ETC/Orphan Drug
I.V.

Fabagal®
(agalsidase beta for injection)

Description
Fabagal is a recombinant analogue of Human a-galactosidase A and is produced by recombinant DNA technology using Chinese Hamster Ovary(CHO) cell culture.
Fabry disease is an x-linked inherited metabolic disease that results from deficiency of α-galactosidase A (hydrolase in lysosome) activity. Deficiency of α-galactosidase A or lack of such enzyme activity leads to the abnormality of lipometabolism or progressive accumulation of glycosphingolipids, such as GL-3 (Glybotriaosy*l*ceramide), in cells or the walls of blood *v*essels. The defect would make narrowing channels of blood vessels and decrease blood flow with decreasing nourishment of the tissues. This process occurs in all blood vessels throughout the body, and damages the function of tissue or organ particularly affecting small blood vessel in the skin, kidney, heart, and nervous system.

The Quantitative Composition (per 1 vial)
Active ingredient: Agalsidase beta (in-house) 37 mg
Stabilizer: D-mannitol 222 mg
Inactive ingredients: Sodium Phosphate Monobasic Dihydrate, Sodium Phosphate Dibasic Dihydrate

Appearance
White to off-white lyophilized cake or powder in colorless and transparent vial; and, after reconstitution, each vial will yield a clear and colorless solution.

Indications and Usages
Fabagal is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency*)*.

Dosage and Administration
The recommended dosage of Fabagal is 1 mg/kg body weight infused every two weeks as an intravenous (IV) infusion. Patients should receive antipyretics prior to infusion. The initial IV infusion rate is no more than 0.25 mg/min (15 mg/hr). The infusion rate may be slowed in the event of infusion reactions. After patient tolerance to the infusion is well established, the infusion rate may be increased in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hr) with each subsequent infusion. For patients weighing < 30 kg, the maximum infusion rate should remain at 0.25 mg/min (15 mg/hr). For patients

weighing ≥ 30 kg, the administration duration should not be less than 1.5 hours (based on individual patient tolerability).
Patients who have had a positive skin test to agalsidase beta or who have tested positive for anti-agalsidase beta IgE may be successfully rechallenged with Fabagal. The initial rechallenge administration should be a low dose at a lower infusion rate, (e.g., 1/2 of the therapeutic dose (0.5 mg kg) at 1/25 of the initial standard recommended rate (0.01 mg/min). Once a patient tolerates the infusion, the dose may be increased to reach the approved dose of 1 mg/kg and the infusion rate may be increased by slowly titrating upwards (doubled every 30 minutes up to a maximum rate of 0.25 mg/min), as tolerated.

Reconstitution and Instructions for Use
Fabagal does not contain any preservatives. Vials are for single use only. Discard any unused product. In addition, avoid shaking or agitating this product and do not use filter needles during the preparation of the infusion.

1. Allow Fabagal vials and diluent to reach room temperature prior to reconstitution (approximately 30 minutes). The number of vials needed is based on the patient's body weight (kg) and the recommended dose of 1 mg/kg.
2. Reconstitute each 35 mg vial of Fabagal by slowly injecting 7.2 mL of Sterile Water for Injection, down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5 mg/mL clear, colorless solution (total extractable amount per vial is 35 mg, 7 mL).
3. Visually inspect the reconstituted vials for particulate matter and discoloration. Do not use the reconstituted solution if there is particulate matter or if it is discolored.
4. The reconstituted solution should be further diluted with 0.9% Sodium Chloride Injection to be a total volume of 500mL. Prior to adding the volume of reconstituted Fabagal required for the patient dose, remove an equal volume of 0.9% Sodium Chloride Injection from the infusion bag of 500mL.
• Patient dose (in mg) ÷ 5 mg/mL = Number of mL of reconstituted Fabagal required for patient dose
Example) Patient dose = 80 mg
80 mg ÷ 5 mg/mL = 16 mL of reconstituted Fabagal

Slowly withdraw the reconstituted solution from each vial up to the total volume required for the patient dose. Inject the reconstituted Fabagal solution directly into the Sodium Chloride solution. Do not inject in the airspace within the infusion bag.
5. Gently invert infusion bag to mix the solution, avoiding vigorous shaking and agitation.
6. Do not infuse Fabagal in the same IV line with other products.
7. Administer Fabagal using an in-line low protein binding 0.2 μm filter.

