 500 International Units (IU) of rADAMTS13* activity, as measured in terms of its potency. After reconstitution with the 5 mL solvent provided, the solution has a nominal potency of approximately 100 IU/mL.

ADZYNMA 1500 IU powder for injection with solvent vial

Each vial of powder contains 1500 International Units (IU) of rADAMTS13* activity, as measured in terms of its potency. After reconstitution with the 5 mL solvent provided, the solution has a nominal potency of approximately 300 IU/mL.

*ADZYNMA is a purified human recombinant "A disintegrin and metalloproteinase with thrombospondin motifs 13" (rADAMTS13) expressed in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology (a mixture of native rADAMTS13 Q23 and variant rADAMTS13 R23 with a controlled range of the two variants ratio), referred to as rADAMTS13.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Powder and solvent for injection.
ADZYNMA is formulated as a white lyophilised powder.
The solvent is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ADZYNMA is a recombinant ADAMTS13 (rADAMTS13) enzyme replacement therapy (ERT) indicated for the treatment of ADAMTS13 deficiency in patients with congenital thrombotic thrombocytopenic purpura (cTTP).

ADZYNMA can be used for all age groups.

4.2 DOSE AND METHOD OF ADMINISTRATION

ADZYNMA treatment should be initiated under the supervision of a physician experienced in the management of patients with haematological disorders.

Dosage

Prophylactic enzyme replacement therapy

- Administer 40 IU/kg body weight once every other week.
- The prophylaxis dosing frequency may be adjusted to 40 IU/kg once weekly based on prior prophylactic dosing regimen or based on clinical response.

See Section 5.2 PHARMACOKINETIC PROPERTIES.

On-demand enzyme replacement therapy

In case of acute TTP episode, the recommended dose of ADZYNMA to treat acute TTP episodes is as follows:

- 40 IU/kg body weight on day 1.
- 20 IU/kg body weight on day 2.
- 15 IU/kg body weight starting day 3 once daily until two days after the acute event is resolved.

See Section 5.1 PHARMACODYNAMIC PROPERTIES and
Section 5.2 PHARMACOKINETIC PROPERTIES.

Special Populations

Use in hepatic impairment

As rADAMTS13 is a recombinant protein with high molecular weight, it is cleared via catabolism (rather than hepatic metabolism). No dose adjustment of ADZYNMA is needed for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES). Administration of ADZYNMA in patients with hepatic dysfunction has not been studied.

Use in renal impairment

As rADAMTS13 is a recombinant protein with high molecular weight, it is not excreted renally. No dose adjustment of ADZYNMA is needed for patients with mild or moderate renal impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES). Administration of ADZYNMA in patients with end stage renal disease (ESRD) requring chronic dialysis has not been studied.

Use in the elderly

There is limited data on the use of ADZYNMA in patients over 65 years of age. Based on the results from population pharmacokinetics analysis, no dose adjustment is required for elderly patients (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric use

The recommended body-weight based dosing regimen in paediatric patients is the same as that in adults. There is limited information from controlled studies of ADZYNMA in paediatric patients

below 12 years of age. ADAMTS13 activity exposures are expected to be similar across adult, adolescent, and paediatric patients below 12 years of age (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Method of administration

For intravenous use after reconstitution.

ADZYNMA is administered at a rate of 2 to 4 mL per minute.

Home or self-administration

Home or self-administration under the supervision of a healthcare professional may be considered for patients who are tolerating their infusions well. The decision to have a patient move to home or self-infusion should be made after evaluation and recommendation by the treating physician. Appropriate training should be given by the treating physician and/or nurse to the patient or caregiver prior to initiation of home or self-infusion. Dose and infusion rate (2 to 4 mL per minute) should remain constant, and should not be changed without supervision of a healthcare professional. Treatment should be closely followed by the treating physician. Any patients experiencing early signs of hypersensitivity need to immediately stop the infusion process and seek the attention of a healthcare professional (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Subsequent infusions may need to occur in a clinical setting.

Instructions for use

ADZYNMA is to be administered intravenously after reconstitution of the powder with the provided water for injections.

