

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

ADZYNMA 500 IU powder and solvent for solution for injection
ADZYNMA 1 500 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADZYNMA 500 IU powder and solvent for solution for injection

Each vial of powder contains nominally 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 potency of approximately 100 IU/mL.

ADZYNMA 1 500 IU powder and solvent for solution for injection

Each vial of powder contains nominally 1 500 IU of rADAMTS13* activity, as measured in terms of its potency.

After reconstitution with the 5 mL solvent provided, the solution has a potency of approximately 300 IU/mL.

*ADZYNMA is a purified bivalent 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.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White lyophilised powder.

The solvent is a clear and colourless solution.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADZYNMA is an enzyme replacement therapy (ERT) indicated for the treatment of ADAMTS13 deficiency in children and adult patients with congenital thrombotic thrombocytopenic purpura (cTTP).

ADZYNMA can be used for all age groups.

4.2 Posology and method of administration

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

Posology

Prophylactic enzyme replacement therapy

- 40 IU/kg of body weight once every other week.
- The prophylaxis dosing frequency may be adjusted to 40 IU/kg of body weight once weekly based on clinical response (see sections 5.1 and 5.2).

On-demand enzyme replacement therapy for acute TTP episodes

In case of acute thrombotic thrombocytopenic purpura (TTP) episode, the recommended dose of ADZYNMA to treat acute TTP episodes is as follows:

- 40 IU/kg of body weight on day 1.
- 20 IU/kg of body weight on day 2.
- 15 IU/kg of body weight starting day 3 once daily until two days after the acute event is resolved (see section 5.1).

Special populations

Elderly

There are 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).

Renal impairment

As rADAMTS13 is a recombinant protein with a high molecular weight, it is not excreted renally and no dose adjustment is needed for patients with renal impairment (see section 5.2).

Hepatic impairment

As rADAMTS13 is a recombinant protein with high molecular weight, it is cleared via catabolism (rather than hepatic metabolism), and no dose adjustment is needed for patients with hepatic impairment (see section 5.2).

Paediatric population

The recommended body-weight based dosing regimen in paediatric patients is the same as in adults. Based on the results from population pharmacokinetics analysis, it might be more likely for infants < 10 kg body weight to require adjustment to dosing frequency from every other week to once weekly dosing (see section 5.2).

Method of administration

For intravenous use after reconstitution only.

ADZYNMA 500 IU and ADZYNMA 1 500 IU powder and solvent for solution for injection 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 injections well. The decision to have a patient move to home or

self-administration 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 and/or caregiver prior to initiation of home or self-administration. Dose and administration rate should remain constant while at home, and not be changed without consulting the treating physician. If the patient experiences early signs of hypersensitivity during the home administration, the administration process should be stopped immediately, and appropriate treatment should be initiated (see section 4.4). Subsequent injections need to occur in a clinical setting. Treatment should be closely followed by the treating physician.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Life-threatening hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

Hypersensitivity reactions

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, paraesthesia, restlessness, and may progress to anaphylactic shock. If signs and symptoms of severe allergic reactions occur, the administration of this medicinal product should be discontinued immediately and appropriate supportive care should be provided.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Patients may develop antibodies to rADAMTS13 following treatment with ADZYNMA which could potentially result in a decreased response to rADAMTS13 (see section 5.1). If such antibodies are suspected and there is a lack of efficacy, consider other therapeutic strategies.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of ADZYNMA in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). 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.

Breast-feeding

There is insufficient information on the excretion of rADAMTS13 in human or animal milk but it is unlikely that it is excreted in human milk due to its high molecular weight. The decision either to discontinue breast-feeding or discontinue ADZYNMA should take into account the importance of this medicinal product to the mother.

Fertility

No human data are available on the effects of rADAMTS13 on male and female fertility. Animal data do not indicate direct or indirect harmful effects with respect to male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Recombinant ADAMTS13 may have a minor influence on the ability to drive and use machines. Dizziness and somnolence may occur following the administration of ADZYNMA (see section 4.8).

4.8 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 list of adverse reactions

The adverse drug reactions (ADRs) 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ to $< 1/1\ 000$); very rare ($< 1/10\ 000$); not known (cannot be estimated from the available data). 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 (SOC)	Adverse reaction by preferred term (PT)	Frequency category by subject
Infections and infestations	Upper respiratory tract infection	Very common
Blood and lymphatic system disorders	Thrombocytosis	Common
Nervous system disorders	Headache	Very common
	Dizziness	Very common
	Migraine	Very common
	Somnolence	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Nausea	Very common
	Constipation	Common
	Abdominal distension	Common

General disorders and administration site conditions	Asthenia	Common
	Feeling hot	Common
Investigations	ADAMTS13 activity abnormal	Common

Paediatric population

There is limited information from controlled 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 (fresh frozen plasma [FFP], pooled solvent/detergent [S/D] treated plasma, or factor VIII: von Willebrand factor [FVIII-VWF] concentrates, as assigned by the investigator) 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 these 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 years of prophylactic treatment.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

In clinical studies, single doses up to 160 IU/kg were used and their safety profile was generally consistent with results from clinical study results in cTTP patients.

In case of overdose, based on the pharmacological action of rADAMTS13, there is the potential for increased risk of bleeding (see section 5.1).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, enzymes, ATC code: B01AD13

Mechanism of action

rADAMTS13 is a recombinant form of the endogenous ADAMTS13. 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 VWF and its propensity to form microthrombi. rADAMTS13 is expected to reduce or eliminate the spontaneous formation of VWF-platelet microthrombi that leads to platelet consumption and thrombocytopenia in patients with cTTP.

