ETC/Orphan Drug
I.V.

Abcertin®
(Imiglucerase for injection)
400 Units

Description

Abcertin® (imiglucerase for injection) is an analogue of the human enzyme β-glucocerebrosidase, produced by recombinant DNA technology. β-Glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase) is a lysosomal glycoprotein enzyme which catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide. The pathogenesis of Gaucher disease was identified as genetic mutations that caused deficiency of the enzyme activity of β-glucocerebrosidase, which is necessary in breakdown of the lipid glucocerebroside, for intracellular lipid metabolism of human body. The deficiency of the enzyme glucocerebrosidase leads to the accumulation of the lipid glucocerebroside within the lysosomes of macrophages. This accumulation again leads to symptoms like anemia, thrombocytopenia, hepatomegaly, splenomegaly, bone crisis and neurological manifestations.

The Quantitative composition of 1 vial

Active ingredient: Imiglucerase (in-house) 424 Units
Stabilizer: D-mannitol 340 mg, Polysorbate 80 1.06 mg
Inactive ingredients: Trisodium Citrate, Disodium Citrate, Citric Acid Hydrate, Sodium Hydroxide

Appearance

White to off white lyophilized cake in colorless and transparent vial, After reconstitution colorless and clear liquid

Indication and Usage

Abcertin® (imiglucerase for injection) is indicated for use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Type 1 Gaucher disease who show symptom in one or more of the following conditions.

* anemia after exclusion of other causes, such as iron deficiency
* thrombocytopenia
* bone disease after exclusion of other causes such as Vitamin D deficiency
* hepatomegaly or splenomegaly

Dosage and Administration

Abcertin® (imiglucerase for injection) is administered by intravenous infusion over 1-2 hours. Dosage should be individualized to each patient. Initial dosages range from 2.5U/kg of body weight 3 times a week to 60 U/kg once every 2 weeks. 60 U/kg every 2 weeks is the dosage for which the most data are available. Disease severity may dictate that treatment is initiated at a relatively high dose or relatively frequent administration. Dosage adjustments should be made on an individual basis and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patient's clinical manifestations. On the day of use, after the correct amount of Abcertin to be administered to the patient has been determined, the appropriate numbers of vials are each reconstituted with Sterile Water for Injection, USP. The final concentrations and administration volumes are provided in the following table:

	400 Unit vial
Sterile water for reconstitution	10.2 mL
Final volume of reconstituted product	10.6 mL
Concentration after reconstitution	40 U/mL
Withdrawal volume	10.0 mL
Units of enzyme within final volume	400 Unit

A nominal 10.0 mL for the 400 unit vial is withdrawn from each vial. The appropriate amount of Abcertin for each patient is diluted with 0.9% Sodium Chloride Injection, USP, to a final volume of 100-200 mL. Abcertin is administered by intravenous infusion over 1-2 hours. Aseptic techniques should be used when diluting the dose. Since Abcertin does not contain any preservative, after reconstitution, vials should be promptly diluted and not stored for subsequent use. Abcertin, after reconstitution, has been shown to be stable for up to 12 hours when stored at room temperature (25°C) and at 2-8°C. Abcertin, when diluted, has been shown to be stable for up to 24 hours when stored at 2-8°C. Relatively low toxicity, combined with the extended time course of response, allows small dosage adjustments to be made occasionally to avoid discarding partially used bottles. Thus, the dosage administered in individual infusions may be slightly increased or decreased to utilize fully each vial as long as the monthly administered dosage remains substantially unaltered.

Special warning and precaution for use

1. Warning

Hypersensitivity

There have been no cases reported that IgG antibody against Abcertin had developed. Approximately 15% of patients treated and tested to date have developed IgG antibody to imiglucerase during the first year of therapy. Patients who developed IgG antibody did so largely within 6 months of treatment and rarely developed antibodies to imiglucerase after 12 months of therapy. It is suggested that patients suspected of a decreased response to the treatment be monitored periodically for lgG antibody formation to

imiglucerase.

Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity. Since patients with antibody to imiglucerase have a higher risk of hypersensitivity reactions, periodical examination is advised whether IgG antibody is developed for 1 year after treatment initiation. However, all the patients who show hypersensitivity reaction do not have IgG antibody on the detectable level. If a patient experiences a reaction suggestive of hypersensitivity, subsequent testing for imiglucerase antibodies is advised and treated with caution during Abcertin treatment.

As with any intravenous protein product, severe allergic-type hypersensitivity reactions are possible, but occur uncommonly. If these reactions occur, immediate discontinuation of the Abcertin infusion is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment are to be observed.

Anaphylactoid reaction has been reported in less than 1% (< 1%) of the patient population. Most patients have successfully continued therapy after a reduction in rate of infusion and pretreatment with antihistamines and/or corticosteroids.

2. Do not administer

It is contraindicated in patients who are hypersensitive to the active ingredient or excipient of this drug.

3. Adverse reaction

Adverse reactions were reported as below in patients who were administered with Abcertin. Most of the responses were mild or moderate, without any significance in relation to this drug.

Total patients (N=5) Adverse Event (Total incidence No.)		Patients No.(%)	Severity
Infections and infestations (4)	Nasopharyngitis	3(60%)	Mild
	Acute tonsillitis	1(20%)	Moderate
Musculoskeletal and connective tissue disorders (2)	Arthralgia	1(20%)	Mild
Gastrointestinal disorders (2)	Diarrhea	1(20%)	Mild
	Abdominal pain	1(20%)	Mild
Respiratory thoracic and mediastinal disorders (1)	Cough	1(20%)	Mild
Reproductive system and breast disorders (1)	Vaginal discharge	1(20%)	Mild

Through the studies and clinical references about imiglucerase, the frequency of adverse reactions are listed in below table. Common: more than 1/100 and less than 1/10 (≥1/100, ≤1/10) Uncommon: more than 1/1000 and less than 1/100 (≥1/1000, <1/100) Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions	Frequency	Symptom
Nervous system disorders	Uncommon	Dizziness, headache, paraesthesia
Cardiac disorders	Uncommon	Tachycardia, cyanosis
Vascular disorders	Uncommon	Flushing, hypotension
Respiratory, thoracic and mediastinal disorders	Common	Respiratory syndrome
Gastrointestinal disorders	Uncommon	Vomiting, nausea, abdominal cramping, diarrhoea
Skin and subcutaneous tissue disorders	Common	Urticaria/angioedema, pruritus, rash
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia, backache
General disorders and administration site conditions	Uncommon	Infusion site discomfort, infusion site burning, infusion site swelling, injection site sterile abscess, chest discomfort, fever, rigors, fatigue

Some of the adverse reactions were related to the route of administration. These include discomfort, pruritus, burning, swelling or sterile abscess at the site of venipuncture. Symptoms suggestive of hypersensitivity have been noted in approximately 6.6% of patients. The onset of such symptoms has occurred during or shortly after infusions; these symptoms include pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension. Anaphylactoid reaction has also been reported (see WARNINGS). Each of these events was found to occur in < 1.5% of the total patient population. Pre-treatment with antihistamines and/or corticosteroids and reduced rate of infusion have allowed continued use of imiglucerase in most patients. Additional adverse reactions that have been reported in approximately 6.5% of patients treated with imiglucerase include: nausea, abdominal pain, vomiting, diarrhea, rash, fatigue, headache, fever, dizziness, chills, backache, and tachycardia. Each of these events was found to occur in < 1.5% of the total patient population.
Among the spontaneously reported adverse events, the most commonly reported adverse events in children (defined as ages 2 - 12 years) included dyspnea, fever, nausea, flushing, vomiting, and coughing, whereas in adolescents (13 - 16 years) and in adults the most commonly reported events included a headache, pruritus, and rash.

