AUSTRALIAN PRODUCT INFORMATION – XYNTHA® (MOROCTOCOG ALFA) POWDER FOR INJECTION

1. NAME OF THE MEDICINE

moroctocog alfa

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

XYNTHA is formulated as a sterile, non-pyrogenic, lyophilised powder for intravenous (IV) injection. It is available in single use vials and in single use prefilled dual chamber syringes containing the labelled amount of factor VIII activity, expressed in IUs.

Each vial contains nominally 250, 500, 1000 or 2000 IU of XYNTHA per vial.

Each prefilled dual chamber syringe contains nominally 250, 500, 1000, 2000 or 3000 IU of XYNTHA per syringe.

Each vial/prefilled dual chamber syringe of XYNTHA contains 1.23 mmol (or 29 mg) sodium, to be taken into consideration by patients on a controlled sodium diet.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for injection.

The product reconstituted with 4 mL Sodium Chloride Diluent [(9 mg/mL (0.9%)] is a clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XYNTHA is indicated for the control and prevention of haemorrhagic episodes in patients with haemophilia A, including control and prevention of bleeding in surgical settings. XYNTHA does not contain von Willebrand factor and should not be used by patients with von Willebrand's disease.

4.2 Dose and method of administration

Treatment with XYNTHA should be initiated under the supervision of a physician experienced in the treatment of haemophilia A.

Dosage and duration of treatment depend on the severity of the factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition. Individual patients may

vary in their response to factor VIII, achieving different levels of recovery and demonstrating different half-lives. Doses administered should be titrated to the patient's clinical response. In the presence of an inhibitor, higher doses or appropriate specific treatment may be required. Dosage adjustment for patients with renal or hepatic impairment has not been studied in clinical trials.

XYNTHA is appropriate for use in both adults and children.

The number of units of factor VIII administered is expressed in IU, which is related to the current WHO international standard for factor VIII activity. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IUs (relative to an International Standard for factor VIII in plasma).

One IU of factor VIII activity corresponds approximately to the quantity of factor VIII activity in one mL of normal human plasma. The calculation of the required dosage of factor VIII is based upon the empirical finding that on average 1 IU of factor VIII per kg body weight raises the plasma factor VIII activity by approximately 2 IU/dL. The required dosage is determined using the following formula:

Required units (IU) = body weight (kg) x desired factor VIII rise (%) x 0.5 IU/kg

The example for a 20 kg child requiring 100 IU (or 100%) replacement would be:

20 (kg) x 100 (%) x 0.5 (IU/kg) = 1000 IU required units.

Plasma factor VIII activity monitoring

The labelled potency of XYNTHA is based on the European Pharmacopoeia chromogenic substrate assay in which the Wyeth manufacturing potency standard has been calibrated using a one-stage clotting assay. With XYNTHA clinical monitoring using the chromogenic assay typically yields results that are as much as 100% higher than the results obtained with the one-stage clotting assay.

Clinical data support the use of the one-stage clotting assay for monitoring XYNTHA therapy.

When monitoring patients' factor VIII activity levels during treatment with XYNTHA, the one-stage clotting assay should be used. Most patients in clinical trials were monitored with the one-stage clotting assay. It is necessary to adhere to the incubation/activation times and other test conditions as specified by the assay manufacturers.

Precise monitoring of the replacement therapy by means of coagulation analysis (plasma factor VIII activity) is recommended, particularly for surgical intervention.

When switching between products it is important to individually titrate each patient's dose in order to ensure an adequate therapeutic response (see Section 4.4 Special warnings and precautions for use).

Dosing for bleeding and surgery

In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma levels (in % of normal or in IU/dL) in the corresponding period.

Type of Haemorrhage	*Factor VIII Level Required (%)*	*Frequency of Doses (h)/Duration of Therapy (d)*
Minor Early haemarthrosis, superficial muscle or soft tissue and oral bleeds	20-40	Repeat every 12 to 24 hours as necessary until resolved. At least 1 day, depending upon the severity of the haemorrhage.
Moderate Haemorrhages into muscles. Mild head trauma. Minor operations including tooth extraction. Haemorrhages into the oral cavity.	30-60	Repeat infusion every 12-24 hours for 3-4 days or until adequate wound healing. For tooth extraction a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient.
Major Gastrointestinal bleeding. Intracranial, intra abdominal or intrathoracic haemorrhages. Fractures. Major operations.	60-100	Repeat infusion every 8-24 hours until threat is resolved or in the case of surgery until adequate wound healing; then therapy for at least another 7 days.