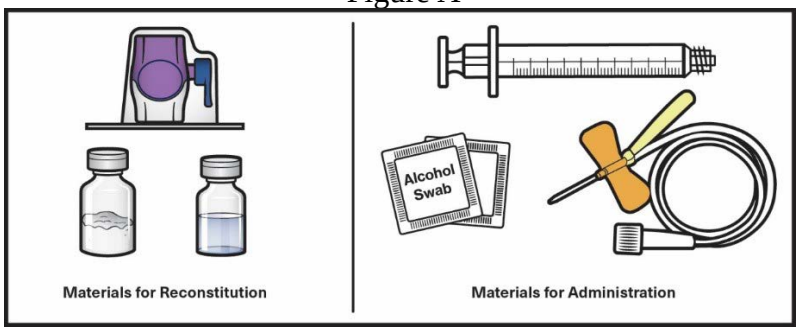
General Instructions

- Calculate administration dose and volume based on the patient's body weight.
- Use aseptic technique throughout the procedure.
- Check the expiration date of the product prior to use.
- Do not use ADZYNMA if the expiration date has passed.
- If the patient needs more than one vial of ADZYNMA per injection, reconstitute each vial according to the instructions stated under 'Reconstitution'. Please note that the BAXJECT II Hi-Flow device is intended for use with a single vial of ADZYNMA and water for injections only, therefore reconstituting and withdrawing a second vial into the syringe requires a second BAXJECT II Hi-Flow device.
- Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted ADZYNMA solution should be clear and colorless in appearance.
- Do not administer if particulate matter or discoloration is observed.
- Administer ADZYNMA within 3 hours after reconstitution when stored at room temperature.
- Do not administer ADZYNMA in the same tubing or container at the same time with other medicinal products for infusion.

Reconstitutions

1. Prepare a clean flat surface and gather all the materials you will need for the reconstitution and administration (Figure A).

Figure A

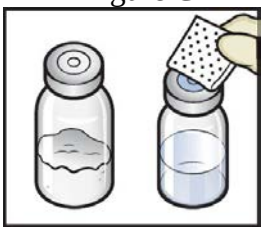


2. Allow the vials of ADZYNMA and diluent to reach room temperature before use.

3. Wash and dry your hands thoroughly.

Figure B

Figure C

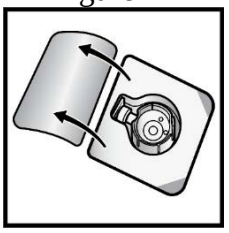


4. Remove plastic caps from the ADZYNMA and diluent vials and place the vials on a flat surface (Figure B).

5. Wipe the rubber stoppers with an alcohol swab and allow them to dry prior to use (Figure C).

6. Open the BAXJECT II Hi-Flow device package by peeling away the lid, without touching the inside (Figure D).

Figure D



- Do not remove the BAXJECT II Hi-Flow device from the package.
- Do not touch the clear plastic spike.

7. Turn the package with the BAXJECT II Hi-Flow device upside down and place it over the top of the diluent vial. Press straight down until the clear plastic spike pierces through the diluent vial stopper (Figure E).

8. Grip the BAXJECT II Hi-Flow device package at its edge and pull the package off the device (Figure F).

Figure E

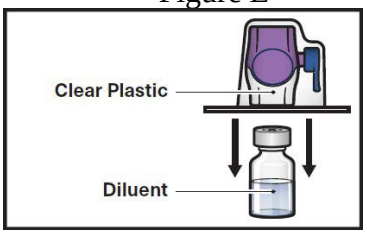
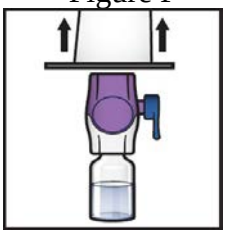


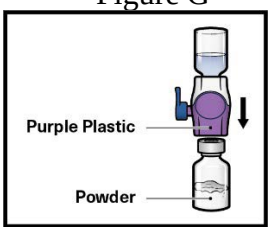
Figure F



- Do not remove the blue cap from the BAXJECT II Hi-Flow device.
- Do not touch the exposed purple plastic spike.

