Unit: Technical Assessment Unit

Public assessment report for biological products

Fabrazyme

Administrative information:

Trade name of the medicinal product:	Fabrazyme
INN (or common name) of the active substance(s):	Agalsidase beta
Manufacturer of the finished product	Genzyme Ireland Limited, IDA Industrial Park Old Kilmeaden Road, Waterford-Ireland
Marketing Authorization holder	Sanofi BV.,Paasheuvelweg 25, 1105 BP Amsterdam, The Netherlands
Applied Indication(s):	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency). Fabrazyme is indicated in adults, children and adolescents aged 8 years and older
Pharmaceutical form(s) and strength(s):	Powder for concentrate for solution for infusion (35 mg/vial)
Route of administration	I.V infusion
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

CHO: Chinese Hamster Ovary
eGFR: estimated glomerular filtration rate
Fz: Fabrazyme
Fz-ICB: Fabrazyme-ICB, manufactured by the new process, integrated continuous biomanufacturing
GL-3: globotriaosylceramide
IARs: Infusion-associated reactions
IgG: Immunoglobulin G
IV: Intravenous
M6P: Mannose-6-phosphate
r-hαGAL: recombinant human α-galactosidase
SD: Sprague Dawley

Table of contents

1. **General introduction about the product including brief description of the AI, its mode of action and indications.**

Agalsidase beta is a recombinant human α-galactosidase an enzyme with the same amino acid sequence as the native enzyme. Purified agalsidase beta is a homodimeric glycoprotein with molecular weight approximately 100 kD. The mature protein is composed of 2 subunits of 398 amino acids (approximately 51 kD), each of which contains 3 N-linked glycosylation sites.

Fabrazyme is intended to provide an exogenous source of α-galactosidase A to patients with Fabry disease. During the life cycle of Fabrazyme, the manufacturing process was changed to animal derived component-free (ADC-free) integrated continuous biomanufacturing (henceforth referred to as Fabrazyme-ICB [Fz-ICB]) in a chemically defined medium based on ICH Q5E bio comparability guidelines.

2. **<u>Quality aspects:</u>**

2.2.1 Introduction

As mentioned in the aforementioned section.

2.2.2 Drug Substance (Active ingredient)

- **General information**

- International non-proprietary Name (INN): Agalsidase beta
- It is a recombinant human α-galactosidase; Abbreviated as rhαGAL
- The molecular formula of r-hαGAL is C2029H3080N544O587S27
- Details regarding the structure, the physicochemical and biological properties are provided in the MA file.

- **Manufacture, process controls and characterization:**

➢ **Manufacturer**

Genzyme Corporation 8, 45, 68, 74, 80 New York Avenue Framingham, MA 01701 USA

➢ **Description of Manufacturing Process and Process Controls**

- Flow charts describing the manufacturing process steps are provided.
- Effective microbial control is achieved throughout the manufacturing process by implementing an overall strategy to prevent product and/or facility contamination.

➢ **Control of Materials**

- Compendial raw materials are sourced from approved vendors. Water for injection (WFI) used throughout the agalsidase-beta drug substance manufacturing process is manufactured and tested to ensure conformance with USP-NF, European Pharmacopeia (Ph. Eur.), British Pharmacopeia (BP) and Japanese Pharmacopeia (JP)

requirements.
- All non-compendial materials are subjected to the same quality control systems as the compendial materials. Specifically, the non-compendial materials are procured from approved vendors per Sanofi internal material specifications. All COAs of non-compendial raw material are provided.

➢ **Controls of Critical Steps and Intermediates**
- A formal risk assessment (FMEA) was performed to determine the criticality of process parameters, Process parameters assessed as potentially critical to product quality (CPP) or impactful to process consistency (KPP) were evaluated experimentally to establish Proven Acceptable Ranges.
- In-process controls, Acceptance Criteria and Action Limits and Justification of Action Limits are provided in file.
- Hold times at defined temperatures have been established for commercial-scale process intermediates held in small containers constructed of the same product-contact materials.

➢ **Process Validation**

Each PPQ module included acceptance criteria for each CPP, KPP and IPC defined for each corresponding unit operation, as described in file. Any result outside of the defined acceptance criteria was assessed for root cause and impact to the PPQ. Results for each of the PPQ modules are provided in file.

➢ **Manufacturing Process Development**

Range-finding studies and optimization studies were conducted on both upstream and downstream unit operations to establish a baseline Fz-ICB process with acceptable productivity and product quality. These studies and their conclusions are described in file and ultimately led to a process that was ready for characterization and control strategy development.