Dosage for prophylaxis

For routine prophylaxis to prevent, or reduce the frequency of spontaneous musculoskeletal haemorrhage in patients with haemophilia A, doses of 10 to 50 IU of factor VIII per kg body weight should be given at least twice a week. XYNTHA has been administered prophylactically in a pivotal clinical trial in adolescent and adult previously treated patients at a dose of 30 ± 5 IU/kg given 3 times weekly. XYNTHA manufactured by the previous process has been evaluated in a prophylactic setting in paediatric patients. In some cases, especially paediatric patients, shorter dosage intervals or higher doses may be necessary.

Inhibitors

Patients using factor VIII replacement therapy should be monitored for the development of factor VIII inhibitors. In patients with inhibitors (especially high level inhibitors, above 5 Bethesda Units, BUs), factor VIII therapy may not be effective and other therapeutic options should be considered. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing should be performed to determine if a factor VIII inhibitor is present. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia (see Section 4.4 Special warnings and precautions for use).

Instructions for use

XYNTHA is for single use in one patient only. Discard any residue. Treatment with XYNTHA should be initiated under the supervision of a physician experienced in the treatment of haemophilia A. Patients should follow the specific reconstitution and administration procedures provided by their physicians and the *Instructions for Preparing and Giving an Injection of XYNTHA* supplied with the product.

XYNTHA is administered by intravenous (IV) infusion after reconstitution of the lyophilised powder for injection with the supplied diluent (9 mg/mL (0.9%) sodium chloride solution 4 mL). XYNTHA should be administered using the infusion set provided in the kit.

The reconstituted solution should be used immediately or within 3 hours.

XYNTHA should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level.

Reconstitution

Always wash your hands before performing the reconstitution and administration procedures. Aseptic technique should be used during the reconstitution procedure.

For the vial presentation, the lyophilised powder in the vial must be reconstituted with the solvent [sodium chloride 9 mg/ml (0.9%) solution] in the diluent syringe. The vial with the diluent syringe attached should be gently rotated until all of the powder is dissolved.

For the prefilled dual chamber syringes, the lyophilised powder in the top chamber of the syringe must be reconstituted with the solvent [sodium chloride 9 mg/ml (0.9%) solution] in the bottom chamber of the syringe. The syringe should be gently rotated until all of the powder is dissolved.

Refer to the *Instructions for Preparing and Giving an Injection of Xyntha* supplied with the product for reconstitution and administration procedures.

Note: If more than one vial/prefilled dual chamber syringe of XYNTHA per infusion is used, each vial/prefilled dual chamber syringe should be reconstituted as per the instructions. For the vial presentation, the diluent syringe should be removed, leaving the vial adapter in place, and a separate larger luer lock syringe may be used to draw back the reconstituted contents of each individual vial. Do not detach the diluent syringes or the large luer lock syringe until you are ready to attach the large luer lock syringe to the next vial adaptor. For the prefilled dual chamber syringes, a separate 10 mL or larger luer lock syringe (not included in the kit) may be used to draw back the reconstituted contents of each individual syringe.

The reconstituted solution should be used as soon as possible after reconstitution. If storage after reconstitution is necessary, hold at 2°C to 8°C and use within 3 hours.

XYNTHA, when reconstituted, contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from polyvinylchloride (PVC). This should be considered during preparation and administration of XYNTHA, including storage time elapsed in a PVC container following reconstitution. It is important that the recommendations in Section 4.2 Dose and method of administration be followed closely.

Method of administration (Intravenous Injection)

XYNTHA should be administered using the infusion set provided in the kit. The protective blue vented cap on the prefilled dual chamber syringe must be removed before attaching it to the infusion set.