9. Turn the system over so that the diluent vial is now on top. Press the BAXJECT II Hi-Flow device straight down until the purple plastic spike pierces through the ADZYNMA powder vial stopper (Figure G). The vacuum will draw the diluent into the ADZYNMA powder vial.

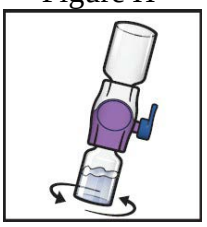
Figure G



- You may notice some bubbles or foam – this is normal and should soon disappear.

10. Swirl the connected vials gently and continuously until the powder is completely dissolved (Figure H).
    - Do not shake the vial.

Figure H



11. Visually inspect the reconstituted solution for particulate matter before administration.
    - Do not use the product if particulate matter or discoloration is observed.
12. If the dose requires more than one vial of ADZYNMA, reconstitute each vial using the above steps.
    - Use a different BAXJECT II Hi-Flow device to reconstitute each vial of ADZYNMA and diluent.

Administration

Figure I

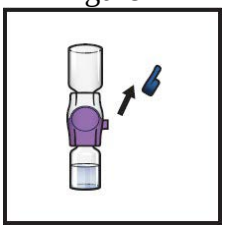
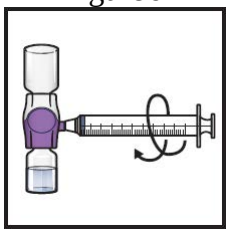


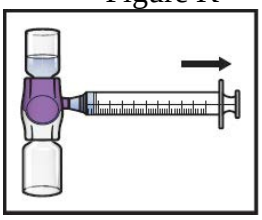
Figure J



13. Take off the blue cap from the BAXJECT II Hi-Flow device (Figure I).

    Attach a Luer lock syringe (Figure J).
    - Do not inject air into the system.
14. Turn the system upside down (ADZYNMA vial is now on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly (Figure K).

Figure K



15. If a patient is to receive more than one vial of ADZYNMA, the contents of multiple vials can be drawn into the same syringe. Repeat this process for all reconstituted vials of ADZYNMA until the total volume to be administered is reached.
16. Disconnect the syringe and attach a suitable injection needle or an infusion set.
17. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.
18. Apply a tourniquet and clean the chosen infusion site with an alcohol swab (Figure L).
19. Insert the needle into the vein and remove the tourniquet.
20. Infuse the reconstituted ADZYNMA slowly, at a rate of 2 to 4 mL per minute (Figure M).
    - A syringe pump may be used to control the rate of administration.

Figure L

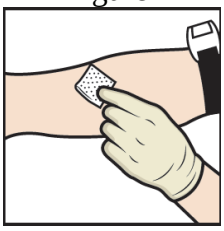
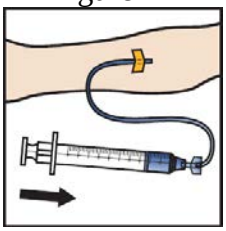


Figure M



21. Take the needle out of the vein and put pressure on the infusion site for several minutes.
    - Do not recap the needle.
22. Place the needle, syringe, and empty vials in a puncture-resistant sharps container.
    - Do not dispose of syringes and needles in the household waste. See section 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL.

4.3 CONTRAINDICATIONS

Do not use in patients who have manifested life-threatening hypersensitivity reactions to ADZYNMA or its components (see Section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Traceability

In order to improve the tracebility of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Allergic-type hypersensitivity including anaphylactic reactions may occur. Patients should be informed of the early signs of hypersensitivity reactions including but not limited to tachycardia, tightness of the chest, wheezing and/or acute respiratory distress, hypotension, generalised urticaria, pruritus, rhinoconjunctivitis, angioedema, lethargy, nausea, vomiting, paresthesia, restlessness, and may progress to anaphylactic shock. If signs and symptoms of severe allergic reactions occur, administration of ADZYNMA should be discontinued immediately and appropriate supportive care should be provided.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Neutralising antibodies were not reported in patients treated with ADZYNMA in the cTTP clinical trials. Patients may develop antibodies to rADAMTS13 following treatment with ADZYNMA which could potentially result in a decreased response to rADAMTS13 (see Section 5.1 PHARMACODYNAMIC PROPERTIES). If such antibodies are suspected and there is a lack of efficacy, consider other therapeutic strategies.