Warnings and Precautions
1. Warnings
1) Anaphylaxis and Allergic Reactions
The anaphylactic and severe allergic reactions have been observed in patients during agalsidase beta infusions. Reactions have included localized angioedema (including swelling of the face, mouth and throat), bronchospasm, hypotension, generalized

urticaria, dysphagia, rash, dyspnea, flushing, chest discomfort, pruritus, and nasal congestion. Interventions have included cardiopulmonary resuscitation, oxygen supplementation, IV fluids, hospitalization, and treatment with inhaled beta-adrenergic agonists, epinephrine, and I corticosteroids. In clinical trials and postmarketing safety experience with agalsidase beta, approximately 1% of patients developed anaphylactic or severe allergic reactions during agalsidase beta infusion. If anaphylactic or severe allergic reactions occur, immediately discontinue the administration of Fabagal and initiate necessary emergency treatment. Because of the potential for severe allergic reactions, appropriate medical support measures should be readily available when Fabagal is administered.

2) Infusion Reactions

In the patients participated in clinical trials with Fabagal, each one patient experienced the infusion reactions of somnolence, dizziness and hypertension, which were moderate. In addition, other infusion reactions were observed, including mild fever, chills, vomiting, diarrhea, headache and abdominal pain.

In previous clinical trials with agalsidase beta, approximately 50-55% of patients experienced infusion reactions during agalsidase beta administration, some of which were severe. Severe infusion reactions experienced by more than one patient in clinical studies with agalsidase beta included chills, vomiting, hypotension, and paresthesia. Other infusion reactions included pyrexia, feeling hot or cold, dyspnea, nausea, flushing, headache, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, urticaria, bradycardia, and somnolence. Most patients in clinical trials were pretreated with acetaminophen. In patients experiencing infusion reactions, pretreatment with an antipyretic and antihistamine is recommended. Infusion reactions occurred in some patients after receiving pretreatment with antipyretics, antihistamines, and oral steroids. Infusion reactions tended to decline in frequency with continued use of agalsidase beta. However, infusion reactions may still occur despite extended duration of agalsidase beta treatment.

If an infusion reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administrating additional antipyretics, antihistamines, and/or steroids may ameliorate the symptoms.

If severe infusion reactions occur, immediate discontinuation of the administration of Fabagal should be considered, and appropriate medical treatment should be initiated. Severe reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. Because of the potential for severe infusion reactions, appropriate medical support measures should be readily available when Fabagal is administered. Patients who have experienced infusion reactions should be treated with caution when re administering Fabagal.

3) Compromised Cardiac Function

Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion reactions. Patients with compromised cardiac function should be monitored closely it the decision is made to administer Fabagal.

4) Immunogenicity and Re-challenge
In previous clinical trials with agalsidase beta, a few patients developed IgE antibodies or skin test reactivity specific to agalsidase beta. Two of six patients in the re-challenge study discontinued treatment with agalsidase beta prematurely due to recurrent infusion reactions. Four serious infusion reactions occurred in three patients during agalsidase beta infusions, including bronchospasm, urticaria, hypotension, and development of agalsidase beta-specific antibodies. Other infusion-related reactions occurring in more than one patient during the study included rigors, hypertension, nausea, vomiting, and pruritus. Physicians should consider testing for IgE antibodies in patients who experienced suspected allergic reactions and consider the risks and benefits of continued treatment in patients with anti-agalsidase beta IgE antibodies.
Patients who have had a positive skin test to agalsidase beta or who have tested positive for agalsidase beta-specific IgE antibody have been re-challenged with agalsidase beta using a re-challenge protocol. Re challenge of these patients should only occur under the direct supervision of qualified personnel, with appropriate medical support measures readily available.

2. Contraindications
Life-threatening anaphylactic reaction to the active substance or to any of the excipients.

3. Adverse Reactions
1) Adverse Reactions in Clinical Studies
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in patients in clinical practice. In clinical trials with Fabagal, related adverse events were moderate dizziness and somnolence, and mild pyrexia, dysgeusia, vomiting, chills and pruritus. Additionally, in the moderate adverse reactions, hypertension was moderate, and others were mild.
The table below shows 43 adverse reactions occurred in 10 Fabry disease patients aged from 21 to 54 after 1 mg/kg administration of Fabagal for months. The adverse reactions were classified using MedDRA (Medical Dictionary for Regulatory Activities).