1. Attach the syringe to the luer end of the infusion set.
2. Apply a tourniquet and prepare the injection site by wiping the skin well with an alcohol swab provided in the kit.
3. Insert the needle on the infusion set tubing into the vein and remove the tourniquet.
4. The reconstituted XYNTHA should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level.
5. After completion of XYNTHA treatment remove the infusion set and discard appropriately.

4.3 Contraindications

XYNTHA has not been studied in patients with a known history of hypersensitivity to hamster proteins. XYNTHA is contraindicated in patients with a known history of hypersensitivity to any of the constituents of the preparation and in patients with a known history of hypersensitivity to hamster proteins.

4.4 Special warnings and precautions for use

Use with caution in the following circumstances:

Activity-neutralising antibodies (inhibitors)

Activity neutralising antibodies (inhibitors) may develop in patients receiving coagulation factor VIII-containing products. As with all coagulation factor VIII products, patients should be monitored for the development of inhibitors that should be titrated in Bethesda Units (BU) using appropriate biological testing. If plasma factor VIII levels fail to reach expected levels, or if bleeding is not controlled after adequate dosage, appropriate laboratory tests to detect the presence of inhibitor should be performed (see Section 4.2 Dose and method of administration).

These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in BU using the Bethesda assay. The risk of developing inhibitors is correlated to the exposure to anti-haemophilic factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Inhibitors are common in previously untreated patients and have been observed in previously treated patients on factor VIII products (see Section 4.2 Dose and method of administration).

Less than expected therapeutic effect

Reports of less than expected therapeutic effect (without inhibitor development), both in the prophylaxis and on demand setting, have been received during clinical trials and in the post-marketing setting for XYNTHA. The reported less than expected therapeutic effect has been described as bleeding into target joints, bleeding into new joints or a subjective feeling by the patient of new onset bleeding

In a pivotal clinical trial, the incidence of less than expected therapeutic effect occurred at a rate of 0.4% (25/6404 prophylactic infusions) when XYNTHA was administered for prophylaxis and 0.5% (1/187 episodes) when administered for on-demand treatment.

When prescribing XYNTHA, it is important to individually titrate and monitor each patient's factor level in order to ensure an adequate therapeutic response (see Section 4.8 Adverse effects (undesirable effects) and Section 4.2 Dose and method of administration).

It is recommended that, whenever possible, every time XYNTHA is administered to patients, that the name and batch number of the product are documented. The peel-off label found on the vial/prefilled dual chamber syringe may be affixed in diaries to document the batch number or for reporting any side effects.

Hypersensitivity

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis (see Section 4.8 Adverse effects (undesirable effects)).

If allergic or anaphylactic reactions occur, administration of XYNTHA should be stopped immediately, and appropriate medical management should be given, which may include treatment for shock. Patients should be advised to discontinue the use of the product and contact their physician and/or seek immediate emergency care, depending on the type or severity of the reaction, if any of these symptoms occur. Patients experiencing allergic reactions should be evaluated for the presence of inhibitor.

As XYNTHA contains trace amounts of hamster protein (maximum of 30 ng/1000 IU), the remote possibility exists that patients treated with this product may develop hypersensitivity to this non-human mammalian protein.

Interchangeability with other factor VIII products

Due to differences in methods used by different manufacturers to assign potency of FVIII products, there is the potential for differences in protein content per IU when switching between products. Therefore when switching between products, consideration should be given to monitoring factor VIII replacement therapy by means of coagulation analysis (plasma factor VIII activity). Individual patients should also be monitored for their clinical responses with their respective factor VIII dosing titrated accordingly.

Usage while travelling

Based on their current regimen, individuals with haemophilia using XYNTHA should be advised to bring an adequate supply of XYNTHA for anticipated treatment when travelling. Patients should be advised to consult with their healthcare professional prior to travel.

Use in the elderly

No data available.

Paediatric use

XYNTHA is appropriate for use in adults and children of all ages, including newborns. In infants and children, shorter dosage intervals or higher doses may be necessary.