Use in the elderly

There is limited data on the use of ADZYNMA in patients over 65 years of age. See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Special Populations – Use in the elderly.

Paediatric use

There is limited information from controlled studies of ADZYNMA in paediatric patients below 12 years of age. See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Special Populations – Paediatric use.

Effects on laboratory tests

In clinical trials, no clinically meaningful trends over time in laboratory parameters (other than cTTP-related laboratory assessments) were observed throughout treatment with ADZYNMA.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed with ADZYNMA.

4.6 ERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data are available on the effects of rADAMTS13 on male and female fertility.
No adverse effects on fertility were observed in female rats administered rADAMTS13 via IV up to 400 U/kg once every 3 days from 2 weeks prior to mating through the period of organogenesis, resulting in 3.3 times the plasma AUC in patients at a clinical dose of 40 IU/kg/week. No effects on sperm or male reproductive tissues to suggest impairment of fertility were seen in rats receiving rADAMTS13 at IV doses up to 400 U/kg once every 3 days for 26 weeks, yielding approximately 7 times the plasma AUC in patients at a clinical dose of 40 IU/kg/week.

Use in pregnancy (Category B1)

The safety of ADZYNMA for use in pregnant women has not been established in controlled clinical trials. Limited data with ADZYNMA use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes.

There are limited data from the use of ADZYNMA in cTTP patients who have been exposed to ADZYNMA during pregnancy from clinical trials, published reports, and compassionate use of ADZYNMA.

Available data on use of ADZYNMA in at least three pregnant women include one patient from study 2 who was found to be pregnant approximately one week following her last dose of ADZYNMA and two cTTP patients who were treated with ADZYNMA in a compassionate use program during pregnancy.

Minimal placental transfer of rADAMTS13 was seen in rats (fetal serum levels were 0.6% of maternal serum levels). In developmental toxicity studies in rats, no adverse effects on embryofetal development were seen with rADAMTS13 at IV doses up to 400 U/kg of once every 3 days given 2 weeks prior to mating through the period of organogenesis or given from the time of plantation to weaning. Maximum exposures (AUC) were 3.3 times the plasma AUC in patients at a clinical dose of 40 IU/kg/week.

The use of ADZYNMA during pregnancy may only be considered after a thorough individual risk benefit analysis by the treating physician before and during treatment.

Use in lactation

It is not known whether rADAMTS13 is present in human milk, affects milk production, or has effects on the breastfed infant. Due to its high molecular weight, rADAMTS13 is not likely to be excreted in human milk and the gastrointestinal absorption of the intact protein in infants is unlikely.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADZYNMA and any potential adverse effects to the breastfed child.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of ADZYNMA on the ability to drive or operate automobiles or other heavy machinery have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The most common adverse reactions reported in clinical studies were headache (31.5%), diarrhoea (17.8%), dizziness (16.4%), upper respiratory tract infection (15.1%), nausea (13.7%), and migraine (11%).

Tabulated summary of adverse reactions

The safety profile of ADZYNMA compared to plasma-based therapies (fresh frozen plasma [FFP], pooled solvent/detergent [S/D] treated plasma, or FVIII:VWF concentrates, as assigned by the investigator) was evaluated in one Phase 3, prospective, randomised, controlled, open-label, multicenter, two-period crossover study (Study 281102) and one Phase 3b prospective, open-label, multicenter, single treatment arm, continuation study (Study 3002) conducted in patients with cTTP due to ADAMTS13 deficiency (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

The adverse drug reactions (ADR) are listed in Table 1.

