NEW ZEALAND DATA SHEET

1. PRODUCT NAME

XYNTHA 250 IU powder and solvent for solution for injection.
XYNTHA 500 IU powder and solvent for solution for injection.
XYNTHA 1000 IU powder and solvent for solution for injection.
XYNTHA 2000 IU powder and solvent for solution for injection.
XYNTHA 250 IU powder and solvent for solution for injection in prefilled syringe.
XYNTHA 500 IU powder and solvent for solution for injection in prefilled syringe.
XYNTHA 1000 IU powder and solvent for solution for injection in prefilled syringe.
XYNTHA 2000 IU powder and solvent for solution for injection in prefilled syringe.
XYNTHA 3000 IU powder and solvent for solution for injection in prefilled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial/prefilled syringe of XYNTHA 250 IU contains nominally 250 IU* of moroctocog alfa (recombinant coagulation factor VIII)**. After reconstitution with the accompanying 4 mL sodium chloride solution for injection (9 mg/mL (0.9%)), each mL of the solution contains approximately 62.5 IU moroctocog alfa.

Each vial/prefilled syringe of XYNTHA 500 IU contains nominally 500 IU* of moroctocog alfa (recombinant coagulation factor VIII)**. After reconstitution with the accompanying 4 mL sodium chloride solution for injection (9 mg/mL (0.9%)), each mL of the solution contains approximately 125 IU moroctocog alfa.

Each vial/prefilled syringe of XYNTHA 1000 IU contains nominally 1000 IU* of moroctocog alfa (recombinant coagulation factor VIII)**. After reconstitution with the accompanying 4 mL sodium chloride solution for injection (9 mg/mL (0.9%)), each mL of the solution contains approximately 250 IU moroctocog alfa.

Each vial/prefilled syringe of XYNTHA 2000 IU contains nominally 2000 IU* of moroctocog alfa (recombinant coagulation factor VIII)**. After reconstitution with the accompanying 4 mL sodium chloride solution for injection (9 mg/mL (0.9%)), each mL of the solution contains approximately 500 IU moroctocog alfa.

Each prefilled syringe of XYNTHA 3000 IU contains nominally 3000 IU* of moroctocog alfa (recombinant coagulation factor VIII)8*. After reconstitution with the accompanying 4 mL sodium chloride solution for injection (9 mg/mL (0.9%)), each mL of the solution contains approximately 750 IU moroctocog alfa.

* 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.

** Human coagulation factor VIII produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.

Excipients with known effect:

- After reconstitution, 1.23 mmol (29 mg) sodium per vial or prefilled syringe.

- Sucrose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

XYNTHA is formulated as a sterile, non-pyrogenic, lyophilised white to off-white cake/powder and clear, colourless solvent.

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 IUs, 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).

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).

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.

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

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 (BUs) 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).

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).

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. 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 4.2 and section 4.8).

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 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).

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.

Paediatric population

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).

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.

4.5 Interaction with other medicines and other forms of interaction

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

Pregnancy

Pregnancy category B2.

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.

Breastfeeding

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.

Fertility

No studies have investigated the effect of XYNTHA on fertility.

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 Undesirable effects

Adverse effects based on experience from clinical trials with predecessor product ReFacto and XYNTHA are presented below by system organ class and frequency of occurrence per infusion using the following convention: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%). Within each frequency grouping, adverse effects are presented in order of decreasing seriousness. These frequencies have been estimated on a per-infusion basis.