Safety of XYNTHA was studied in previously treated children and adolescents (n=18, age 12-16) in a pivotal study. Adverse event data from patients who were ≤ 16 years of age were compared with data from those >16 years of age. Eighteen (18) patients were ≤ 16 years of age and 76 were > 16 years of age. Extent of exposure was similar for patients in two of the groups. Treatment emergent adverse events were similar in severity and incidence in the two age groups. The safety and efficacy of XYNTHA has not been studied in subjects under the age of 12 years. There are no clinical data in previously untreated patients (PUPs) treated with XYNTHA.

XYNTHA may be used in the same manner as predecessor product ReFacto, because it is biochemically comparable to predecessor product ReFacto and has demonstrated similar pharmacokinetic characteristics with predecessor product ReFacto. Safety and efficacy of

predecessor product ReFacto has been studied both in previously treated children and adolescents (n = 31, ages 5-18) and in previously untreated neonates infants, and children (n = 10, ages <1-52 months).

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

No formal drug interaction studies have been conducted with XYNTHA. No interactions of recombinant coagulation factor VIII products with other medicinal products are known.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No studies have investigated the effect of XYNTHA on fertility.

Use in pregnancy – Pregnancy Category B2

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Animal reproduction studies have not been conducted with XYNTHA. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy is not available. It is not known whether factor VIII products can affect reproductive capacity or cause fetal harm when given to pregnant women. Therefore, factor VIII products should be administered to pregnant women only if clearly indicated.

Use in lactation

Animal reproduction studies have not been conducted with XYNTHA. It is not known whether this drug is excreted into human milk. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII products during breastfeeding is not available. Therefore, XYNTHA should be administered to breastfeeding women only if clearly indicated.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and to use machines have been performed. However, there are no indications that XYNTHA may impair the ability to drive or operate machines.

4.8 Adverse effects (undesirable effects)

Safety data for XYNTHA are derived from the all-causality treatment-emergent adverse events (TEAEs) observed in the pooled dataset of 8 completed clinical studies with XYNTHA

and 2 completed clinical studies with its predecessor product, ReFacto. The pooled dataset comprised a total of 765 patients, including 124 previously untreated patients (PUPs) and 641 previously treated patients (PTPs).

Adverse effects are presented in the table below by system organ class (SOC) and frequency of occurrence per patient. These frequencies have been estimated on a per-patient basis across the completed studies based on a denominator of 765 patients. The incidence of the AE Factor VIII inhibition is presented separately for PTPs and PUPs.

Table 1: Adverse effects by SOC and frequency of occurrence per patient

System Organ Class	**Very Common (≥10%)**	**Common (≥1% and <10%)**	**Uncommon (≥0.1% and <1%)**	**Very rare (<0.01%)**
Immune system disorders			Anaphylactic reaction	
Metabolism and nutrition disorders		Decreased appetite		
Nervous system disorders	Headache	Dizziness	Neuropathy peripheral; somnolence; dysgeusia	
Vascular disorders		Haemorrhage; haematoma	Hypotension; thrombophlebitis; flushing	
Cardiac disorders			Angina pectoris, tachycardia, palpitations	
Respiratory, thoracic and mediastinal disorders	Cough		Dyspnoea	
Gastrointestinal disorders		Diarrhoea; vomiting; abdominal pain; nausea		
Skin and subcutaneous tissue disorders		Urticaria; rash; pruritus	Hyperhidrosis	
Musculoskeletal and connective tissue disorders	Arthralgia	Myalgia		Muscle weakness^

General disorders and administration site conditions	Pyrexia	Chills; catheter site related reaction	Asthenia, injection site reaction, injection site pain, injection site inflammation	Feeling cold^
Investigations		Antibody test positive; anti-factor VIII antibody positive; human anti-mouse antibody positive[§]; liver function test abnormal	Blood creatinine phosphokinase increased	
Eye disorders				Blurred vision^
Blood and lymphatic system disorders	Factor VIII inhibition (PUPs)†	Factor VIII inhibition (PTPs)†		

Abbreviations: PTPs=previously treated patients; PUPs=previously untreated patients.
(^) Frequencies of these adverse effects are estimated from a "per-infusion" denominator of 149,692 infusions.
(§) Adverse reaction reported for predecessor product ReFacto only.
(†) See Factor VIII inhibitors section below.

