건 명	헌터라제 3mL 인서트(말레이시아)		
규 격 (가로x세로)	120x280mm	Q A	오창
		표시문안	6pt
색 상	먹 1도	후 가 공	
업체제작일	2025.07.22.	작 업 처	(주)트리스톤

K 칼선 PANTONE 185C

※인쇄진행시, 인쇄사양과 다를경우
녹십자로 즉시 연락주시기 바랍니다.

Hunterase 2 mg/ml Solution for Injection

[PRODUCT DESCRIPTION]
Hunterase is an injection in a colorless and transparent vial containing a clear to slightly opalescent, colorless solution.
1 vial (3 ml) contains,
Idursulfase beta (Host: CHO DG44, Vector: pJk-dhfr-Or2-IDS) ..... 6.0 mg
Sodium Dihydrogen Phosphate Monohydrate ..... 6.75 mg
Sodium Phosphate Dibasic Heptahydrate ..... 2.97 mg
Sodium Chloride ..... 24 mg
Polysorbate 20 ..... 0.66 mg
Water for Injection ..... q.s.

[INDICATION]
Hunterase 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.
2. Method of Administration
Hunterase should be prepared and administered by a health care professional. 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 (vials)
(Round up to determine the number of whole vials needed from which to withdraw the calculated volume of Hunterase to be administered.)
For instructions on preparation and dilution of the medicinal product before administration, see the instruction for use.
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 minutes 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 are to occur.

[CONTRAINDICATIONS]
Hypersensitivity to the active substance or to any of the excipients listed in the product description.

[WARNINGS AND 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. Infusion with Care
- Patients with serious recurrent reactions related to infusion of Hunterase
- Patients with history of anaphylaxis to ingredients of Hunterase
- Patients with history of shock to ingredients of Hunterase

3. 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. Due to potential severe infusion reactions, appropriate medical support should be readily available when Hunterase is administered. When severe infusion reactions occur, 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.

[ADVERSE EVENTS]
1. Summary of the safety profile
The integrated safety analysis of three clinical trials (GC1111_P1/2, GC1111_C_P3b, and GC1111_P3) included a total of 50 patients treated with idursulfase beta. Of these, a total of 40 patients were treated with 0.5 mg/kg idursulfase beta, which is the licensed dose, and the remaining 10 patients were treated with 1.0 mg/kg idursulfase beta, which is a higher dose than the licensed dose in the GC1111_P1/2 clinical trial. The serious adverse events reported in patients treated with idursulfase beta were gastroenteritis, otitis media, splenic infarction, and rash, of which the serious adverse reactions that could not rule out the causal relationship with idursulfase beta were splenic infarction and rash. The most common adverse events reported in patients treated with idursulfase beta were upper respiratory tract infection (44%), and the most frequently reported adverse events (≥5%) were cough, nasopharyngitis, pyrexia, urticaria, bronchitis, otitis media, rhinorrhoea, cardiac valve disease, rash, pruritus, diarrhoea, pharyngotonsillitis, dermatitis, gastroenteritis, sinusitis, enteritis, productive cough, oropharyngeal pain, stomatitis, vomiting, and nausea.
2. Tabulated list of adverse reactions
Adverse reactions that could not rule out the causal relationship with idursulfase beta reported in clinical trials are listed in Table 1 according to the MedDRA System Organ Class and the following frequency criteria: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000).
Table 1. Adverse reactions from clinical trials in patients treated with idursulfase beta