Adverse reactions are listed below by MedDRA system organ class and by frequency. Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each System Organ Class (SOC), ADRs are presented in order of decreasing frequency. Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Table 1. Adverse reactions reported in patients treated with ADZYNMA

MedDRA System Organ Class	Adverse reaction by Preferred Term	Frequency category by subject
Infections and infestations	Upper respiratory tract infection	Very common
Blood and lymphatic system disorders	Thrombocytosis	Common
Nervous system disorders	Headache Dizziness Migrane Somnolence	Very common Very common Very common Common
Gastrointestinal disorders	Diarrhoea Nausea Constipation Abdominal distension	Very common Very common Common Common
General disorders and administration site conditions	Asthenia Feeling hot	Common Common
Investigations	ADAMTS13 activity abnormal	Common

No serious adverse events assessed as related to ADZYNMA were observed. In periods 1, 2, and 3 of Study 281102, no patients receiving ADZYNMA had adverse events leading to treatment discontinuation or interruption, compared to 1 out of 48 (2.1%) patients receiving plasma-based therapies with an adverse event leading to treatment discontinuation and, 13 out of 48 (27.1%) patients had a total of 18 adverse events leading to treatment interruption while receiving plasma-based therapies.

Paediatric population

There is limited information from clinical studies of ADZYNMA in paediatric patients. The safety assessment in paediatric patients is based on the safety data from one phase 3 clinical study comparing ADZYNMA to plasma-based therapies and one phase 3b study. The studies included 20 and 1 paediatric patients aged 2 to 17 years of age in the prophylactic and on-demand cohorts, respectively. Overall, the safety profile in the paediatric patients was similar to that observed in the adult population.

One neonate aged 36 hours old was treated with ADZYNMA in a compassionate use program and had no reported safety or immunogenicity concerns after 2 year of prophylactic treatment.

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting suspected adverse effects

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

There are no data on overdosage of ADZYNMA in patients. In case of overdose, based on the pharmacological action of rADAMTS13, there is the potential for an increased risk of bleeding (Section 5.1 PHARMACODYNAMIC PROPERTIES).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antithrombotic agents, enzymes
ATC code: B01AD13

Mechanism of action

ADAMTS13 is a plasma zinc metalloprotease that regulates the activity of von Willebrand factor (VWF) by cleaving large and ultra-large VWF multimers to smaller units and thereby reducing the platelet binding properties of large and ultra-large VWF and its propensity to form microthrombi.

rADAMTS13 in ADZYNMA is a recombinant form of the endogenous ADAMTS13 with similar pharmacokinetic (PK) and pharmacodynamic (PD) properties. The use of ADZYNMA in patients with cTTP provides targeted ADAMTS13 supplementation and replenishment of plasma ADAMTS13 activity which is expected to reduce or eliminate the spontaneous formation of VWF-platelet microthrombi that leads to platelet consumption and thrombocytopenia, which is a marker of disease activity in patients with cTTP.

Pharmacodynamic effects

VWF:ristocetin cofactor activity (VWF:RCo) was used to assess VWF activity. Following intravenous doses of ADZYNMA at the recommended dose, both VWF antigen and VWF:RCo transiently decreased for 1 to 2 days with a 15% to 25% change from baseline.

Immunogenicity

All subjects were monitored for neutralizing antibodies (inhibitors) to rADAMTS13 in cTTP clinical trials. No cTTP patients have developed neutralizing antibodies to ADAMTS13.

Low titre binding antibodies against ADAMTS13 were detected in 17 of 76 (22.4%) patients treated with ADZYNMA with confirmed cTTP. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Clinical trials

The clinical efficacy and safety were assessed in two ongoing studies (Study 281102 and Study 3002).

Study 281102

ADZYNMA was studied in a global phase 3, prospective, randomised, controlled, open-label, multicentre, two period crossover study followed by a single arm continuation period (Study 281102) evaluating the efficacy and safety of the prophylactic and on-demand ERT with ADZYNMA compared to plasma based therapies in patients with cTTP.

Prophylactic enzyme replacement therapy in patients with cTTP

The efficacy of ADZYNMA in the prophylactic treatment of patients with cTTP was evaluated in 45 patients in the prophylaxis cohort who were randomised to receive 6 months of prophylactic treatment with either 40 IU/kg (± 4 IU/kg) of ADZYNMA or plasma based therapies (period 1) then crossed over to the other treatment for 6 months (period 2). After periods 1 and 2, 45 patients entered a 6 month single arm treatment period with ADZYNMA (period 3).