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, hives, generalised urticaria, headache, tightness of the chest, tingling, vomiting, wheezing, hypotension, lethargy, nausea, restlessness, tachycardia) have been observed infrequently, and may in some cases progress to severe anaphylaxis (including shock) (see Section 4.4 Special warnings and precautions for use). Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly and appropriate counter measures and supportive therapy should be administered.

Factor VIII inhibitors

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII (See Section 4.4 Special warnings and precautions for use and Section 4.2 Dose and method of administration). If such inhibitors occur, the condition may manifest itself as an insufficient clinical response or an unexpectedly low yield of plasma factor VIII activity. In such cases, it is recommended that a specialised haemophilia centre be contacted.

In a pivotal Phase 3 study, where the incidence of factor VIII inhibitors was the primary safety endpoint, previously treated patients (PTPs) with haemophilia A received XYNTHA for routine prophylaxis and on-demand treatment. Of the 89 subjects who received ≥50 ED, two were reported with inhibitors. These results were consistent with the pre-specified value that no more than 2 patients with inhibitors may be observed in at least 81 subjects. In a Bayesian

statistical analysis, results from this study were used to update PTP results from a prior supporting study of XYNTHA manufactured at a pilot facility, where one de novo and two recurrent inhibitor cases were observed in 110 subjects, and the experience with the predecessor product (ReFacto) manufactured by the previous process (1 inhibitor case in 113 subjects). This Bayesian analysis indicates that the population (true) inhibitor rate for XYNTHA, the estimate of the 95% upper limit of the true inhibitor rate, was 4.2%, vs a deemed acceptable limit of 4.4%.

In a pivotal phase 3 study for surgical prophylaxis in patients with haemophilia A, one low titre persistent inhibitor and one transient false-positive inhibitor were reported.

In a clinical study in paediatric (6 months to <16 years) PTPs (≥20 ED) with haemophilia A (FVIII:C ≤2%), 1 low-titre, clinically silent inhibitor was observed in 49 patients at risk in the study for developing an inhibitor.

If any reaction takes place that is thought to be related to the administration of XYNTHA, the rate of infusion should be decreased or the infusion stopped, as dictated by the response of the patient.

There have been spontaneous post-marketing reports of high titre inhibitors developing in previously treated patients.

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

No symptoms of overdose have been reported with recombinant coagulation factor VIII products.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

XYNTHA is a recombinant DNA-based substance, which has functional characteristics comparable to those of endogenous factor VIII. Activated factor VIII acts as a cofactor for activated factor IX accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed. Factor VIII activity is greatly reduced in patients with haemophilia A. Administration of XYNTHA increases plasma levels of factor VIII activity and can temporarily correct the coagulation defect in these patients.

Clinical trials

In a pivotal phase 3 study, the efficacy of XYNTHA was evaluated in routine prophylaxis and on-demand treatment. Prophylaxis was to be initiated at a dose of 30 IU/kg given 3 times per week. The on-demand treatment dosing regimen was to be determined by the investigator. Ninety-four (94) PTPs with moderately severe or severe haemophilia A (FVIII:C ≤ 2%) received at least 1 dose of XYNTHA and were included in the intent-to-treat (ITT) population. Eighty-nine (89) patients accrued at least 50 exposure days (EDs) to XYNTHA in the study.

Of the 94 patients in the ITT population, 30 patients with FVIII:C ≤ 1% also participated in the double-blind, randomised, crossover PK period of the study and were included in the per-protocol population for analyses of bioequivalence versus another rFVIII product, Advate®, and full pharmacokinetic characterisation. Both endpoints were surrogate markers for clinical efficacy. The results of these analyses show that XYNTHA is bioequivalent to Advate® (using the one stage assay to measure factor VIII levels) and the pharmacokinetic profile of XYNTHA remained stable after 6 months of repeated use.