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Very common	Nasopharyngitis
	Common	Otitis media chronic, Laryngitis
Blood and lymphatic system disorders	Common	Splenic infarction, Thrombocytopenia
Nervous system disorders	Common	Tonic convulsion
Eye disorders	Common	Panophthalmitis
Cardiac disorders	Common	Cardiac valve disease, Cardiomegaly, Right atrial enlargement, Right ventricular hypertrophy
Respiratory, thoracic and mediastinal disorders	Common	Cough, Productive cough, Respiratory disorder
Gastrointestinal disorders	Common	Diarrhoea, Abdominal pain, Lip swelling, Mouth ulceration
Skin and subcutaneous tissue disorders	Very common	Urticaria
	Common	Rash, Pruritus, Angioedema
Musculoskeletal and connective tissue disorders	Common	Arthralgia, Joint swelling
Renal and urinary disorders	Common	Haematuria
General disorders and administration site conditions	Common	Condition aggravated, Peripheral swelling
Investigations	Common	Ejection fraction decreased, Electrocardiogram low voltage
Injury, posioning and procedural complications	Common	Foreign body in ear

3. Immunogenicity
In the clinical trial (GC1111_P3) involving Hunter syndrome patients aged 5 years and older with no prior experience with ERT, out of 24 patients receiving 0.5 mg/kg idursulfase beta once a week for 53 weeks, 23 (95.83%) patients tested positive for anti-idursulfase beta antibodies at least one time, and 21 (87.50%) patients tested positive for antibodies at three or more consecutive time points. Nevertheless, at the end of the trial, only 12 (52.17%) patients tested positive for antibodies. 9 patients out of the 23 (39.13%) antibody-positive patients also tested positive for antibodies that neutralize idursulfase beta uptake into cells or enzymatic activity at least one time, and 4 (19.05%) of antibody-positive patients tested postive for neutralizing antibodies at three or more consecutive time points. The clear relationship between the presence of neutralizing antibodies and therapeutic response was not observed in the clinical trial. The immunogenicity results are highly dependent on the sensitivity and specificity of the assay. The observed incidence of positive antibody in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to idursulfase beta with the incidence of antibodies to other products may be misleading. Table 2 shows the impact of antibody status and genetic mutations on the occurrence of serious adverse events and acute adverse events in Hunter syndrome patients aged 5 years and older receiving Hunterase who had no prior experience with ERT.
Table 2. Impact of Antibody Status and Genetic Mutations on Occurrence of Serious Adverse Events and Acute Adverse Events in patients treated with Hunterase (Based on number of patients)

Antibody type		Anti-idursulfase beta antibody (n=24)		Neutralizing antibody (n=23)	
Antibody Status Reported[1]		Positive	Negtative	Positve	Negative
		23	1	9	14
Serious Adverse Events		2	0	2	0
Acute Adverse Events[2]		3	0	2	1
Genotyping group 1[3]	Antibody Status	7	0	1	6
	Serious Adverse Events	0	0	0	0
	Acute Adverse Events	1	0	0	1
Genotyping group 2[4]	Antibody Status	16	1	8	8
	Serious Adverse Events	2	0	2	0
	Acute Adverse Events	2	0	2	0

[1] If the anti-idursulfase beta antibody and neutralizing antibody test results are tested to be positive even at least one time during the entire clinical trial period, it is classified as positive. However, a neutralizing antibody test is performed only if the anti-idursulfase beta antibody is positive
[2] Anaphylaxis, dyspnea, hypoxia, hypotension, urticaria, angioedema of throat or tongue, bronchospasam, cyanosis, erythema, rash, edema, hot flush, vomiting, and wheezing
[3] Missense mutation
[4] Complete gene deletion, large gene rearrangement, nonsense mutation, frameshift mutation, splice site mutation, unknown, others
Patients with positive anti-idursulfase beta antibodies in genotyping group 2 showed a higher incidence of neutralizing antibodies and an increased occurrence of acute and serious adverse events, in comparison to those in genotyping group 1.

[INTERACTIONS WITH OTHER MEDICINAL PRODUCTS]
No formal medicinal product interaction studies have been conducted with idursulfase beta.
Based on its metabolism in cellular lysosomes, idursulfase beta would not be a candidate for cytochrome P450 mediated interactions.