Table 1. Adverse Reaction Summary in Fabagal® administrated patients

Organ system category and Adverse Reaction	The number of patients (%)
Nervous system disorders	
Headache	3 (30)
Somnolence	2 (20)
Dizziness	2 (20)
Dysgeusia	1 (10)
Gastrointestinal disorders	
Diarrhea	2 (20)
Indigestion	2 (20)

Abdominal pain	1 (10)
Vomiting	1 (10)
Infections	
Epipharyngitis	1 (10)
Rhinitis	1 (10)
Pharyngitis	1 (10)
Abscess	1 (10)
Infections disease of airway	1 (10)
General disorders and administration site conditions	
Pyrexia	2 (20)
Chills	1 (10)
Musculoskeletal and connective tissue disorders	
Arthralgia	2 (20)
Joint swelling	1 (10)
Arthritis	1 (10)
Skin and Subcutaneous tissue disorders	
Pruritus	2 (20)
Acne	1 (10)
Complications with damage and addiction	
Bruise	1 (10)
Thermal Bum	1 (10)
Investigations	
Increase of alanine aminotransferase	1 (10)
Increase of aspartate aminotransferase	1 (10)
Vascular disorders	
Hypertension	1 (10)
Ophthalmology disorders	
Conjunctivitis	1 (10)

The most serious adverse reactions reported with agalsidase beta treatment during clinical trials were anaphylactic and allergic reactions. The most common adverse reactions reported with agalsidase beta are infusion reactions, some of which were severe.

Serious and/or frequently occurring (≥ 5% incidence) related adverse reactions consisted of one or more of the following: chills, pyrexia, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, paresthesia, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, pallor, bradycardia, urticaria hypotension, face edema, rash, and somnolence. The occurrence of somnolence can be attributed to clinical trial specified pretreatment with antihistamines. Most infusion-related reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administration of antipyretics, antihistamines, or steroids. Other reported serious adverse events included stroke, pain, ataxia,

bradycardia, cardiac arrhythmia, cardiac arrest, decreased cardiac output, vertigo, hypoacusis, and nephrotic syndrome. These adverse events also occur as manifestations of Fabry disease; an alteration in frequency or severity cannot be determined from the small numbers of patients studied.

The data described below reflect exposure of 80 patients, ages 16 to 61 years, to 1 mg/kg agalsidase beta every two weeks in two separate double-blind, placebo-controlled clinical trials, for periods ranging from 1 to 35 months (mean 15.5 months). All 58 patients enrolled in one of the two studies continued into an open-label extension study of agalsidase beta treatment for up to 54 additional months. Patients were treated with antipyretics and antihistamines prior to the infusions. The following Table 2 enumerates adverse reactions (regardless of Adverse drug reaction) that occurred during the double-blind treatment periods of the two placebo-controlled trials (Study 1 and Study 2). Reported adverse reactions have been classified by MedDRA terminology System Organ Class and Preferred Term.

Table 2. Summary of Adverse Reactions Occurring in agalsidase beta-Treated Patients at an incidence Greater than 2.5% Compared to Placebo-Treated Patients (regardless of Adverse drug reaction)

MedDRA System Organ Class/ Preferred Term	Agalsidase beta n=80 (%)	Placebo n=60 (%)
Cardiac Disorders		
Tachycardia	7 (9)	2 (3)
Ventricular wall thickening	4 (5)	1 (2)
Ear and Labyrinth Disorders		
Tinnitus	6 (8)	2 (3)
Hypoacusis	4 (5)	0
Gastrointestinal Disorders		
Toothache	5(6)	2 (3)
Dry mouth	3(4)	0
General Disorders and Administration Site Conditions		
Chills	34 (43)	7 (12)
Pyrexia	31 (39)	13 (22)
Fatigue	19 (24)	10 (17)
Edema peripheral	17 (21)	4 (7)
Pain	13 (16)	8 (13)
Feeling cold	9 (11)	1 (2)
Adverse event	8 (10)	3 (5)
Chest discomfort	4(5)	1 (2)

Infections and Infestations		
Upper respiratory tract infection	35 (44)	18 (30)
Lower respiratory tract infection	14 (18)	4 (7)
Sinusitis	7 (9)	2 (3)
Pharyngitis	5 (6)	1 (2)
Fungal infection	4 (5)	0
Viral infection	4 (5)	0
Localized infection	3 (4)	0
Injury, Poisoning and Procedural Complications		
Procedural pain	20 (25)	12 (20)
Post-procedural complication	8 (10)	1 (2)
Excoriation	7 (9)	1 (2)
Fall	5 (6)	2(3)
Contusion	3 (4)	0
Thermal burn	3 (4)	0
Investigation		
Blood creatinine increased	7 (9)	3 (5)
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	15 (19)	5 (8)
Back pain	13 (16)	6 (10)
Myalgia	11 (14)	3 (5)
Muscle spasms	4 (5)	1 (2)
Nervous System Disorders		
Headache	31 (39)	17 (28)
Paresthesia	25 (31)	11 (18)
Dizziness	17 (21)	5 (8)
Burning sensation	5 (6)	0
Psychiatric Disorders		
Anxiety	5 (6)	2 (3)
Depression	5 (6)	1 (2)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	26 (33)	15 (25)
Nasal congestion	15 (19)	9 (15)
Dyspnea	6 (8)	1 (2)
Respiratory tract congestion	6 (8)	1 (2)
Wheezing	5 (6)	0