Intent-to-treat analysis of clinical efficacy variables in the open-label safety and efficacy period yielded similarly positive outcomes. All 94 patients received XYNTHA for routine prophylaxis; the median dose administered was 30.2 IU/kg (range 6.8 to 76.9 IU/kg). Most patients (57/94; 60.6%) reported no spontaneous bleeding while on routine prophylaxis. The median annualised bleeding rate (ABR) for all bleeding episodes was 1.9 (mean 3.9, range 0 to 42.1), indicating effective prevention of bleeding in the study population. Fifty-three (53) of 94 patients received XYNTHA for on-demand treatment; the median dose administered was 30.6 IU/kg (range, 6.4 to 74.4 IU/kg). The majority of bleeding episodes (173/187; 92.5%) resolved with 1 or 2 infusions. This outcome was not restricted to any particular bleeding location as similar efficacy was seen in bleeding occurring in joints, soft tissues/muscles, and other sites. A wide range of doses was used to initiate treatment of bleeding; however, the distribution of doses used to initiate treatment of bleeding was similar regardless of location of bleeding. Patients rated the majority of infusions used to initiate treatment of bleeding as either excellent or good (132 of 187; 70.6%). The incidence of less than expected therapeutic effect (LETE) occurred at a rate of 0.4% (25/6404 prophylactic infusions) when XYNTHA was administered for prophylaxis and 0.5% (1/187 episodes) when administered for on-demand treatment.

A pivotal phase 3 study for surgical prophylaxis in patients with haemophilia A included PTPs with severe or moderately severe (FVIII:C ≤ 2%) haemophilia A undergoing major surgical procedures who received XYNTHA. Thirty (30) patients were treated with XYNTHA and comprised the ITT population; 29 patients underwent major surgery and completed the study. Thirty (30) subjects were assigned to receive XYNTHA by bolus injection (BI; 22 patients) or by continuous infusion (CI; 8 patients) at the physician's discretion to support surgical haemostasis followed by inpatient and outpatient postoperative care. One subject assigned to CI received XYNTHA for a pre-surgery pharmacokinetic assessment only and subsequently elected not to undergo surgery. The 22 patients treated by BI received a total of 942 infusions (ranging from 16 to 72 infusions per patient) for a cumulative total dose of 2,037,386 IU of XYNTHA over 682 cumulative total exposure days (EDs) (ranging from 15 to 40 EDs per patient). The 8 patients assigned to treatment by CI, including one patient who received only 1 dose for pK assessment, received a total dose of 529,977 IU of XYNTHA over 204 EDs (range =1 to 37 EDs per patient).

Of the 29 patients who underwent surgery, 25 were included in the efficacy evaluable population, with 20 treated by BI and 5 treated by CI. Major surgical procedures for the 25 efficacy evaluable subjects were 11 total knee replacements, 1 hip replacement, 5 synovectomies, 1 left ulnar nerve transposition release, 1 ventral hernia repair/scar revision, 1 knee arthroscopy, 1 revision and debridement of the knee after a total knee replacement, 1 hip arthroplasty revision, 1 stapes replacement, 1 ankle arthrodesis, and 1 pseudotumor excision. For the 25 surgical subjects, investigator's ratings of the efficacy at the end of surgery and at the end of the initial postoperative period were excellent or good for all assessments, intraoperative blood loss was reported as normal or absent for all procedures. Thirteen of the 25 evaluable patients had blood loss in the postoperative period, and in 10 cases the postoperative blood loss was rated normal. In 3 cases the postoperative blood loss was rated abnormal: 1 due to haemorrhage following surgical trauma to the epigastric artery, 1 due to an 800 mL blood loss after hip replacement surgery, and 1 after an elbow synovectomy where the blood loss could not be measured by the investigator.

5.2 Pharmacokinetic properties

In a pivotal cross-over clinical study, the pharmacokinetics of XYNTHA was compared to another recombinant factor VIII product (rFVIII, Advate®*) in 30 previously treated patients (≥ 12 years) following a single infusion of 50 IU/kg. The 90% confidence intervals for the mean $AUC_{0-\infty}$ ratio of XYNTHA to Advate® was shown to be within the bioequivalence range of 80-125% using the one stage assay to measure factor VIII levels.

In a 6-month follow-up assessment in 25 patients, the pharmacokinetic profile of XYNTHA was comparable between baseline and month 6 (see Table 2). The 90% confidence intervals for the 6 month-to-baseline ratios of mean recovery and $AUC_{0-\infty}$ were both within the equivalence range of 80-125%, suggesting negligible time dependent changes in the pharmacokinetic properties of XYNTHA.