Pharmacodynamic effects

Immunogenicity

Anti-drug antibodies (ADA) were very commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited (see section 4.4).

Clinical efficacy and safety

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, randomized, 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 severe cTTP (ADAMTS13 activity < 10%).

Prophylactic enzyme replacement therapy in patients with cTTP

The efficacy of ADZYNMA in the prophylactic treatment of patients with cTTP was evaluated in 46 patients in the prophylaxis cohort who were randomized to receive 6 months of prophylactic treatment with either 40 IU/kg (\pm 4 IU/kg) of ADZYNMA or plasma-based therapies (period 1) once weekly (for patients who were previously treated with plasma-based therapies once weekly prior to joining the study) or every other week then crossed over to the other treatment for 6 months (period 2). After periods 1 and 2, all patients entered a 6 month single arm treatment period with ADZYNMA (period 3). The initial ADZYNMA prophylactic treatment frequency was every other week for 35 (76.1%) patients and once weekly for 9 (19.6%) patients.

The mean (SD) age was 30.5 (16.0) years (range: 3 to 58 years). Of the 46 patients, 4 (8.7%) were < 6 years of age, 4 (8.7%) were \geq 6 to < 12 years of age, 4 (8.7%) were \geq 12 to < 18 years of age, and 34 (73.9%) were \geq 18 years of age. The mean (SD) weight was 65.9 kg (21.8) (range: 18.5 to 102.4 kg), and the majority of patients were white (65.2%), and were female (58.7%) of whom 74.1% were of child-bearing potential.

Prior to joining the study, the majority (69.6%) of patients received FFP treatment, 21.7% received solvent/detergent (S/D) plasma and 6.5% 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 (as defined by a drop in platelet count [\geq 50% of baseline or a platelet count < 100 x 10⁹/L] and an elevation of lactate dehydrogenase [LDH] [$>$ 2 \times baseline or $>$ 2 \times upper limit normal (ULN)]), subacute TTP events (as 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), 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).

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

	ADZYNMA N = 45	Plasma-Based Therapies N = 46
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)	13 (49)	23 (91)
Model based annualized event rate, ^b LSM (SE)	0.92 (0.262)	1.72 (0.457)
Microangiopathic haemolytic anaemia events^c		
Number of subjects with event (number of events)	8 (23)	12 (32)
Model based annualized event rate, ^b LSM (SE)	0.37 (0.136)	0.59 (0.194)
Neurological symptoms events^d		
Number of subjects with event (number of events)	4 (18)	7 (29)
Model based annualized event rate, ^b LSM (SE)	0.13 (0.068)	0.23 (0.109)
Renal dysfunction events^e		
Number of subjects with event (number of events)	5 (11)	2 (5)
Model based annualized event rate, ^b LSM (SE)	0.17 (0.090)	0.08 (0.052)
Abdominal pain events		
Number of subjects with event (number of events)	2 (4)	6 (8)
Model based annualized event rate, ^b LSM (SE)	0.09 (0.055)	0.17 (0.086)

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

^a Drop in platelet count $\geq 25\%$ of baseline or a platelet count $< 150 \times 10^9/L$.

^b From a negative binominal mixed-effects model.

^c Elevation of LDH $> 1.5 \times$ baseline or $> 1.5 \times$ ULN.

^d Nervous system disorders (e.g., headache, confusion, memory issues, irritability, paraesthesia, dysarthria, dysphonia, visual disturbances, focal or general motor symptoms including seizures).

^e An increase in serum creatinine $> 1.5 \times$ baseline.

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

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 $\geq 150 \times 10^9/L$ or platelet count was within 25% of baseline, whichever occurs first, and LDH $\leq 1.5 \times$ baseline or $\leq 1.5 \times$ 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 randomized to receive on-demand treatment with ADZYNMA and 4 patients were randomized to receive plasma-based therapies. All 7 acute TTP events resolved after treatment with either ADZYNMA or plasma-based therapies within 5 days.

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 long-term continuation study (Study 3002). The prophylaxis cohort included 65 patients among which 40 rolled over from Study 281102 and 25 were naïve patients. Of the 40 roll-over patients, 7 (17.5%) were ≥ 12 to < 18 years of age, and 33 (82.5%) were ≥ 18 years of age. Of the 25 naïve patients, 3 (12%) were < 6 years of age, 3 (12%) were ≥ 6 to < 12 years of age, 3 (12%) were ≥ 12 to < 18 years of age, and 16 (64%) were ≥ 18 years of age. The on-demand cohort included 1 patient aged ≥ 6 to < 12 years. All patients were treated with ADZYNMA. The mean and maximum prophylactic treatment durations were 0.98 years and 2.17 years, respectively. Incidence rates of acute and subacute TPP events and TPP manifestations were consistent with the results from Study 281102.

Paediatric population

Overall, the efficacy in paediatric patients was similar to that observed in the adult population.

The European Medicines Agency has deferred the obligation to submit the results of studies with ADZYNMA in one or more subsets of the paediatric population in the treatment of congenital thrombotic thrombocytopenic purpura (see section 4.2 for information on paediatric use).