The mean (SD) age was 30.4 (16.2) years (range: 3 to 58 years). Of the 45 patients, 4 (8.9%) were < 6 years of age, 4 (8.9%) were ≥ 6 to < 12 years of age, 4 (8.9%) were ≥ 12 to < 18 years of age, and 33 (73.3%) were ≥ 18 years of age. The mean (SD) weight was 65.5 kg (21.8) (range: 18.5 to 102.4 kg). Majority of patients were white (64.4%), and were female (57.8%) of whom 73.1% were of child-bearing potential.

Prior to joining the study, the majority (68.9%) of patients received FFP treatment, 24.4% received S/D plasma and 6.7% received FVIII:VWF concentrate.

The efficacy of prophylactic treatment with ADZYNMA in patients with cTTP was evaluated based on the incidence of acute TTP events, subacute TTP events, and TTP manifestations (such as thrombocytopenia, microangiopathic haemolytic anaemia, neurological symptoms, renal dysfunction and abdominal pain); as well as the incidence of supplemental doses prompted by subacute TTP events (see Table 2).

Acute TTP events were as defined by a drop in platelet count [≥ 50% of baseline or a platelet count < 100 x 10^9/L] and an elevation of lactate dehydrogenase (LDH) [> 2% x baseline or > 2 x upper limit normal (ULN)]. Subacute TTP events were defined by a thrombocytopenia event or a microangiopathic haemolytic anaemia event; and organ specific signs and symptoms including but not limited to renal dysfunction events, neurological symptoms events, fever, fatigue/lethargy, and/or abdominal pain).

Table 2. Prophylactic cohort efficacy results in cTTP patients (periods 1 and 2)

	ADZYNMA N=44	Plasma-based therapies N=45
Acute TTP events		
Number of subjects with event (number of events)	0 (0)	1 (1)
Subacute TTP events		
Number of subjects with event (number of events)	1 (1)	6 (7)
Number of subjects receiving a supplemental dose prompted by a subacute event	0	4
Number of supplemental doses prompted by a subacute event	0	9
TTP manifestations		
Thrombocytopenia events[a] Number of subjects with event (number of events) Model based annualised event rate[b], LSM (SE)	13 (50) 0.91 (0.268)	21 (89) 1.62 (0.453)
Microangiopathic haemolytic anaemia events[c] Number of subjects with event (number of events) Model based annualised event rate[b], LSM (SE)	8 (23) 0.38 (0.139)	12 (31) 0.59 (0.195)
Neurological symptoms events[d] Number of subjects with event (number of events) Model based annualised event rate[b], LSM (SE)	4 (18) 0.14 (0.072)	7 (28) 0.23 (0.111)
Renal dysfunction events[e] Number of subjects with event (number of events) Model based annualised event rate[b], LSM (SE)	5 (11) 0.18 (0.093)	2 (5) 0.08 (0.054)
Abdominal pain events Number of subjects with event (number of events) Model based annualised event rate[b], LSM (SE)	2 (4) 0.09 (0.056)	6 (8) 0.17 (0.088)
Other TTP manifestations[f] Number of subjects with event (number of events) Model based annualised event rate[b], LSM (SE)	5 (7) 0.22 (0.095)	12 (19) 0.52 (0.172)
Composite TTP manifestations (not including Other TTP manifestations) Number of subjects with event (number of events) Model based annualised event rate[b], LSM (SE)	24 (102) 2.56 (0.606) *	27 (142) 3.54 (0.815)

LSM = least squares mean; SE = standard error; TTP = thrombotic thrombocytopenic purpura.

[a] Thrombocytopenia events were defined as a a drop in platlet count ≥ 25% of baseline or a platelet count < 150 x 10^9/L.

[b] From a negative binominal mixed-effects model.

[c] Microangiopathic haemolytic anaemia events were defined as an elevation of LDH > 1.5 x baseline or > 1.5 ULN.

[d] Neurological symptoms events inlcuded TTP symptoms of nervous system disorders (e.g., headache, confusion, memory issues, irritability, paraesthesia, dysarthria, dysphonia, visual disturbances, focal or general motor symptoms including seizures).

[e] Renal dysfunction events were defined as an increase in serum creatinine > 1.5 x baseline.