Table 2: Pharmacokinetic Parameter Estimates at Baseline and Month 6 in Previously Treated Patients with Haemophilia A.

Visit	**C_{max}** (IU/mL)	**$AUC_{0-\infty}$** (IU·hr/mL)	**T½** (hr)	**CL** (mL/hr/kg)	**Vss** (mL/kg)	**Recovery** (IU/dL per IU/kg)
Baseline						
Mean ± SD	1.12 ± 0.19	14.2 ± 5.5	11.8 ± 5.1	4.21 ± 2.08	65.1 ± 35.1	2.23 ± 0.39
(Min, Max)	(0.59, 1.41)	(4.7, 25.0)	(6.4; 33.9)	(2.0; 10.6)	(34.8; 195.1)	(1.19, 2.83)
Month 6						
Mean ± SD	1.24 ± 0.42	15.0 ± 7.5	11.8 ± 6.2[a]	4.04 ± 1.87	67.4 ± 32.6	2.47 ± 0.84
(Min, Max)	(0.65, 2.60)	(5.3, 42.0)	(5.8; 75.7)	(1.19; 9.45)	(18.5; 168.8)	(1.29, 5.20)

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity;
C_{max} = peak concentration; CL= clearance; Vss=Steady date volume of distribution; SD = standard deviation; [a] One subject was excluded from the calculation due to lack of a well-defined terminal phase.

In a pivotal phase 3 study for surgical prophylaxis, XYNTHA pharmacokinetics were evaluated during the perioperative management of patients with haemophilia A who were undergoing major surgery. At the baseline visit, all patients received a single dose of XYNTHA of approximately 50 IU/kg. Plasma samples were analyzed for FVIII activity using a validated one-stage (OS) clotting method. Recovery data are available for a total of 30 patients; the mean (± standard deviation [SD]) was 2.11 (± 0.43) IU/dL per IU/kg.

In previously untreated patients (PUPs), pharmacokinetic parameters of XYNTHA manufactured by a previous process were evaluated using the chromogenic assay. These

patients (n=59; median age 10 ± 8.3 months) had a mean recovery at Week 0 of 1.5 ± 0.6 IU/dL per IU/kg (range 0.2 to 2.8 IU/dL per IU/kg) which was lower than that obtained in PTPs at Week 0 with a mean value of 2.4 ± 0.4 IU/dL per IU/kg (range 1.1 to 3.8 IU/dL per IU/kg). In the PUPs, the mean recovery was stable over time (5 visits during a 2 year period) and ranged from 1.5 to 1.8 IU/dL per IU/kg. Population pharmacokinetic modeling using data from 44 PUPs led to a mean estimated half-life of 8.0 ± 2.2 hours.

5.3 Preclinical safety data

Genotoxicity

ReFacto, manufactured by the process previous to XYNTHA, showed no genotoxic properties in a mouse micronucleus assay. No other genotoxicity studies have been conducted.

Carcinogenicity

No carcinogenicity studies have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sucrose, histidine, calcium chloride dihydrate, and polysorbate 80.

6.2 Incompatibilities

Because the use of XYNTHA by continuous infusion has not been evaluated, XYNTHA should not be mixed with infusion solutions. In the absence of incompatibility studies, reconstituted XYNTHA should not be administered in the same tubing or container with other medicinal products. Treatment failure can occur as a consequence of human coagulation factor VIII adsorption to the internal surfaces of some infusion equipment. Infusion kit components supplied in the carton are compatible with XYNTHA for administration.

6.3 Shelf life

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

6.4 Special precautions for storage

Store and transport refrigerated at 2°C to 8°C. Do not freeze, in order to prevent damage to the vial/prefilled dual chamber syringe.

XYNTHA does not contain a preservative. To reduce the possibility of microbiological hazard from environmental contamination, the reconstituted solution should be used as soon as possible after reconstitution. If storage after reconstitution is necessary, hold at 2°C to 8°C and use within 3 hours.