Exceptional circumstances

This medicinal product has been authorised under ‘exceptional circumstances’. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetic (PK) profile of ADZYNMA was determined based on clinical study 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-administration or earlier. At clinical dose of 40 IU/kg the mean (SD) half-life and mean residence time (MRT) in adults and adolescents were 47.8 (13.7) hours and 63.8 (16.0) hours, respectively.

The population PK parameters of ADAMTS13 activity following intravenous administration of ADZYNMA at 40 IU/kg 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 = 83)
C_{max} (IU/mL)	1.13 (0.29) 0.72; 2.29
AUC (IU*h/mL)	72.8 (37.4) 38.7; 274
Duration ADAMTS13 activity above 10% (days)	8.85 (2.45) 4.51; 14.0

AUC = area under ADAMTS13 activity-time curve; C_{max} = maximum ADAMTS13 activity.

Note: 1 IU/mL ADAMTS13 activity corresponds to 100% average normal activity.

ADZYNMA intravenous administration at 40 IU/kg resulted in approximately greater than 5-fold higher ADAMTS13 activity exposures (C_{max} , AUC, and duration above 10% ADAMTS13 activity) and lower variability when compared to plasma-based therapies.

Special populations

Age, gender, race, and other intrinsic factors

Besides body-weight dosing regimen, 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 activity PK characteristics (MRT, steady-state volume of distribution [V_{ss}], and clearance [CL]) were similar across age groups in patients with cTTP. Body weight-based ADZYNMA dosing provides similar ADAMTS13 activity PK parameters (C_{max} and average ADAMTS13 activity [C_{ave}]) across the different age groups including paediatric patients < 12 years of age.

In infants < 10 kg body weight, median duration above 10% ADAMTS13 activity was estimated to be shorter (approximately 5-6 days) compared to adults (approximately 10 days).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, single dose toxicity, toxicity to reproduction and development, local tolerance and immunogenicity. Studies to evaluate the mutagenic and carcinogenic potential of rADAMTS13 have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sodium chloride
Calcium chloride dihydrate
L-Histidine
Mannitol
Sucrose
Polysorbate 80 (E433)

Solvent

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

3 years

After reconstitution

Chemical and physical in-use stability has been demonstrated for 6 hours at 25 °C.

From a microbiological point of view, unless the method of opening/reconstituting/dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Powder

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.

ADZYNMA may be stored at room temperature up to 30 °C for a period of up to 6 months in lyophilized form, but not exceeding the expiry date.

Do not return ADZYNMA to refrigerated storage after storage at room temperature.

Record on the carton the date ADZYNMA is removed from refrigeration.

After reconstitution

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

ADZYNMA 500 IU powder and solvent for solution for injection

Each pack contains:

- powder in a vial (type I glass), with a butyl rubber stopper
- 5 mL of solvent in a vial (type I glass), with a butyl rubber stopper
- one reconstitution device (BAXJECT II Hi-Flow)
- one disposable 10 mL syringe
- one 25-gauge infusion set
- two alcohol swabs

ADZYNMA 1 500 IU powder and solvent for solution for injection

Each pack contains:

- powder in a vial (type I glass), with a butyl rubber stopper
- 5 mL of solvent in a vial (type I glass), with a butyl rubber stopper
- one reconstitution device (BAXJECT II Hi-Flow)
- one disposable 20 mL syringe
- one 25-gauge infusion set
- two alcohol swabs

6.6 Special precautions for disposal and other handling

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

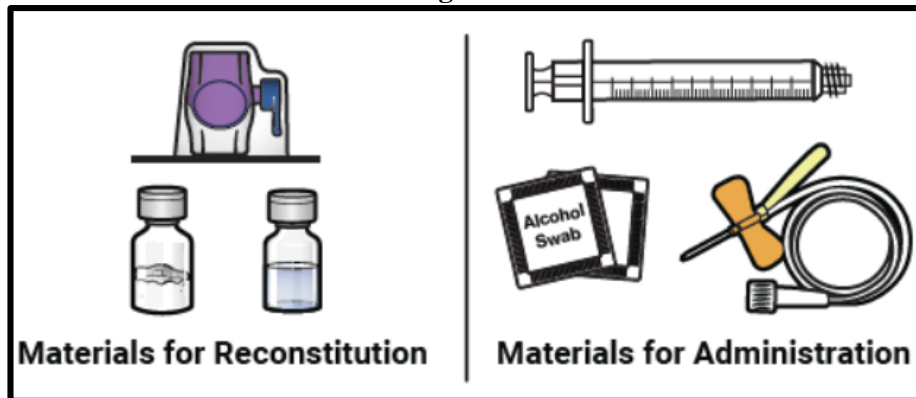
General instructions

- Calculate administration dose and volume based on the patient's body weight.
- Use aseptic technique throughout the procedure.
- Check expiry date of the product prior to use.
- Do not use ADZYNMA if the expiry 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 colourless 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.

Reconstitution

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

Figure B



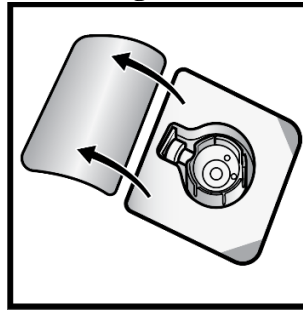
5. Wipe the rubber stoppers with an alcohol swab and allow them to dry prior to use (**Figure C**).

