Hunterase
(Idursulfase-β)

[DESCRIPTION]
Hunterase (Idursulfase-β) is an injection in a colorless and transparent vial containing a clear to slightly whitish, colorless solution.

[COMPOSITION] 1 vial (3mL) contains,

Idursulfase- β(Host : CHO DG44, Vector : pJK-dhfr-Or2-IDS)	6.0 mg
Monobasic Sodium Phosphate Monohydrate	6.75 mg
Dibasic Sodium Phosphate Heptahydrate	2.97 mg
Sodium Chloride	24 mg
Polysorbate 20	0.66 mg
Water for Injection	q.s.

[INDICATIONS]
Hunterase (Idursulfase- β) is indicated for patients with Hunter Syndrome (Mucopolysaccharidosis II, MPS II) as an enzyme replacement therapy.

[DOSAGE AND ADMINISTRATION]
1. RECOMMENDED DOSAGE
The recommended dosage regimen of Hunterase is 0.5 mg/kg of body weight administered every week as an intravenous infusion. Hunterase is a concentrated solution for intravenous infusion and must be diluted in 100 mL of 0.9% Sodium Chloride Injection. Each vial of Hunterase contains a 2.0 mg/mL solution of idursulfase- β protein (6.0 mg) in an extractable volume of 3.0 mL and is for single use only. Use of an infusion set equipped with a 0.2 micrometer (μm) filter is recommended.
The total volume of infusion may be administered over a period of 1 to 3 hours. Patients may require longer infusion times due to infusion reactions; however, infusion times should not exceed 8 hours. The initial infusion rate should be 8 mL/hr for the first 15 minutes. If the infusion is well tolerated, the rate may be increased by 8 mL/hr increments at 15 minute intervals in order to administer the full volume within the desired period of time. However, at no time should the infusion rate exceed 100 mL/hr. The infusion rate may be slowed and/or temporarily stopped, or administration may be stopped, based on clinical judgment, if infusion reactions were to occur. Hunterase should not be infused with other products in the infusion tubing.

2. PREPARATION AND ADMINISTRATION INSTRUCTIONS : USE ASEPTIC TECHNIQUES
Hunterase should be prepared and administered by a health care professional.
1. Determine the total volume of Hunterase to be administered and the number of vials needed based on the patient's weight and the recommended dose of 0.5 mg/kg.

Patient's weight (kg) x 0.5 mg/kg of Hunterase ÷2 mg/mL = Total # (mL) of Hunterase
Total # (mL) of Hunterase ÷3 mL/vial = Total # of (vial)

(Round up to determine the number of whole vials needed from which to withdraw the calculated volume of Hunterase to be administered.)
2. Perform a visual inspection of each vial. Hunterase is a clear to slightly whitish, colorless solution. Do not use if the solution in the vials is discolored or particulate matter is present. Hunterase should not be shaken.
3. Dilute the total calculated volume of Hunterase in 100 mL of 0.9% Sodium Chloride Injection. After dilution, the solution in the infusion bag should be mixed gently, but not shaken. Diluted solution should be discarded if not administered or refrigerated within 8 hours of preparation. Diluted solution may be stored refrigerated for up to 48 hours.
4. Hunterase is for single-use only. Remaining Hunterase after use should be discarded immediately.

[PRECAUTIONS]
1. WARNING
Patients with compromised respiratory function or acute respiratory disease may be at higher risk of life-threatening complications from infusion reactions.
2. INJECT WITH CARE
(1) Patients with serious recurrent reactions related to injection after infusion of Hunterase.
(2) Patients with history of anaphylaxis to ingredients of Hunterase.
(3) Patients with history of shock to ingredients of Hunterase.

3. ADVERSE REACTIONS

All adverse reactions occurring in patients treated with Hunterase weekly in the 24-week controlled trial compared to the reference drug during clinical trial is shown in below table. 3 serious adverse reactions were observed; 2 cases of otitis media and 1 case of gastroenteritis. However, all cases were determined as 'not-related' to Hunterase. Adverse reactions associated with Hunterase were urticaria, rashes, and pruritus. All adverse reactions were minor and minimized by adjusting the infusion rate and using proper drug treatments.