XYNTHA may be removed from refrigerated storage and stored at room temperature (below 25°C) for one single period of maximum 3 months. After room temperature storage, XYNTHA may be returned to refrigerated storage until the expiration date. Do not store XYNTHA at room temperature and return it to refrigerated storage more than once.

During storage, avoid prolonged exposure of XYNTHA to light. Do not use XYNTHA after the expiry date on the label.

6.5 Nature and contents of container

XYNTHA lyophilised powder for reconstitution is supplied in strengths of 250 IU, 500 IU, 1000 IU and 2000 IU in a glass vial, with a butyl rubber stopper and flip off seal. The glass pre-filled diluent syringe containing 4 mL sodium chloride solution (9 mg/mL) has a butyl rubber plunger stopper and butyl rubber tip-cap.

The administration set provided with each vial of XYNTHA comprises: 1 vial adapter, 2 alcohol swabs, 1 sterile infusion set, sticking plaster and gauze.

XYNTHA is also supplied in a prefilled dual chamber syringe containing 250 IU, 500 IU, 1000 IU, 2000 IU or 3000 IU of XYNTHA lyophilised powder for reconstitution in one chamber and 4 mL sodium chloride solution (9 mg/mL) in the second chamber.

Each prefilled dual chamber syringe is supplied with a vented cap that is attached to the tip of the syringe prior to reconstitution, a plunger rod, 2 alcohol swabs, a sterile infusion set, sticking plaster and gauze.

Not all presentations may be marketed.

6.6 Special precautions for disposal

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

6.7 Physicochemical properties

XYNTHA contains moroctocog alfa (rch) (cho), also known as recombinant coagulation factor VIII. Moroctocog alfa rch is a purified protein produced by recombinant DNA technology for use in therapy of factor VIII deficiency (haemophilia A or classic haemophilia). XYNTHA is a purified glycoprotein with an approximate molecular mass of 170 kDa, consisting of 1438 amino acids, which does not contain the non-functional B-domain. The amino acid sequence of moroctocog alfa is comparable to the 90 + 80 kDa form of factor VIII. (The post-translational modifications and *in vitro* functional characteristics of moroctocog alfa are comparable to those of endogenous factor VIII).

Morocotocog alfa is secreted by a genetically engineered Chinese hamster ovary (CHO) cell line. The CHO cell line has been extensively studied and found to be free of detectable viruses. The cell line is grown in a chemically defined cell culture medium that does not contain any materials derived from human or animal sources. The purification process has been refined to affinity purify moroctocog alfa using a column chromatography method that employs chemically synthesised affinity ligand, replacing the murine monoclonal antibody Sepharose

resin and eliminating a potential risk of viral contamination associated with murine monoclonal antibody and its manufacture.

Because XYNTHA is not purified from human blood and is manufactured from a well-characterised cell line in the absence of human- or animal-derived materials, it minimises the risk of transmission of human blood-borne pathogens, such as human immunodeficiency virus (HIV), hepatitis viruses and parvovirus. The viral safety profile is further enhanced by the inclusion of a solvent-detergent viral inactivation step and a virus-retaining nanofiltration step during purification.

The protein is purified by a chromatography purification process that yields a high-purity, active product. The potency expressed in International Units (IU) is determined using the chromogenic assay of the European Pharmacopoeia. The Wyeth manufacturing reference standard for potency has been calibrated against the World Health Organisation (WHO) International Standard for factor VIII activity using the one-stage clotting assay. The specific activity of XYNTHA is 5500 to 9900 IU per mg protein.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Not scheduled.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

26 June 2009

10. DATE OF REVISION

16 January 2023

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Summary Table of Changes

Section changed	Summary of new information
4.8	Addition of a summary of the studies from which the safety data for XYNTHA are derived. Reporting of AEs changed from "per-infusion" to "per-patient" frequencies, with footnotes. Frequency of occurrence of 'pyrexia' updated based on study data. Inclusion of information pertaining to FVIII inhibitor development based on the results from a clinical study in paediatric PTPs. Editorial changes.
5.2	Editorial changes. References to 'K-value/incremental recovery' and '*in vivo* recovery' removed.
6.1	Excipient name changed to AAN.