Figure C



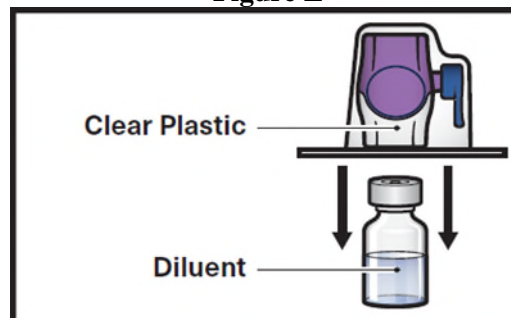
6. Open the BAXJECT II Hi-Flow device package by peeling away the lid, without touching the inside (**Figure D**).
 - **Do not** remove the BAXJECT II Hi-Flow device from the package.
 - **Do not** touch the **clear plastic spike**.

Figure D



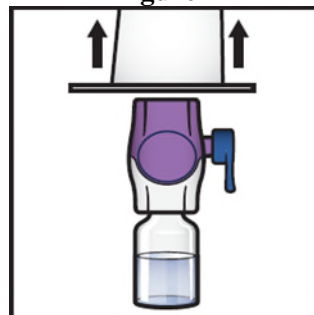
7. Turn the package with the BAXJECT II Hi-Flow device upside down and place it over the top of the diluent vial. Press straight down until the **clear plastic spike** pierces through the **diluent vial stopper** (**Figure E**).

Figure E



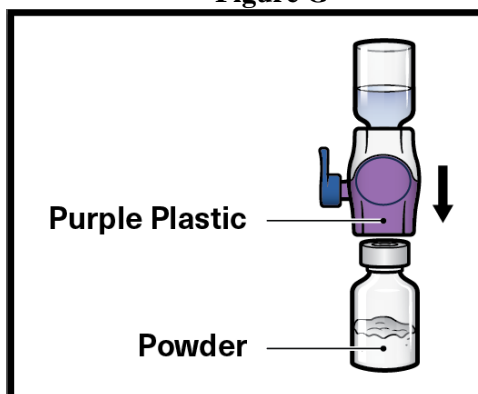
8. Grip the BAXJECT II Hi-Flow device package at its edge and pull the package off the device (**Figure F**).
 - **Do not** remove the **blue cap** from the BAXJECT II Hi-Flow device.
 - **Do not** touch the exposed **purple plastic spike**.

Figure F



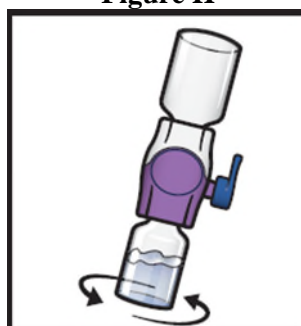
9. **Turn the system over** so that the **diluent vial** is now on top. Press the BAXJECT II Hi-Flow device straight down until the **purple plastic spike** pierces through the **ADZYNMA powder vial stopper** (**Figure G**). The vacuum will draw the diluent into the **ADZYNMA powder vial**.
 - You may notice some bubbles or foam – this is normal and should soon disappear.

Figure G



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 instructions

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.

Figure I

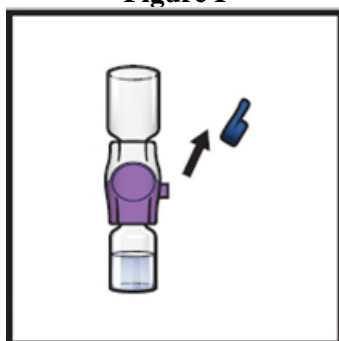
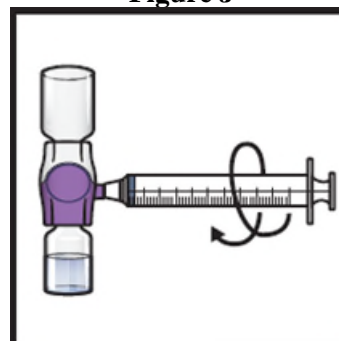
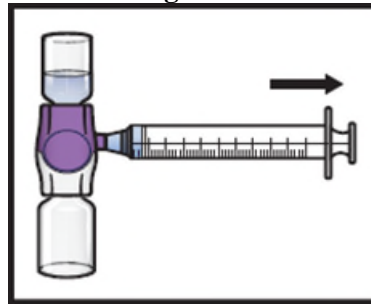


Figure J



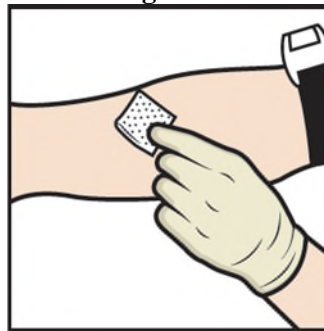
14. **Turn the system upside down** (ADZYNMA vial is now on top). Draw the **reconstituted solution** into the syringe by pulling the plunger back slowly (**Figure K**).

Figure K



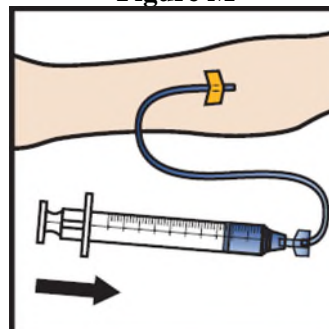
15. If a patient is to receive more than one vial of ADZYNMA, the contents of multiple vials can be drawn into the same syringe. Repeat this process for all reconstituted vials of ADZYNMA until the total volume to be administered is reached.
16. Disconnect the syringe and attach a suitable injection 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 injection site with an alcohol swab (**Figure L**).