[SYMPTOMS AND TREATMENT OF OVERDOSE]
There is limited information regarding overdose with Hunterase. 1.0 mg/kg idursulfase beta was administered to a limited number of patients with Hunter syndrome once a week for 24 weeks without serious adverse reactions in the clinical trial (GC1111_P1/2). The adverse events were similar to those in patients receiving licensed dose of idursulfase beta.

[FERTILITY, PREGNANCY, AND LACTATION]
1. Pregnancy
Reproduction studies in pregnant female animals have not been conducted with this medicine. It is also not known whether this medicine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.
2. Breast-feeding
It is unknown whether idursulfase beta is excreted in human milk.
3. Fertility
No effects on male fertility were seen in reproductive studies in male rats.

[EFFECTS ON ABILITY TO DRIVE AND USE MACHINE]
Idursulfase beta has no or negligible influence on the ability to drive and use machines.

[PHARMACODYNAMICS]
1. Mechanism of action
Hunter syndrome, or mucopolysaccharidosis type II (MPS II), is a rare lysosomal storage disease inherited in a X-chromosomal recessive fashion, which is caused by a deficient enzyme, iduronate-2-sulfatase. This enzyme cleaves O-linked sulphate moieties from the glycosaminoglycans (GAGs) dermatan sulphate and heparan sulphate as the first step in their degradative pathway. Hunterase is an injectable dosage form containing the active substance idursulfase beta, a purified form of recombinant human iduronate-2-sulfatase (rhIDS), a lysosomal enzyme. rhIDS is produced by recombinant DNA technology in Chinese hamster ovary (CHO) DG44 cell line. Hunterase is a glycoprotein of 525-amino acid, with a molecular weight of approximately 78 kDa measured by mass spectrometry. The enzyme contains eight sites of glycosylation linked to asparagine occupied by complex oligosaccharide structures. The enzyme activity of Hunterase is known to be dependent on the post-translational modification of a specific cysteine (Cys59) to formylglycine. Enzyme replacement therapy (ERT) with Hunterase provides exogenous iduronate-2-sulfatase to the patients with MPS II whose iduronate-2-sulfatase gene is missing or mutated. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains of the glycoprotein enzyme allow specific binding of iduronate-2-sulfatase to M6P receptors on the cell surface, leading to cellular internalisation and targeting of the enzyme to lysosomes, and subsequent catabolism of accumulated glycosaminoglycans (GAGs).
2. Clinical efficacy and safety
The safety and efficacy of Hunterase has been shown in three clinical trials: Phase 3, double-blind, randomized, active-controlled (Part 1) and open-label, historical placebo controlled (Part 2) clinical trial (GC1111_P3) in patients 5 years and older with no prior ERT, Phase 1/2, single-blind, randomized, active-controlled clinical trial (GC1111_P1/2) in patients between 6 to 35 years with prior ERT, and Phase 3b, open-label clinical trial (GC1111_C_P3b) in children between the age of 38 months and 5 years with prior ERT.
Clinical trial GC1111_P3
GC1111_P3 is the phase 3 clinical trial to demonstrate the superiority of the Hunterase group to the past Elaprase phase 2/3 placebo group based on mean change in 6-minute walk test (6-MWT) and to assess the efficacy and safety in patients 5 years and older with no prior ERT. In a group of 24 patients who received Hunterase 0.5 mg/kg intravenously once a week for 52 weeks, the mean change (±standard deviation) in 6-MWT after 53 weeks compared to baseline, which was the primary efficacy endpoint, was 62.22±40.48m, and demonstrated the superiority to the past Elaprase phase 2/3 placebo group (7.3m).
In addition, the mean change and % change (±standard deviation) in Total Urine GAG after 53 weeks from baseline, which is one of the secondary efficacy endpoints, was -258.11±137.53 mg GAG/g Creatinine and -71.13±36.09%, respectively, in the Hunterase group, and showed a statistically significant difference compared to the past Elaprase phase 2/3 placebo (18.16 mg GAG/g Creatinine, 21.39%).
Clinical trial GC1111_C_P3b
This was an open-label, single-arm trial to assess the efficacy and safety in patients between the age of 38 months and 5 years with prior ERT. A total of 6 patients were treated with Hunterase 0.5 mg/kg intravenously once a week for 52 weeks. During the clinical trial, no significant changes were found regarding safety, which was the primary objective of this clinical trial, and there were no cases of death or withdrawal from the trial due to adverse drug reactions. In addition, the mean change in Urine GAG after 53 weeks compared to baseline was statistically significant.