Total number of Subjects	Reference Drug 0.5 mg/kg (n=11)		Hunterase 0.5 mg/kg (n=10)		Hunterase 1.0 mg/kg (n=10)	
	All Adverse Events	Adverse Events Related to the Drug	All Adverse Events	Adverse Events Related to the Drug	All Adverse Events	Adverse Events Related to the Drug
Total number of subjects in Safety population	11 Subjects		10 Subjects		10 Subjects	
Total number of Adverse Events	10 (90.9%)	2 (18.2%)	9 (90%)	1 (10%)	10 (100%)	2 (20%)
INFECTIONS AND INFESTATIONS	8 (72.7%)	–	9 (90%)	–	9 (90%)	–
UPPER RESPIRATORY TRACT INFECTION	8 (72.7%)	–	8 (80%)	–	7 (70%)	–
OTITIS MEDIA	–	–	1 (10%)	–	2 (10%)*	–
PHARYNGOTONSILLITIS	–	–	1 (10%)	–	1 (10%)	–
BRONCHITIS	–	–	1 (10%)	–	1 (10%)	–
OTITIS MEDIA ACUTE	–	–	1 (10%)	–	1 (10%)	–
EYE INFECTION	–	–	1 (10%)	–	–	–
HORDEOLUM	–	–	1 (10%)	–	–	–
PNEUMONIA	–	–	–	–	1 (10%)	–
SINUSITIS	–	–	–	–	1 (10%)	–
TINEA PEDIS	–	–	1 (10%)	–	–	–
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	5 (45.5%)	2 (18.2%)	6 (60%)	1 (10%)	5 (50%)	2 (20%)
URITICARIA	2 (20%)	2 (18.2%)	3 (30%)	1 (10%)	2 (20%)	2 (20%)
RASH	3 (27.3%)	1 (9.1%)	–	–	–	–
DERMATITIS	1 (9.1%)	–	–	–	2 (20%)	–
PRURITUS	1 (9.1%)	1 (9.1%)	2 (20%)	1 (10%)	–	–
RASH ERYTHEMATOUS	1 (9.1%)	1 (9.1%)	1 (10%)	–	–	–
TINEA PEDIS	1 (9.1%)	–	1 (10%)	–	–	–
DERMATITIS ATOPIC	–	–	1 (10%)	–	1 (10%)	–
ECZEMA	–	–	1 (10%)	–	–	–
MACULE	–	–	1 (10%)	–	–	–

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (36.4%)	1 (9.1%)	6 (60%)	–	4 (40%)	–
COUGH	2 (18.2%)	–	2 (20%)	–	3 (30%)	–
RHINORRHOEA	2 (18.2%)	–	2 (20%)	–	1 (10%)	–
RHINITIS ALLERGIC	2 (18.2%)	–	2 (20%)	–	–	–
ASTHMA	–	–	1 (10%)	–	–	–
EPISTAXIS	–	–	1 (10%)	–	–	–
PRODUCTIVE COUGH	–	–	–	–	1 (10%)	–
RESPIRATORY DISTRESS	1 (9.1%)	1 (9.1%)	–	–	–	–
GASTROINTESTINAL DISORDERS	4 (36.4%)		4 (40%)		1 (10%)	–
DIARRHOEA	2 (18,2%)	–	2 (20%)	–	–	–
GASTROENTERITIS		–	3 (30%)*	–	–	–
NAUSEA	1 (9.1%)	–	–	–	1 (10%)	–
VOMITNG	1 (9.1%)	–	–	–	1 (10%)	–
CONSTIPATION	–	–	1 (10%)	–	–	–
GINGIVITIS	1 (9.1%)	–	–	–	–	–
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (27.3 %)	–	3 (30%)	1 (10%)	–	–
PYREXIA	1 (9.1%)	–	2 (20%)	–	–	–
CHEST DISCOMFORT	1 (9.1%)	–	–	–	–	–
CONCITION AGGRAVATED	–	–	1 (10%)	1 (10%)	–	–
OEDEMA PERIPHERAL	1 (9.1%)	–	–	–	–	–
MUSCULOSKELTETAL AND CONNECTIVE TISSUE DISORDERS	2 (18.2%)	–	2 (20%)	–	–	–
MUSCLE SPASMS	–	–	1 (10%)	–	–	–
MUSCULOSKELETAL PAIN	1 (9.1%)	–	–	–	–	–
ARTHRALGIA	1 (9.1%)	–	–	–	–	–
MYALGIA	–	–	1 (10%)	–	–	–
EYE DISORDERS	–	–	1 (10%)	–	1 (10%)	–
CONJUNCTIVITIS ALLERGIC	–	–	–	–	1 (10%)	–
CONJUNCTIVITIS	–	–	1 (10%)	–	–	–
KERATOCONJUNCTIVITIS SICCA	–	–	–	–	1 (10%)	–
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	–	–	1 (10%)	–	1 (10%)	–
INFUSION RELATED REACTION	–	–	1 (10%)	–	–	–
OPEN WOUND	–	–	–	–	1 (10%)	–
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	–	–	–	–	1 (10%)	–
BALANOPOSTHITIS	–	–	–	–	1 (10%)	–