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 M



21. Take the needle out of the vein and put pressure on the injection 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBERS

EU/1/24/1837/001
EU/1/24/1837/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Takeda Manufacturing Singapore Pte Ltd
2A Woodlands Industrial Park D Street 2
Singapore 737779

Name and address of the manufacturer responsible for batch release

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna, Austria

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the use of ADZYNMA in home/self-administration, the Marketing Authorization Holder (MAH) must agree about the content and format of the educational materials for use of ADZYNMA in home/self-administration, including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authority.

The educational materials for the use are aimed at providing guidance on how to manage risks of hypersensitivity with home/self-administration.

The MAH shall ensure that in each Member State where ADZYNMA is marketed, all healthcare professionals who are expected to prescribe and patients/caregivers who are expected to use ADZYNMA have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Healthcare professionals (HCP) guide for hypersensitivity in home/self-administration for ADZYNMA
- Patient/caregiver alert card for hypersensitivity in home/self-administration for ADZYNMA
- **Guide for healthcare professionals:**
 - The HCP will receive information on the risk of hypersensitivity associated with ADZYNMA
 - Likelihood of hypersensitivity should be factored into the eligibility assessment for home/self-administration
 - The HCP should communicate the signs and symptoms of hypersensitivity and action steps to advise the patient should take if hypersensitivity occur
 - The HCP will be provided with the key points to counselling patients on risk and use of the Patient/caregiver alert card
- **Patient/caregiver alert card:**
 - Hypersensitivity reactions may occur while on ADZYNMA
 - Information on signs and symptoms related to hypersensitivity reactions and when to seek attention from healthcare professionals
 - Understand the action steps (i.e., seek immediate medical attention) should signs and symptoms occur
 - Contact details of ADZYNMA prescriber

The patient information pack:

- Patient information leaflet

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with congenital thrombotic thrombocytopenic purpura (cTTP), the MAH shall submit the results of study 281102, a phase 3, prospective, randomized, controlled, open-label, multicentre study.	December 2024
In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with cTTP, the MAH shall submit the final results of study TAK-755-3002, a phase 3b, prospective, open-label, multicentre, single treatment arm.	September 2027
In order to further evaluate the safety concerns of rADAMTS13 in patients with cTTP, the MAH shall conduct and submit the results of a post-authorisation safety study (PASS) in patients receiving rADAMTS13 according to an agreed protocol.	Final study report: December 2030

Description	Due date
In order to ensure adequate monitoring of safety and efficacy of rADAMTS13 in the treatment of patients with cTTP, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of rADAMTS13.	Annually within the annual reassessment

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (500 IU)

1. NAME OF THE MEDICINAL PRODUCT

ADZYNMA 500 IU powder and solvent for solution for injection
rADAMTS13

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 500 IU rADAMTS13, approx. 100 IU/mL after reconstitution with 5 mL solvent.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, calcium chloride dihydrate, L-histidine, mannitol, sucrose, polysorbate 80 (E433) and water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Content: 1 powder vial, 1 vial with solvent (5 mL), 1 BAXJECT II Hi-Flow device, 1 disposable 10 mL syringe, 1 infusion set (25 gauge), 2 alcohol swabs

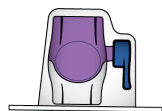
Materials for reconstitution



(1) 500 IU ADZYNMA single-dose vial



(1) vial with 5 mL solvent for ADZYNMA

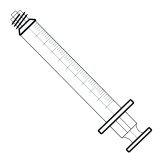


(1) BAXJECT II Hi-Flow device

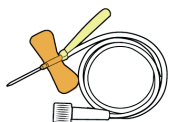
Materials for administration



(2) alcohol swabs



(1) 10 mL syringe



(1) 25 gauge infusion set

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use after reconstitution.
Read the package leaflet before use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 30 °C) for a period up to 6 months, but not exceeding expiry date.

Date removed from refrigerator: _____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER

EU/1/24/1837/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADZYNMA 500 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADZYNMA 500 IU powder for solution for injection
rADAMTS13
IV use after reconstitution

2. METHOD OF ADMINISTRATION

Single use only.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (1 500 IU)

1. NAME OF THE MEDICINAL PRODUCT

ADZYNMA 1 500 IU powder and solvent for solution for injection
rADAMTS13

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 1 500 IU rADAMTS13, approx. 300 IU/mL after reconstitution with 5 mL solvent.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, calcium chloride dihydrate, L-histidine, mannitol, sucrose, polysorbate 80 (E433) and water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Content: 1 powder vial, 1 vial with solvent (5 mL), 1 BAXJECT II Hi-Flow device, 1 disposable 20 mL syringe, 1 infusion set (25 gauge), 2 alcohol swabs

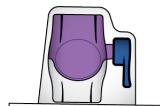
Materials for reconstitution



(1) 1 500 IU ADZYNMA single-dose vial



(1) vial with 5 mL solvent for ADZYNMA

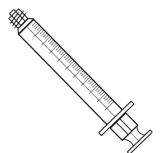


(1) BAXJECT II Hi-Flow device

Materials for administration



(2) alcohol swabs



(1) 20 mL syringe



(1) 25 gauge infusion set

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use after reconstitution.
Read the package leaflet before use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store in the original package in order to protect from light.

Can be stored at room temperature (up to 30 °C) for a period up to 6 months, but not exceeding expiry date.