[f] Other TTP manifestations included all adverse events reported by investigators that were considered related or possibly related to cTTP and were not captured as neurological symptoms, abdominal pain, thrombocytopenia, increased LDH, or increased creatinine.
[*] Nominal p-value <0.05 for treatment difference in model-based annualised event rates.

Overall ADZYNMA efficacy results were consistent throughout the study, including period 3, and across age groups.

Treatment satisfaction and Health-Related Quality of Life (HRQoL) were also evaluated during this study. Patient reported outcomes (PROs), based on relevant questionnaires, were captured at screening (baseline) and at the end of each period for the prophylactic cohort. Overall, patient-reported disease-related symptoms, impacts and HRQoL domain scores remained consistent across study assessment time points for patients receiving ADZYNMA and plasma-based therapies. Patients receiving ADZYNMA consistently reported higher scores for treatment satisfaction domains, assessed using Treatment Satisfaction Questionnaire for Medication (TSQM-9), as compared to patients treated with plasma-based therapies and compared to baseline scores indicating higher perceived efficacy, convenience, and satisfaction with ADZYNMA.

On-demand enzyme replacement therapy for acute TTP episodes

The efficacy of the on-demand enzyme replacement therapy for acute TTP episodes was evaluated based on the proportion of acute TTP events responding to ADZYNMA in both the prophylactic and the on-demand cohorts throughout the duration of the study.

An acute TTP event responding to ADZYNMA was defined as a resolved TTP event when platelet count was ≥ 150 x 10^9/L or platelet count was within 25% of baseline, whichever occurs first, and LDH ≤ 1.5 x baseline or ≤ 1.5 x ULN, without requiring the use of another ADAMTS13-containing agent.

The on-demand cohort included 5 adult patients (≥ 18 years of age) and 1 paediatric patient (< 6 years of age). Patients enrolled in this cohort had a total of 7 acute TTP events. Of these 6 patients, 2 patients were randomised to receive on-demand treatment with ADZYNMA and 4 patients were randomised to receive plasma based therapies. Six out of 7 acute TTP events resolved after treatment with either ADZYNMA or plasma based therapies within 5 days with 1 event taking 14.75 days to resolve after treament with a plasma-based therapy.

Most patients (66.7%) were male, white (50%) with a median (min, max) age of 20 (5, 36) years, a mean (SD) weight of 56.4 (18.6) kg and a median (min, max) weight of 64.3 (23.0, 74.0) kg.

Study 3002 (Continuation study)

Patients who completed the Phase 3 study (Study 281102) were eligible to enrol in a Phase 3b, prospective, open-label, multicenter, single treatment arm, continuation study (Study 3002) evaluating the safety and efficacy of ADZYNMA in the prophylactic and on-demand treatment of patients with cTTP.

The prophylaxis cohort included 75 patients among which 46 rolled over from Study 281102 and 29 were naive patients. They included 52 patients ≥18 years of age, 11 patients ≥ 12 to < 18 years of age, 8 patients 6 to < 12 years of age, and 4 patients < 6 years of age. Two patients enrolled in the on-demand cohort. All patients were treated with ADZYNMA. The mean and maximum prophylactic treatment durations were 1.5 years and 3 years, respectively. Incidence rates of acute and subacute TPP events and TPP manifestations were consistent with the results from Study 281102.

5.2 PHARMACOKINETIC PROPERTIES

The PK profile of ADZYNMA was determined based on clinical trial ADAMTS13 activity data analyses.

Following single-dose intravenous administration of ADZYNMA at 5 IU/kg, 20 IU/kg, and 40 IU/kg to adults and adolescents, dose-related increases in individual ADAMTS13 activity were observed and reached a maximum at approximately 1 hour post-infusion or earlier. At clinical dose of 40 IU/kg the mean (SD) half-life and mean residence time (MRT) in adults and adolescents were 60.5 (13.5) hours and 87.7 (26.3) hours, respectively.

The PK parameters of ADAMTS13 activity following intravenous administration of ADZYNMA at 40 IU/kg every other week in adults, adolescents and younger children are described in Table 3.