4. General caution
Though pulmonary hypertension and pneumonia have not been shown in the patients who had been administered with Abcertin, in less than 1% of the patient population, pulmonary hypertension and pneumonia have also been observed during treatment with imiglucerase. Pulmonary hypertension and pneumonia are known complications of Gaucher disease and have been observed both in patients receiving and not receiving imiglucerase. No causal relationship with imiglucerase has been established. Patients with respiratory symptoms in the absence of fever should be evaluated for the presence of pulmonary hypertension. Therapy with imiglucerase should be directed by physicians knowledgeable in the management of patients with Gaucher disease. When administered

Abcertin to patients who had developed antibody and showed hypersensitive symptoms during imiglucerase treatment, treat with caution during Abcertin treatment.

*5. Pregnan*t w*omen and Nursing mothers and women of childbearing age*
Animal reproduction studies have not been conducted with Abcertin. It is also not known whether Abcertin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Abcertin should not be administered during pregnancy except when the indication and need are clear and the potential benefit is judged by the physician to substantially justify the risk. It is not known whether this drug is excreted in human milk.

Limited experience from 150 pregnancy outcomes (primarily based on spontaneous reporting and literature review) is available suggesting that use of imiglucerase is beneficial to control the underlying Gaucher disease in pregnancy. Furthermore, these data indicate no malformation toxicity for the fetus by imiglucerase, although the statistical evidence is low. Fetal demise has been reported rarely, although it is not clear whether this related to the use of imiglucerase in or to the underlying Gaucher disease. In pregnant Gaucher patients and those intending to become pregnant, a risk-benefit treatment assessment is required for each pregnancy. Patients who have Gaucher disease and become pregnant may experience a period of increased disease severity during pregnancy and the puerperium. This includes an increased risk of skeletal manifestations, exacerbation of cytopenia, hemorrhage, and an increased need fortransfusion. Both pregnancy and lactation are known to stress maternal calcium homeostasis and to accelerate bone turnover. This may contribute to skeletal disease burden in Gaucher disease.

Treatment naïve women should be advised to consider commencing therapy prior to conception in order to attain optimal health. In women receiving Abcertin treatment, continuation throughout pregnancy should be considered. Close monitoring of the pregnancy and clinical manifestations of Gaucher disease is necessary for the individualization of dose according to the patient's needs and therapeutic response.

6. Pediatric use
Safety and effectiveness of Abcertin were configured for patients between 2 and 15 *y*ears old. The safety and effectiveness of imiglucerase have been established in patients between 2 and 16 years of age. Imiglucerase in this age group is supported by evidence from adequate and well-controlled studies, with additional data obtained from the medical literature and from long-term post-marketing experience.
Imiglucerase has been administered to patients younger than 2 years of age, howe*v*er the safety and effectiveness in patients younger than 2 have not been established.

7. Overdose
No case of overdose has been reported about Abcertin. But, experience with doses up to 240U/kg e*v*ery 2 weeks has been reported in previous study.

8. Special caution
Before further dilution, visually inspect the reconstituted solution of each vial for foreign particles and discoloration. Do not use vials that exhibit foreign particles or discoloration.

Also, do not use Abcertin after the expiration date on the label. Because this is a protein solution, slight flocculation (described as this translucent fibers) occurs occasionally after dilution. The diluted solution may be filtered through an in-line low protein-binding 0.2 μm filter during administration.

9*. Special precautions for storag*e
Store in a refrigerator (2 ~ 8°C).

10. Others
Studies have not yet been conducted to evaluate potential risk of carcinogenicity, mutagenicity and reproductivity damage of the drug in animal or human.

Package unit
400 Units/vial

Storage condition
Hermetic containers, refrigeration (2 ~ 8°C)

* If you find that you ha*v*e products after their expiry date, return them to your local pharmacist who will dispose of them properly.

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