Date removed from refrigerator: _____

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Industriestrasse 67
1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1837/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ADZYNMA 1500 IU

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

ADZYNMA 1 500 IU powder for solution for injection
rADAMTS13
IV use after reconstitution

2. METHOD OF ADMINISTRATION

Single use only.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
SOLVENT VIAL LABEL (5 mL)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Solvent for ADZYNMA

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ADZYNMA 500 IU powder and solvent for solution for injection ADZYNMA 1 500 IU powder and solvent for solution for injection rADAMTS13

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ADZYNMA is and what it is used for
2. What you need to know before you use ADZYNMA
3. How to use ADZYNMA
4. Possible side effects
5. How to store ADZYNMA
6. Contents of the pack and other information
7. Instructions for use

1. What ADZYNMA is and what it is used for

ADZYNMA contains the active substance rADAMTS13, which is a manmade copy of the natural enzyme (protein) ADAMTS13. This enzyme is lacking in people with congenital thrombotic thrombocytopenic purpura (cTTP).

Congenital TTP is a very rare inherited blood disorder in which blood clots form in small blood vessels throughout the body. These clots can block the flow of blood and oxygen to the body's organs, which leads to a lower-than-normal number of platelets (components that help the blood to clot) in the blood.

Congenital TTP is caused by a lack of the ADAMTS13 enzyme in the blood. ADAMTS13 helps prevent blood clots by breaking down large molecules called von Willebrand factor (VWF). When VWF molecules are too large, they can cause dangerous blood clots. ADZYNMA is used to replenish levels of the lacking ADAMTS13. This helps break up these larger molecules into smaller ones, reducing the likelihood of blood clots forming and potentially preventing low blood platelet levels in patients with cTTP.

2. What you need to know before you use ADZYNMA

Do not use ADZYNMA

- if you have experienced severe or potentially life-threatening allergic reactions to rADAMTS13 or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using ADZYNMA.

Allergic reactions

There is a risk that you may experience an allergic-type hypersensitivity reaction to ADZYNMA. Your doctor should inform you about early signs of severe allergic reactions such as:

- fast heart rate
- tightness of the chest
- wheezing and/or sudden onset of difficulty in breathing
- low blood pressure
- hives, rash and itchy skin
- runny nose or nasal congestion
- red eyes
- sneezing
- rapid swelling under the skin in areas such as the face, throat, arms and legs
- tiredness
- nausea (feeling sick)
- vomiting
- sensations like numbness, tingling, pins and needles
- restlessness
- anaphylaxis (severe allergic reaction that can cause difficulty in swallowing and/or breathing, red or swollen face and/or hands).

If any of these symptoms occur, your doctor will decide if your treatment with ADZYNMA should be stopped and will give you appropriate medicines to treat the allergic reaction. Severe symptoms, including difficulty in breathing and dizziness, require prompt emergency treatment.

Inhibitors

Neutralising antibodies (called inhibitors) may develop in some patients receiving ADZYNMA. These inhibitors could potentially cause the treatment to stop working properly. Tell your doctor if you think your medicine is not working for you.

Other medicines and ADZYNMA

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You must not receive ADZYNMA during pregnancy unless your doctor specifically recommends it. You and your doctor should decide if you can use ADZYNMA if you are breast-feeding.

Driving and using machines

This medicine may have a minor influence on the ability to drive and use machines. Dizziness and somnolence (sleepiness) may occur following the use of ADZYNMA.

Keeping a record

In order to improve the traceability of biological medicinal products, the name and the batch number of the medicine should be clearly recorded.

ADZYNMA contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium free'.

ADZYNMA contains polysorbate 80

This medicine contains 2.7 mg of polysorbate 80 in each ADZYNMA 500 IU or 1 500 IU vial which is equivalent to up to 0.216 mg/kg. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use ADZYNMA

Treatment with ADZYNMA will be given to you under the supervision of a doctor who is experienced in the care of patients with blood disorders.

ADZYNMA is given by intravenous (into a vein) injection. It is supplied to your doctor as a powder that will be dissolved (reconstituted) using the provided solvent (a liquid that is able to dissolve the powder) before it is given.

The dose is calculated based on your body weight.

Taking the medicine at home

Your doctor may consider that you can use ADZYNMA at home if you are tolerating your injections well. When you are able to inject ADZYNMA yourself (or it is given to you by a caregiver) after appropriate training by the treating physician and/or nurse, your doctor will continue to monitor your response to the treatment. If you get any side effects when taking the medicine at home, you need to immediately stop the injection and seek the attention of a healthcare professional.

Recommended dose

Preventative enzyme replacement therapy

The usual dose is 40 IU per kg of body weight, given every other week.

Your doctor may change the frequency to once weekly if ADZYNMA every other week is not working for you.

On-demand enzyme replacement therapy for sudden episodes of TTP

If you develop a sudden episode of thrombotic thrombocytopenia purpura (TTP), the recommended dose of ADZYNMA is as follows:

- 40 IU/kg of body weight on day 1.
- 20 IU/kg of body weight on day 2.
- 15 IU/kg of body weight starting day 3, once daily until two days after the sudden episode of TTP is resolved.

If you take more ADZYNMA than you should

Taking too much of this medicine may result in bleeding.

If you forget to use ADZYNMA

If you have missed an injection of ADZYNMA, tell your doctor as soon as possible. Do not take a double dose to make up for a forgotten dose.