Skin and Subcutaneous Tissue Disorders		
Rash	16 (20)	6 (10)
Pruritus	8 (10)	2 (3)
Vascular Disorders		
Hypertension	11 (14)	3 (5)
Hot flush	4 (5)	0

Adverse reactions observed in the Phase 1/2 study and the open-label extension study following the controlled study were not different in nature or intensity. The safety profile of agalsidase beta in pediatric Fabry disease patients, ages 8 to 16 years, was found to be consistent with that seen in adults. The safety of agalsidase beta in patients younger than 8 years of age has not been evaluated.

2) Immunogenicity

In the completed clinical study for Fabagal, the antibody was observed in 1 patient receiving Fagagal for 10 weeks, among 5 patients who had not developed antibodies against Fabagal prior to the first administration of Fabagal. But, other patients who did not developed antibodies against Fabagal prior to the first administration did not develop antibodies during the clinical study period of 6 months. Additionally, it was confirmed that the antibody developed in one patient has no effect to reduce the efficacy of Fabagal (neutralizing antibody), and this patient completed this clinical trial without any severe adverse reaction. In the previous clinical studies for agalsidase beta, Ninety-five of 121 (79%) adult patients and 11 of 16 (69%) pediatric patients (106 of 137, 74% of all patients) treated with agalsidase beta in clinical studies have developed IgG antibodies to agalsidase beta. Most patients who are developed IgG antibodies indicated within the first 3 months after exposure. IgG seroconversion in pediatric patients was associated with prolonged half-life of agalsidase beta, this phenomenon rarely observed in adult patients. A possible cause for this prolongation likely pertains to the ability of antibodies to act as "carriers" for their antigens. Among the 14 female patients exposed to agalsidase beta in clinical studies, six (adult patients) developed IgG antibodies to agalsidase beta. IgG antibodies to agalsidase beta were purified from 15 patients with high antibody titers (≥ 12,800) and studied for inhibition of in vitro enzyme activity. Under the conditions of this assay, most of these 15 patients had inhibition of in vitro enzyme activity ranging between 21-74% at one or more time points during the study. Assessment of inhibition of enzyme uptake in cells has not been performed. No general pattern was seen in individual patient reactivity over time. The clinical significance of binding and/or inhibitory antibodies to agalsidase beta is not known. In patients followed in the open-label extension study, reduction of GL3 in plasma and GL3 inclusions in superficial skin capillaries was maintained after antibody formation. As with other therapeutic proteins, there is potential for immunogenicity. The data reflect the incidence of patients whose test results were considered positive for antibodies to agalsidase beta using an ELISA and radioimmunoprecipitation (RIP) assay for antibodies. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of

sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to agalsidase beta with the incidence of antibodies to other products may be misleading. Testing for IgE antibodies was performed in approximately 60 patients in clinical trials who experienced moderate to severe infusion reactions or in whom mast cell activation was suspected. Seven of these patients tested positive for agalsidase beta-specific IgE antibodies or had a positive skin test to agalsidase beta. Patients who have had a positive skin test to agalsidase beta, or who have tested positive for agalsidase beta specific IgE antibodies in clinical trials with agalsidase beta have been re-challenged.

3) Post Marketing Surveillance
The post marketing surveillance has not been conducted for Fabagal.
The following adverse reactions have been identified during post-approval use of agalsidase beta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
In post marketing experience for agalsidase beta, severe and serious infusion-related reactions have been reported, some of which were life-threatening, including anaphylactic shock. Reactions have included localized angioedema (including auricular swelling, eye swelling, dysphagia, lip swelling, edema, pharyngeal edema, face swelling, and swollen tongue), generalized urticaria, bronchospasm, and hypotension.
Adverse reactions regardless of relationship) resulting in death reported in the aqalsidase beta treatment included cardiorespiratory arrest, respiratory failure, cardiac failure, sepsis, cerebrovascular accident, myocardial infarction, renal failure, and pneumonia. Some of these reactions were reported in fabry disease patients with significant underlying disease.
In addition to the adverse reactions reported in adverse reactions in clinical studies, the following adverse reactions have been reported during use of agalsidase beta: arthralgia, asthenia, erythema, hyperhidrosis, infusion site reaction, lacrimation increased, leukocytoclastic vasculitis, lymphadenopathy, hypoesthesia, oral hypoesthesia, palpitations, rhinorrhea, oxygen saturation decreased, and hypoxia.