System Organ Class AE Frequency per infusion	Adverse Effect(s)
Immune system disorders	
Very rare	Anaphylactic reaction
Metabolism and nutrition disorders	
Very rare	Decreased appetite
Nervous system disorders	
Uncommon	Headache
Rare	Dizziness
Very rare	Dysgeusia, neuropathy peripheral[#], somnolence
Vascular disorders	
Rare	Haemorrhage, haematoma
Very rare	Hypotension, thrombophlebitis[#], flushing[#]
Cardiac disorders	
Very rare	Angina pectoris, tachycardia, palpitations[#]
Respiratory, thoracic and mediastinal disorders	
Rare	Cough
Very rare	Dyspnoea
Gastrointestinal disorders	
Rare	Diarrhoea, vomiting[#], abdominal pain, nausea
Skin and subcutaneous tissue disorders	
Rare	Rash, pruritis
Very rare	Urticaria, hyperhidrosis
Musculoskeletal and connective tissue disorders	
Rare	Arthralgia
Very rare	Myalgia, muscle weakness
General disorders and administration site conditions	
Rare	Catheter site related reaction, pyrexia, chills
Very rare	Asthenia, injection site reaction, injection site pain, injection site inflammation[#], feeling cold

Investigations

Rare	Anti-factor VIII antibody positive, antibody test positive, human anti-mouse antibody positive[§]
Very rare	Liver function test abnormal, blood creatine phosphokinase increased.

Eye disorders

Very rare	Blurred vision

Blood and lymphatic system disorders

Very common	Factor VIII inhibition (PUPs)[†]
Common	Factor VIII inhibition (PTPs)[†]

Adverse reaction frequencies are calculated on an event per infusion basis. For surgical patients receiving continuous infusion (CI), any day CI was administered is considered as one infusion.
([#]) These adverse reactions were totalled from adverse events and haemophilia events across all studies regardless of relatedness to study drug. All other adverse reactions were totalled across all studies from study drug-related adverse events and haemophilia events ONLY.
(§) Adverse reaction reported for predecessor product ReFacto only.
(†) Frequency for the adverse reaction Factor VIII inhibition (PUPs and PTPs) is estimated from a "per patient denominator". See Factor VIII inhibitors section below.

Most adverse reactions reported were considered mild or moderate in severity.

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).

Factor VIII inhibitors

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII (See section 4.2 and section 4.4). 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.

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 of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antihaemorrhagic Blood Coagulation Factor VIII, ATC code B02BD02.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). Moroctocog alfa 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 moroctocog alfa 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.

Mechanism of action

Moroctocog alfa 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 efficacy and safety

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. 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 1). The 90% confidence intervals for the 6 month-to-baseline ratios of mean K-value 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 1: Pharmacokinetic Parameter Estimates for XYNTHA 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)	**K-value** (IU/dL per IU/kg)	**Recovery** (%)
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	105 ± 19
(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)	(53.4, 132)
Month 6							
Mean ± SD	1.24 ± 0.42	15.0 ± 7.5	11.8 ± 6.2*	4.04 ± 1.87	67.4 ± 32.6	2.47 ± 0.84	116 ± 40
(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)	(59.3, 256)

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; K-value = incremental recovery; SD = standard deviation;
*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]) K-value was 2.11 (± 0.43) IU/dL per IU/kg, and the mean (±SD) *in vivo* recovery value was 101.0% (± 20%).

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 incremental 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 K-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 incremental 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

No carcinogenicity studies have been conducted.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for injection:
Calcium chloride dihydrate
Histidine
Polysorbate 80
Sodium chloride
Sucrose

Solvent:
Sodium chloride
Water for injection

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

36 months

The reconstituted solution should be used as soon as possible after reconstitution or within 3 hours after reconstitution (see section 6.4).

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 syringe.

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.

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.

6.5 Nature and contents of container and special equipment for administration

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 and other handling

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.

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* provided with the product for reconstitution and administration procedures.

Note: If more than one vial/prefilled syringe of XYNTHA per infusion is used, each vial/prefilled 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 large 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 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.

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 6.4 be followed closely.

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.

7. MEDICINE SCHEDULE

General sale

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

23 November 2000

10. DATE OF REVISION OF THE TEXT

22 January 2019

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Summary table of changes

Section changed	Summary of new / updated information
All	Re-formatting of Data Sheet to SPC format