- **Characterization**

- Biochemical and biophysical results highlighting the structural, functional and quality attributes of agalsidase beta produced using the ICB process and how those attributes compare to those of Fz1G are described in file.
- Impurities that are present or potentially present in the Fz-ICB drug substance (DS) manufactured using the proposed commercial manufacturing process have been evaluated.

- **Specification**

The specifications for agalsidase beta drug substance are provided in the MA file.

- **Reference Standards or Materials**

Data regarding the Fz-ICB Primary Standard and the Fz-ICB Working Standard and their qualification is provided in the MA file.

- **Container closure system**

- Pre-gamma-sterilized polyethylene bags (Hyclone CX5-14) will be used to ship the drug substance to the fill/finish site. Shipping validation studies were performed using these bags, with the results detailed within Process Validation section of Waterford.
- A container integrity study demonstrated that throughout the transport process, there was no leakage and the polyethylene bags are an effective barrier against microbial ingress.

- **Stability of drug substance**

Based on available stability data:
Approved Shelf Life: 4 months
Approved Storage Conditions: 2°C to 10°C

2.2.3 Drug product:

- **Description and Composition of the Drug Product**

- Fabrazyme® (agalsidase beta) is a sterile lyophilized dosage form packaged in a container closure system consisting of a 20cc or 5cc Type I glass tubing vial, siliconized 20 mm gray butyl lyophilization stopper and a 20 mm aluminum seal with a plastic flip-off cap.
- The nominal content of the 20cc vial is 35 mg of the active substance agalsidase beta.
- Fabrazyme® is administered by I.V. infusion. This route of administration requires that the reconstituted solution be further diluted with 0.9% Sodium Chloride Injection, USP or equivalent diluent.

- **Pharmaceutical Development**

➢ **Components of drug product**

- Active Ingredient: Agalsidase beta
- Excipients: Mannitol, sodium phosphate monobasic monohydrate, dibasic heptahydrate and nitrogen

➢ **Physicochemical and Biological Properties**

A series of preformulation experiments were carried out to determine the effect of buffer species, pH and excipients on the stabilization of r-h□GAL.

- **Manufacturing Process Development**

The route of administration for Fabrazyme® is by I.V. infusion. The I.V. route of administration allows the most direct delivery of agalsidase beta to the target cells. A lyophilized dosage form was chosen to maximize the shelf life.

- **Container closure system and their compatibility**

- Agalsidase beta Formulated Drug Substance is aseptically processed and sterilized by filtration through a 0.22 µm filter. In order to retain the sterility of the product, it is filled into previously depyrogenated final containers, stoppered and sealed.
- Container closure validation has been conducted with bacteriological challenge and sterility testing to ensure integrity of the container closure system.

- **Microbiological Attributes**

- Fabrazyme is aseptically manufactured and sterilized by final filtration through tandem 0.22 µm filters. Sterility assurance is provided through rigorous manufacturing controls such as active environmental and personnel monitoring, validated component preparation procedures, and sterility testing in accordance with compendial standards, which is performed as a release test on every batch of Fabrazyme.
- Fabrazyme is not compounded with a preservative and therefore each vial of Drug Product is intended for single use only.

- **Compatibility**

- The adsorption and stability characteristics of agalsidase beta during clinical administration are discussed in file.
- Compatibility testing "studies" with excipients, diluents and container closure system full described in MA file.

- **Manufacture of the drug product:**
  Description of manufacturing process and process controls along with manufacturers and responsibilities
- **Manufacturer(s):**

Genzyme Ireland Limited
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

- The first steps Pooling, Sterile Filtration, Filling and Lyophilization are typically completed within 24 hours (prior to the start of lyophilization cycle). Upon exit from the lyophilizer, stoppered vials are transferred to the Capping step and are sealed. The subsequent steps Inspection, Labeling and Packaging are typically done step wise.

- **Product specification:**
  - Appropriate specifications have been established for Fabrazyme drug product in accordance with the ICH Q6B guidelines.
  - Full detailed SOPs for all tests in specification sheet are provided in file.
  - These analytical procedures have been fully validated demonstrating that the methods are suitable for their intended purpose.

- **Reference Standards or Materials**
  - The primary reference standard is taken from a representative Drug Substance production lot. The material chosen is produced using the commercial-scale Drug Substance process.
  - Information on the reference standard is provided in the MA file.

- **Container closure system**
  - The Drug Product manufacturing facility uses suppliers who can provide container closure components compliant with both USP/Ph. Eur. monographs. These components are accepted by an identity test and the supplier′s certificates of analysis**.**
  - Validation of container closure integrity is described in the MA file.