Table 3. Pharmacokinetic parameters of ADAMTS13 activity following intravenous administration of ADZYNMA in cTTP patients

Parameter (unit)	**Mean (SD)** **Min; Max** **(N=86)**
$C_{max,ss}$ (IU/mL)	1.07 (0.305) 0.438; 2.14
AUC_{ss} (IU*h/mL)	70.4 (41.7) 15.7; 281
Duration of ADAMTS13 Activity above 10% (days)	8.25 (2.80) 1.94; 14.0

AUCss = area under ADAMTS13 activity-time curve at steady state for a dosing interval of two weeks; $C_{max,ss}$ = maximum ADAMTS13 activity at steady state.
Note: 1 IU/mL ADAMTS13 activity corresponds to 100% average normal activity.

Intravenous administration of ADZYNMA at 40 IU/kg resulted in greater than 5-fold higher ADAMTS13 activity exposures, measured by C_{max}, AUC, and duration above 10% ADAMTS13 activity, compared to plasma-based therapies.

Specific Populations

Besides body-weight dosing regimen, no dose adjustment is required since no intrinsic factors such as age, gender, race, baseline estimated glomerular filtration rate (eGFR), and baseline bilirubin were identified as covariates impacting ADAMTS13 PK.

ADAMTS13 antigen and activity PK characteristics (MRT, V_{ss}, and CL) were similar across age groups in patients with cTTP. Body weight-based dosing provides similar ADAMTS13 activity PK parameters (C_{max} and C_{ave}) across the different age groups including paediatric patients below 12 years of age.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been conducted with the active ingredient in ADZYNMA to assess its mutagenic potential. As a high molecular weight protein, rADAMTS13 is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

No studies have been conducted with the active ingredient in ADZYNMA to assess its carcinogenicity potential. As rADAMTS13 is an endogenous protein and given its pharmacological action, it is not expected to pose a carcinogenicity risk.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder

Sodium chloride
Calcium chloride dihydrate
Histidine
Mannitol
Sucrose
Polysorbate 80

Solvent

Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this product should not be mixed in the same syringe with any other medicinal products.

6.3 SHELF LIFE

Unopened vial

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.

After reconstitution

Discard any unused reconstituted product after 3 hours. From a microbiological point of view, the product should be used immediately.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials

Store at 2°C to 8°C. Refrigerate. Do not freeze.
Store in the original package in order to protect from extreme exposure to light.

After reconstitution

For storage conditions after reconstitution, see Section 6.3 SHELF LIFE – After reconstitution.

6.5 NATURE AND CONTENTS OF CONTAINER

The powder for injection and the solvent are filled in a Type 1 glass vial closed with a butyl rubber stopper.

Each pack of ADZYNMA 500 IU contains:

- one powder vial of 500 IU apadamtase alfa/cinaxadamtase alfa (rADAMTS13)
- one solvent vial of 5 mL water for injections
- one needleless reconstitution device (BAXJECT II Hi-Flow)
- one 10 mL disposable syringe
- one 25-gauge infusion set
- two alcohol swabs

Each pack of ADZYNMA 1500 IU contains:

- one powder vial of 1500 IU apadamtase alfa/cinaxadamtase alfa (rADAMTS13)
- one solvent vial of 5 mL water for injections
- one needleless reconstitution device (BAXJECT II Hi-Flow)
- one 20 mL disposable syringe
- one 25-gauge infusion set
- two alcohol swabs

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

For single use only and for one patient only.
Discard any unused portion of the product.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure

rADAMTS13 is a purified human recombinant “A disintegrin and metalloproteinase with thrombospondin motifs 13” expressed in CHO cells using recombinant DNA technology.

Recombinant ADAMTS13 has a molecular weight of approximately 172 kDa.

The reconstituted solution has a pH of 6.7 to 7.3, and an osmolality of no lower than 240 mOsmol/kg.

CAS number

2086325-24-6

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 39
225 George Street
Sydney NSW 2000
Australia

Telephone: 1800 012 612
www.takeda.com/en-au

9. DATE OF FIRST APPROVAL

DD MMMM YYYY

10. DATE OF REVISION

Not applicable.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Not applicable.	