4. INTERACTION WITH OTHER MEDICINAL PRODUCTS

No formal drug interaction studies have been conducted with Hunterase

5. GENERAL PRECAUTIONS

Life-threatening anaphylactic reactions have been observed in some patients during infusions of a medicine similar to Hunterase. Reactions have included respiratory distress, hypoxia, hypotension, seizure, and/or angioedema. Because of potential of severe infusion reactions, appropriate medical support should be readily available when Hunterase is administered. When severe infusion reactions occurs, subsequent infusions should be managed by using antihistamines and/or corticosteroids prior to or during infusions, a slower rate of Hunterase administration, and/or early discontinuation of the Hunterase infusion if serious symptoms occur.

6. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term studies to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with Hunterase.

1) PREGNANCY

Reproduction studies in pregnant female animals have not been conducted with Hunterase. It is also not known whether Hunterase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

2) NURSING MOTHERS

It is not known whether this product is excreted in human milk.

3) PEDIATRIC USE

Patients in the clinical studies were older than age 38 months and younger than age 35. Children, adolescents, and adults responded similarly to treatment with Hunterase.

7. PRECAUTIONS IN STORAGE AND HANDLING

- Store Hunterase vials under refrigeration at 2°C to 8°C
- Protect from light without freezing and do not shake it.
- Do not use Hunterase after the expiration date on the vial.
- This product contains no preservatives. The diluted solution should be used immediately. If immediate use is not possible, the diluted solution can be stored refrigerated at 2°C to 8°C for up to 48 hours, or must be administered within 8 hours if held at room temperature.

8. OTHERS

The clinical trial result of Hunterase is very limited due to low number of subjects. Of all the patients registered in the clinical trial, 20 patients were administered with Hunterase (10 patients for each different dosing group) and 11 patients were administered with the reference drug. 20 patients in a group of administration with Hunterase and 10 patients in a group of administration with the reference drug were participated in evaluation of effectiveness. The urinary GAG levels prior to administration of testing drugs for Hunterase 0.5 mg/kg group, 1.0 mg/kg group, and reference drug 0.5 mg/kg group were 164(±53.1) mg GAG/g Creatinine, 124.7(±36.1) mg GAG/g Creatinine, and 129.1(±59.9) mg GAG/G Creatinine. Following 24 weeks of treatment, the change in urinary GAG levels were -29.5(±15.5)%, -41.1(±10.2)%, and -18.7(±15.8)% respectively.

[STORAGE AND SHELF-LIFE]

Store at 2°C to 8°C in hermetic container.

The shelf-life of this product is 24 months from the date of manufacture.

[HOW SUPPLIED]

3mL/vial x In-house package unit

녹십자 GREEN CROSS

GREEN CROSS

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