4. General Caution
Patients with severe Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion reactions, and these patients should be monitored closely during administration. Since several administrations of agalsidase beta to patients may cause developing antibody or allergy reaction, these patients should carefully consider the risks and benefits of continued treatment.

5. Drug Interaction
1) Interference with other drug
No drug interaction studies were performed.
No in vitro metabolism studies were performed.
2) Interference in laboratory test
There is no known interference by Fabagal with laboratory tests. Antibody samples should

be collected prior to Fabagal infusions.

6. Use in Pregnancy, Nursing Mothers, Pediatric and Women

1) Pregnancy Category B

There are no studies of Fabagal use in pregnant women. Reproduction studies has been performed in rats at doses up to 30 times the human dose have revealed no evidence of impaired fertility or negative effects on embryo fetal development due to agalsidase beta. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

2) Delivery

There is no information on the effect of agalsidase beta during delivery.

3) Nursing Mothers

It is not known whether agalsidase beta is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Fabagal is administered to a nursing woman.

4) Pediatric Use

The pediatric patients were not involved in the clinical study for Fabagal. The safety and efficacy of agalsidase beta were assessed in a multi-national, multi-center, uncontrolled, open-label study in 16 pediatric patients with Fabry disease (14 males, 2 females), ages 8 to 16 years. Patients younger than 8 years of age were not included in clinical studies. The safety and efficacy in patients younger than 8 years of age have not been evaluated.

5) Geriatric Use

Clinical studies of Fabagal did not include sufficient numbers of subjects aged 65 and older. In addition, other clinical study for agalsidase beta did not include sufficient numbers of subjects aged 65 and older.

6) Renal failure use

No studies in renal failure patients were performed. But, for use of agalsidase beta, adjusting of dosage for renal failure patients was not needed.

7) Dyshepatia

No studies in dyshepatia patients were performed.

7. Driving car and mechanic operation

There is no study to evaluate the effect to behavior of driving a car and operation of mechanics.

8. Overdosage

There have been no reports of overdose with Fabagal. In clinical trials for agasidase beta, patients received doses up to 3 mg/kg body weight. The adverse reactions experienced by patients who received treatment with 3 mg/kg were similar to the adverse reactions experienced by patients who received treatment with 1 mg/kg.

9. Administrative caution

Special care is required for reconstitution and dilution of Fabagal. Reconstitute each vial of Fabagal by slowly injecting of Sterile Water for Injection, down the inside wall of each vial.

Do not inject in the airspace within the infusion bag when injecting the reconstituted

Fabagal solution directly into the Sodium Chloride solution. Visually inspect the reconstituted vials for particulate matter and discoloration during reconstitution or dilution. Do not use the reconstituted solution if there is particulate matter or if it is discolored. Use in line low protein-binding 0.2 μm filter for administration of Fabagal.

10. How supplied/storage and handling
Refrigerate vials of Fabagal at 2°C to 8°C (36 to 46°F). Do not use Fabagal after the expiration date on the vial. Since this product contains no preservatives, reconstituted and diluted solutions of Fabagal should be used immediately.

11. The others (Reactions in women)
Fabry disease is an X-linked genetic disorder. However, some heterozygous women will develop signs and symptoms of Fabry disease due to the variability of the X-chromosome inactivation within cells.
A total of 12 adult female patients with Fabry disease were enrolled in two separate randomized, double-blind, placebo-controlled 2 clinical studies with agalsidase beta, and two female pediatric patients with Fabry disease, ages 11 years, were evaluated in an open-label, uncontrolled pediatric study. Although the safety and efficacy data available in female patients in these clinical studies are limited, there is no indication that female patients respond differently to agalsidase beta compared to males.

[Packaging Unit] 1 vial (35mg)/box
[Storage Condition] Sealed container, refrigeration (2~8°C)
* A drug has passed shelf-life or date of expiration, or adulterate*d*/contaminated or damaged will only be exchanged through pharmacies, sellers of general sales list medicines, and drug distributors; and instructions for exchange of such drugs.

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