- **Stability of the drug product**
  Based on available stability data:
  Approved shelf life: 36 months
  Approved Storage Conditions: 2-8°C

3. Non –clinical aspect:

➢ Fabrazyme is a recombinant human α-galactosidase (r-hαGAL) which is produced by genetically engineered Chinese Hamster Ovary (CHO) cells. Recombinant hαGAL is a highly purified recombinant form of the naturally occurring human lysosomal hydrolase enzyme responsible for the metabolism of ceramide trihexoside.

➢ Fabrazyme restores a level of enzymatic activity sufficient to hydrolyze the accumulated substrate. After administration, agalsidase beta is rapidly removed from the circulation and taken up by vascular endothelial and parenchymal cells into lysosomes, likely through the mannose-6-phosphate, mannose and asialoglycoprotein receptors.

➢ **Pharmacology & pharmacokinetics:**

➢ The applicant developed an animal model for Fabry disease, the αGAL SV129 Knock-out Mouse, to investigate the action and effect of r-hαGAL. These mice have a considerable accumulation of globotriaosylceramide (GL-3) in the liver, skin, spleen, heart and kidneys. After treatment with a single low dose of agalsidase beta, the concentration of GL-3 was

significantly reduced in liver, heart, spleen and plasma. Furthermore, multiple doses of 0.03 to 3.0 mg/kg provided significant progressive reduction of GL-3 in liver, heart, spleen, skin and kidney (98%, 99%, 83%, 77% and 24% respectively). Agalsidase beta reduced accumulation of GL-3 in a dose and time dependent manner. The reduction was maintained for several weeks post administration.

- After intravenous injection in mice and rats, r-hαGAL is rapidly cleared from the circulation uptake with distribution predominantly to the liver and to a lesser extent to the spleen and kidneys. Little or no r-hαGAL activity is recovered from the brain, heart, or lung. In rats and dogs clearance is rapid and serum half-lives are short. Elimination of r-hαGAL from serum in rats and dogs followed first order kinetics at lower doses. At higher doses, elimination was biphasic with a relatively slow initial phase and a faster terminal phase.
- After repeat dosing for 27 weeks in rats, post-dose serum concentrations were 2 fold higher in week 26 compared to post-dose samples on Day 1. In addition, following 27 weekly doses, levels of rh- αGAL in the liver were also increased (2-fold), suggesting a saturable process. At higher doses, each successive dose administration adds to the circulating plasma and/or liver concentration of enzyme remaining from the previous dose or doses, resulting in accumulation. While accumulation was observed following 27 weekly injections of high doses of r-hαGAL, there was no clinical or histopathological evidence of liver toxicity in the rats. The high dose administered to rats is 5 times greater than the dose administered to humans. In addition, because the dosing regimen is every 2 weeks in humans instead of the weekly schedule in the rat, the safety margin in humans for liver accumulation is even higher.
- The results of the comparability studies demonstrated that Fz-ICB is comparable to Fz regarding maximal serum concentration and clearance. No differences in the serum concentrations were observed at early time points in both studies, but the levels of Fz-ICB were slightly lower than Fz at later time points (>30 minutes post dose). This resulted in small differences in systemic exposure (AUC) between Fz and Fz-ICB. These differences are consistent with the increased level of bis-M6P in Fz-ICB which results in higher affinity for the M6P receptor, a slight increase in cellular uptake of Fz-ICB from the circulation.

- **Toxicology:**
- In two acute toxicity studies in rats r-hαGAL was well tolerated at doses up to 27 mg/kg/day. Repeat-dose toxicology studies have also been performed in two mammalian species, one rodent (Sprague-Dawley rat) and one primate (cynomolgus monkey). Symptoms consistent with an anaphylactic response in rodents to r-hαGAL were successfully blocked via pre-administration of diphenhydramine. Administration of r-hαGAL would be expected to produce an immune response in animals as r-hαGAL is a recombinant form of a native human protein. The monkeys in the 25 week repeated dose

study tolerated r-hαGAL well but also demonstrated clinical behavior consistent with a mild hypersensitivity response to a recombinant human protein at the higher dose levels. It should be considered that the highest administered dose was equivalent to 5 times (based upon equivalent body surface area) the highest dose of 1 mg/kg administered in the Phase III study and the maximum recommended therapeutic dose.