[PHARMACOKINETICS]
Idursulfase beta is taken up by selective receptor-mediated mechanisms involving binding to mannose-6-phosphate receptors. Upon internalization by cells, it is localized within cellular lysosomes, thereby limiting distribution of the protein. Degradation of idursulfase beta is achieved by generally well understood protein hydrolysis mechanisms to produce small peptides and amino acids, consequently renal and liver function impairment is not expected to affect the pharmacokinetics of idursulfase beta.
Major pharmacokinetic (PK) parameters measured at Visit 2 (Cycle 1 Day 1) and Visit 26 (Cycle 7 Day 1) of clinical trial GC1111_P3 (Hunterase 0.5 mg/kg weekly arm) are displayed in Table 3. The analysis for Visit 2 shows results for single dosing and the analysis for Visit 26 shows results at the steady state following multiple dosing. There were no apparent diffrences in major PK parameter values between Visit 2 and Visit 26.
Table 3. Major PK parameters at Visit 2 and Visit 26 in Clinical trial GC1111_P3 (Hunterase 0.5 mg/kg weekly)

Major Pharmacokinetic Parameter	Visit 2 (Cycle 1 Day 1) Mean ± SD	Visit 26 (Cycle 7 Day 1) Mean ± SD
AUC_{last} (h*ng/mL)	6866.33 ± 2044.60	6343.28 ± 3673.95
C_{max} (ng/mL)	689.92 ± 163.41	791.18 ± 607.82
$T_{1/2}$ (h)	12.60 ± 3.62	12.14 ± 4.73

[PRECLINICAL SAFETY DATA]
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, repeated dose toxicity, toxicity to reproduction (male fertility).

[INCOMPATIBILITIES]
This medicinal product must not be mixed with other medicinal products except those mentioned in instruction for use.

[INSTRUCTION FOR USE]
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 beta 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. Hunterase should not be infused with other products in the infusion tubing.
- 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.
- Perform a visual inspection of each vial. Hunterase is a clear to slightly opalescent, colorless solution. Do not use if the solution in the vials is discolored or if particulate matter is present. Hunterase should not be shaken.
- 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.
- This product contains no preservatives. The diluted solution should be used immediately. If immediate use is not possible, the diluted solution can be stored at 2°C to 8°C for up to 48 hours, or must be administered within 8 hours if held at room temperature.
- Hunterase is for single-use only. Remaining Hunterase after use should be discarded immediately.

[STORAGE CONDITIONS]
Store in a refrigerator (2°C – 8°C).
Do not freeze.
The shelf-life of this product is 36 months from the date of manufacture.
After dilution
The diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 48 hours at 2 to 8°C or must be administered within 8 hours if held at room temperature.

[DOSAGE FORMS AND PACKAGING AVAILABLE]
3 mL of concentrate for solution for infusion in a 6 mL vial (type I glass) with a stopper (teflon coating rubber), aluminum seal, and violet flip-off plastic cap. 1 vial is in each packaging unit.

[NAME AND ADDRESS OF MANUFACTURER / PRODUCT REGISTRATION HOLDER]
1. Manufactured & Released by
GC Biopharma Corp.
586, Gwahaksaneop 2-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea
2. Product registration holder
AXXESSBIO SDN. BHD.
25-1B, JALAN SEMENYIH SENTRAL 2, SEMENYIH SENTRAL, 43500 SEMENYIH, SELANGOR, MALAYSIA

[DATE OF REVISION OF PI]
7 July 2025

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