If you stop using ADZYNMA

Speak to your doctor if you wish to stop ADZYNMA treatment. The symptoms of your disease may worsen if you stop treatment.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported with ADZYNMA:

Very common (may affect more than 1 in 10 people)

- nose and throat infection
- headache
- feeling dizzy
- migraine
- diarrhoea
- nausea

Common (may affect up to 1 in 10 people)

- high number of platelets in the blood (thrombocytosis)
- feeling sleepy
- constipation
- bloating (abdominal distension)
- weakness (asthenia)
- feeling hot
- ADAMTS13 activity abnormal

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ADZYNMA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Unopened vials

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

The unopened powder vials of ADZYNMA may be stored at room temperature (up to 30 °C) for a period of up to 6 months, but not exceeding the expiry date. Do not return ADZYNMA to the refrigerator after storage at room temperature. Record on the carton the date ADZYNMA is removed from refrigeration.

After reconstitution

Discard any unused reconstituted product after 3 hours.

Do not use this medicine if you notice it is not clear and colourless.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ADZYNMA contains

- The active substance, rADAMTS13, is a purified recombinant human “A disintegrin and metalloproteinase with thrombospondin motifs 13”.
Each powder vial contains 500 or 1 500 IU rADAMTS13 nominal activity.
- The solvent vial contains 5 mL of water for injections.
- The other excipients are sodium chloride, calcium chloride dihydrate, L-histidine, mannitol, sucrose, and polysorbate 80 (E433). See section 2 “ADZYNMA contains sodium” and “ADZYNMA contains polysorbate 80”.

What ADZYNMA looks like and contents of the pack

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

Each pack contains one powder vial, one solvent vial, a device for reconstitution (BAXJECT II Hi-Flow), a disposable syringe, one infusion set and two alcohol swabs.

Marketing Authorisation Holder and Manufacturer

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Lietuva

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This leaflet was last revised in

This medicine has been authorised under ‘exceptional circumstances’. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: <https://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.

7. Instructions for use

This instructions for use contains information on how to reconstitute and infuse ADZYNMA.

This instructions for use is intended for healthcare professionals and for patients/caregivers who will administer ADZYNMA at home after proper training by a healthcare professional.

Treatment with ADZYNMA should be prescribed and supervised by a healthcare professional experienced in the care of patients with blood disorders.

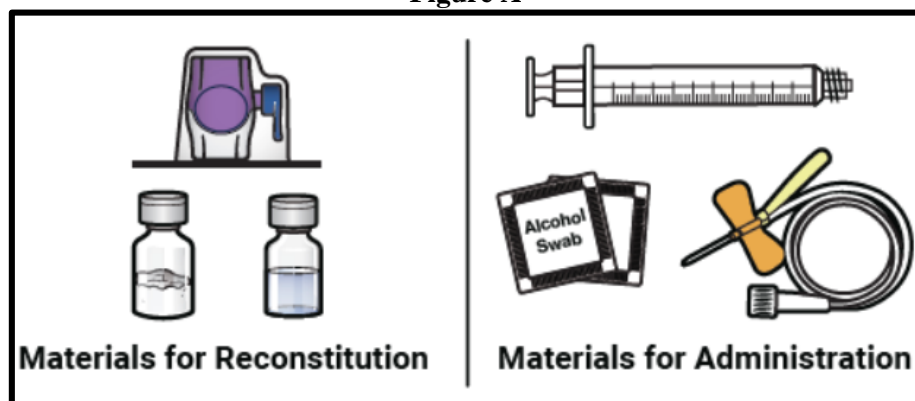
Important:

- **For intravenous injection after reconstitution only.**
- Use aseptic technique throughout the procedure.
- Check the expiry date of the product prior to use.
- **Do not** use ADZYNMA if the expiry 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'.
- Inspect the reconstituted ADZYNMA solution for particulate matter and discoloration prior to administration. The solution should be clear and colourless in appearance.
- **Do not** administer if particulate matter or discoloration is observed.
- Use 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.

Reconstitution

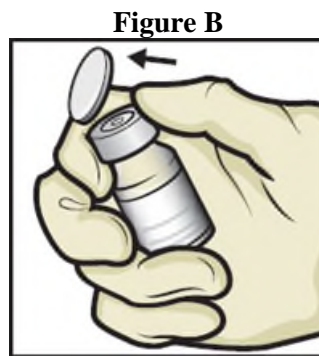
1. Prepare a clean flat surface and gather all the materials you will need for the reconstitution and administration (**Figure A**).

Figure A

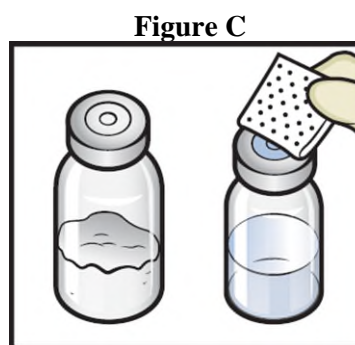


2. Allow the vials of ADZYNMA and diluent to reach room temperature before use.
3. Wash and dry your hands thoroughly.

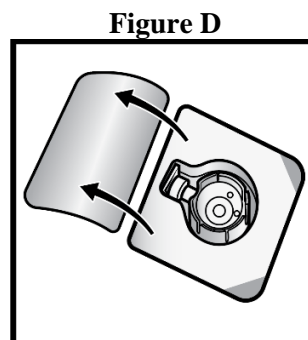
4. Remove plastic caps from the ADZYNMA and diluent vials and place the vials on a flat surface (**Figure B**).