- In the segment II rat embryo-fetal development study, there was a test article related finding, namely, yellow areas on the liver in one middle and five high dosage group rats. Histological evaluation of these livers revealed patchy distribution of hepatocellular necrosis associated with mixed inflammatory cell infiltrates. One additional middle dosage group rat had yellow areas on the right kidney and slight dilation of the renal pelvis of the left kidney. This finding is consistent with the accumulation of test material when administered at high doses daily (appropriate dosing regimen for this study). However, daily dosing is not a clinical consideration and therefore, the findings in the liver are not of clinical relevance.
- Antibody formation was examined in SD rats and the cynomolgus monkeys. The vast majority of rats and monkeys had an immune response to r-hαGAL. Some rats went on to be antibody-free, suggesting possible tolerability to r-hαGAL with repeated administration. There does not appear to be a general dose response. These animal studies indicate that hypersensitivity is the most likely adverse reaction to be expected in humans when treated with r-hαGAL via IV infusion at doses of 1-3 mg/kg.

Overall conclusion: The preclinical data submitted provide adequate evidence for the efficacy and safety of Fabrazyme.

4. Clinical aspect:

Clinical Overview

Fabrazyme (agalsidase beta) is an enzyme replacement therapy used to treat Fabry disease, a rare inherited disorder caused by α-galactosidase A deficiency. Its clinical development program included assessments of pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity in **adults, adolescents, and children**.

Across studies, Fabrazyme was evaluated for its ability to reduce disease-causing GL-3 accumulation in tissues, preserve organ function, and improve long-term outcomes in patients with Fabry disease.

- **Clinical Efficacy and Immunogenicity**

Efficacy

Clinical studies consistently demonstrated that Fabrazyme:

- **Effectively removes and prevents re-accumulation of GL-3** in capillary endothelial cells of the kidney, heart, skin, and other tissues.

- Shows **consistent GL-3 clearance in both treatment-naïve adults and pediatric patients**.
- Helps **preserve kidney function** in most patients, as shown by stable creatinine, eGFR, and proteinuria levels over time.
- Offers greater benefit when **treatment is started early**, especially before irreversible kidney damage occurs.
- Shows a **favorable trend in reducing progression** to major clinical events, including renal, cardiac, or cerebrovascular complications and mortality.

Long-term data from the Fabry Registry (over 7,000 patients) further support Fabrazyme's effectiveness in improving clinical outcomes in both Classic and Non-Classic Fabry disease.

Immunogenicity

Because Fabrazyme is a recombinant human enzyme, IgG antibody formation is expected.
However:

- Antibody development **did not prevent patients from safely receiving long-term treatment**.
- Most patients showed a **decline in antibody levels over time**.
- At the recommended dose (1 mg/kg every 2 weeks), **no significant negative impact on efficacy** was observed in antibody-positive patients.

➢ **Clinical Safety**

Across all completed studies:

- **Fabrazyme demonstrated a favorable and predictable safety profile**.
- Infusion-associated reactions (IARs) were the most common events, generally **mild to moderate** and manageable with standard care.
- The frequency of IARs **decreased with ongoing treatment**, even as infusion times were shortened to ≤3 hours for most patients.
- Safety findings were **consistent across adult and pediatric populations**, as well as across ethnic groups (e.g., Caucasian and Japanese patients).
- Fabrazyme was **safely administered** at doses of 1 mg/kg (recommended) and 3 mg/kg, including in patients with severe renal disease.

Overall, no unexpected safety concerns were identified in either the short- or long-term clinical experience.

- **Overall Conclusion**

Fabrazyme offers a **clinically meaningful and well-established treatment option** for patients with Fabry disease aged **8 years and older**.

It effectively reduces GL-3 accumulation, helps preserve organ function, and provides long-term improvement in clinical outcomes supported by extensive global real-world data. With a predictable and manageable safety profile, Fabrazyme maintains a **favorable benefit–risk balance** for long-term enzyme replacement therapy in Fabry disease.

- **Benefit–Risk Assessment**

Benefits

- Proven reduction of disease-causing GL-3 deposits in multiple organs.
- Demonstrated preservation of kidney function and improvement of long-term clinical outcomes.
- Strong supportive evidence from the global Fabry Registry, representing the **largest Fabry disease dataset worldwide**.
- Effective in both Classic and Non-Classic Fabry disease, and in pediatric patients.

Risks

- Mostly mild to moderate infusion-associated reactions, which decrease over time and are manageable.
- Expected IgG antibody formation, but without meaningful impact on long-term efficacy or safety.

Overall Benefit–Risk: The total clinical evidence shows that **Fabrazyme provides substantial long-term benefit with an acceptable and manageable safety profile** for patients with Fabry disease.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.