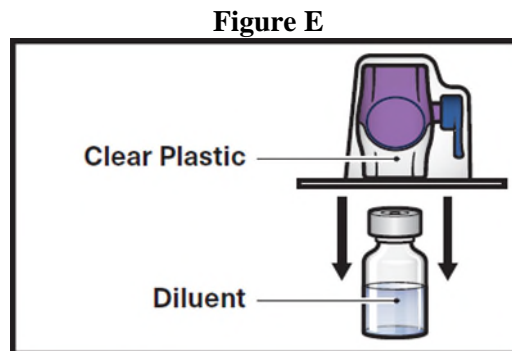
5. Wipe the rubber stoppers with an alcohol swab and allow them to dry prior to use. (**Figure C**).



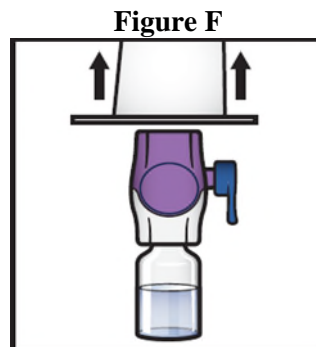
6. Open the BAXJECT II Hi-Flow device package by peeling away the lid, without touching the inside (**Figure D**).
- **Do not** remove the BAXJECT II Hi-Flow device from the package.
 - **Do not** touch the **clear plastic spike**.



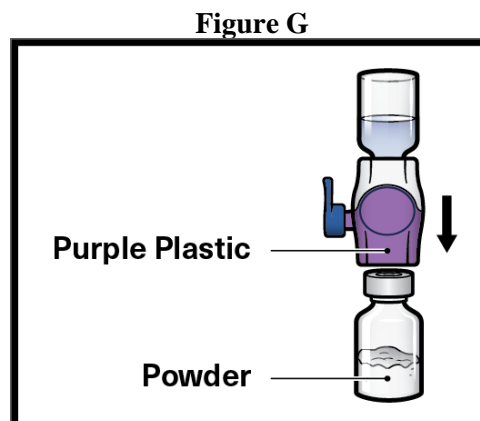
7. Turn the package with the BAXJECT II Hi-Flow device upside down and place it over the top of the diluent vial. Press straight down until the **clear plastic spike** pierces through the **diluent vial** stopper (**Figure E**).



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

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.

Figure I

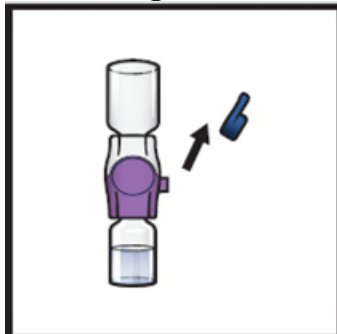
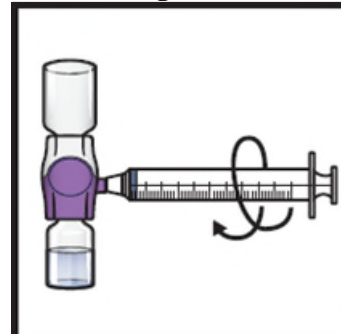
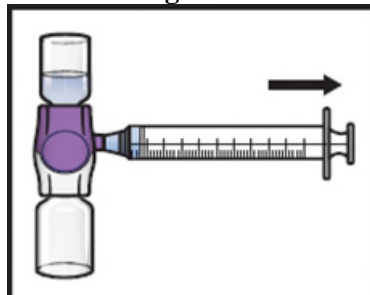


Figure J



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**).

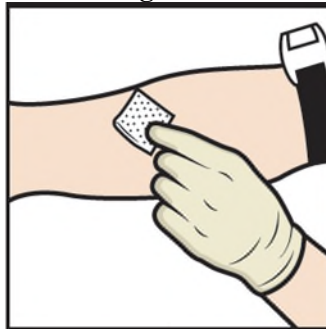
Figure K



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.

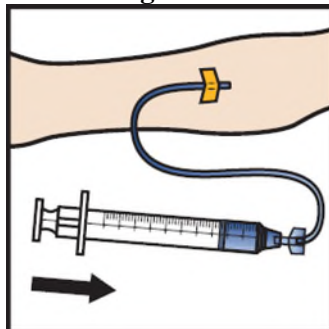
16. Disconnect the syringe and attach a suitable injection needle or an infusion set.
17. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.
18. Apply a tourniquet and clean the chosen injection site with an alcohol swab (**Figure L**).

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 M



21. Take the needle out of the vein and put pressure on the injection site for several minutes.
 - **Do not** recap the needle.

Storing of ADZYNMA

- Store ADZYNMA in a refrigerator (2 °C - 8 °C) or at room temperature (up to 30 °C) for a period of up to 6 months.
- **Do not** return ADZYNMA to refrigerator after storage at room temperature.
- **Record** on the carton the date ADZYNMA is removed from refrigeration.
- **Do not** freeze.
- Store in the original package to protect from light.
- **Do not** use beyond the expiry date stated on the label and carton after EXP.
- Use ADZYNMA **within 3 hours** after reconstitution. Discard any unused reconstituted product if not used within 3 hours after reconstitution.

Disposing of ADZYNMA

- Vials are for **single use** only.
- Dispose used needle, syringe, and empty vials in a puncture-resistant sharps container.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Annex IV

Conclusions on the granting of the marketing authorisation under exceptional circumstances presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.