Verification date:
Revision date:

# Package Insert of Idursulfase β Injection

Please read the package insert carefully and use the drug under the instructions of a physician

**[Drug Name]**

Generic name: Idursulfase β Injection

Product name: Hunterase

English name: Idursulfase beta Injection

Chinese Pinyin: Aiduliusuanzhimeibeita Zhusheye

**[Ingredients]**

Active ingredient: Idursulfase β.

Ingredients: disodium phosphate, sodium dihydrogen phosphate, sodium chloride, polysorbate 20, appropriate amount of water for injection.

**[Description]**

A clear to slightly opalescent, colorless solution.

**[Indications]**

For enzyme replacement therapy in patients with diagnosed mucopolysaccharidosis type II (MPS II, also known as Hunter syndrome).

This product has not been clinically tested in children under 38 months of age.

**[Strength]**

6 mg (3 ml)/vial.

**[Usage and Administration]**

1. Recommended Dosage

The recommended dosage regimen for Hunterase is 0.5 mg/kg body weight, iv, qw. Hunterase is an intravenous concentrate, which must be diluted with 100 mL of 0.9% sodium chloride injection before use. Each vial of Hunterase contains 2.0 mg/mL idursulfase beta protein solution (6.0 mg), with an extractable volume of 3.0 mL, which is for single use only. It is recommended to use an infusion set equipped with a 0.2 micron (μm) filter.

Total volume infusion shall be completed in 1 to 3 hours. If an infusion reaction

occurs, the patient may need to extend the infusion time, but the infusion time should not exceed 8 hours. Within 15 minutes before the start of the infusion, the initial infusion rate should be 8 mL/hr. If the infusion is well tolerated, it can be increased by 8 mL/hr every 15 minutes to give all doses of liquid medicine within the prescribed time. The rate of infusion, however, shall not exceed 100 mL/hr. If an infusion reaction occurs, according to clinical judgment, the infusion rate can be slowed down and/or the infusion can be suspended, or the infusion can be stopped. Hunterase should not be infused simultaneously with other products in the infusion tube.

2. Preparation and Administration Instructions

Using aseptic techniques, Hunterase should be prepared and administered by professional medical workers.

The total volume of Hunterase that should be administered and the number of vials required are determined based on patient's weight and the recommended dose of 0.5 mg/kg.

Patient's weight (kg) × 0.5 mg/kg Hunterase ÷ 2 mg/mL = total volume of Hunterase (mL)

Total volume of Hunterase (mL) ÷ 3 mL/vial = total (vials)

(Round to determine the number of bottles required for the total volume of Hunterase that should be drawn.)

Each vial is visually inspected. Hunterase is a clear to slightly opalescent, colorless solution. If there is discoloration or particulate matter in the solution in the vial, do not use the solution. Do not shake Hunterase.

Dilute the calculated total volume of Hunterase with 100 mL of 0.9% sodium chloride injection. After dilution, gently mix the solution in the infusion bag, but do not shake. If the diluted solution is not used or refrigerated within 8 hours after preparation, it should be discarded. The diluted solution can be stored for up to 48 hours under refrigerated conditions.

**[Adverse Reactions]**

The following content includes four parts, i.e. the adverse reactions in the clinical trials of this product, immunogenicity and post-marketing adverse reactions, and

adverse reactions of similar drugs.

Because clinical trials are conducted under various different conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drug and may not reflect the rate of adverse reaction observed in clinical practice.

**1. Adverse reactions in clinical trials of this product**

Up to now, this product has undergone 3 clinical trials, and all the adverse reactions that occurred during the clinical trials in patients treated with Hunterase once a week are described below.

Phase I/II trials: A 24-week, single-blind, active-drug-controlled Hunterase clinical trial was conducted in 31 male patients aged 6 to 35 years with MPS II. The 31 patients were all Koreans who had previously received enzyme replacement therapy. All subjects were randomly assigned to three test groups (Hunterase 0.5 mg/kg, qw: 10 subjects; Hunterase 1.0 mg/kg, qw: 10 subjects; active control of Elaprase 0.5 mg/kg, qw: 11 subjects). In this trial, the number of adverse reactions (incidence) of Hunterase were: 1 case (10%) of urticaria, 1 case (10%) of pruritus, and 1 case of condition aggregated (10%) in the 0.5 mg/kg group. There were 2 cases (20%) of urticaria in 1.0 mg/kg group.

Phase IIIb trial: A 52-week, single-arm, open-label, uncontrolled Hunterase clinical trial was conducted in 6 male patients younger than 6 years with MPS II. The 6 children were all Koreans who had previously received enzyme replacement therapy. The subjects were given Hunterase 0.5 mg/kg, once a week, for 52 weeks. The adverse reactions in subjects in this trial included 1 case (16.7%) of urticaria, 1 case (16.7%) of cough.

Phase III: It was a 52-week, double-blind, randomized, active-drug-controlled (Elaprase) (Part 1), and an open-label, history placebo-controlled (Part 2) trial, including initially treated Chinese patients with MPS II. In the completed Part 1, 20 initially treated Chinese male MPS II patients aged 5 to 53 were randomly assigned to 2 treatment groups: Hunterase 0.5 mg/kg, qw: 12 subjects; active drug 0.5 mg/kg, qw: 8 subjects. Adverse reactions observed in subjects treated with Hunterase 0.5 mg/kg once a week included: 6 cases (50.0%) of nasopharyngitis, 3 cases (25.0%) of Cardiac

valve disease, 1 case (8.3%) of respiratory disorder, 1 case (8.3%) of laryngitis, 1 case (8.3%) of otitis media chronic, 1 case (8.3%) of cardiomegaly, 1 case (8.3%) of right atrial enlargement, 1 case (8.3%) of right ventricular hypertrophy, 1 case (8.3%) of panophthalmitis, 1 case (8.3%) of thrombocytopenia, 1 case (8.3%) of Mouth ulceration, 1 case (8.3%) of ejection fraction decreased, 1 case (8.3%) of Electrocardiogram low voltage, 1 case (8.3%) of Arthralgia, 1 case (8.3%) of hematuria, 1 case (8.3%) of foreign matter, 1 case (8.3%) of tonic convulsion.

**2. Immunogenicity of this product**

The immunogenicity of this product has been preliminarily evaluated in 2 clinical trials that have been completed (including patients who previously received Idursulfase therapy) and 1 ongoing trial (including naive treated Chinese patients).
In the phase I/II trial, the immunogenicity test results after 24 weeks of treatment showed that the Hunterase antibody and neutralizing antibody status of any subject in the three test groups did not change. In the Phase III b trial, during the 52-week Hunterase administration period, subjects whose Hunterase antibody was negative at the time of enrollment had no developed new antibodies.
In the ongoing phase III clinical trial, exploratory analysis has been performed on part 1 (completed) data on the immunogenicity endpoint. Although statistical analysis was not performed in Part 1, descriptive presentation was conducted on the available data: During the trial, subjects with anti-drug antibody (ADA) / neutralizing antibody positive at least once were defined as ADA positive / neutralizing antibody positive, and the neutralizing antibody test was performed in subjects with antibody positive. In the Hunterase group, the number of ADA-positive subjects was 12 (100.00%). In the Hunterase group, the number of subjects whose ADA was negative at baseline but positive at the end of the visit was 5 (41.67%). At the end of the trial, serum antibody of 6 subjects (50.00%) in the Hunterase group changed from positive to negative. In the Hunterase group, the number of neutralizing antibody-positive subjects confirmed by the cell uptake neutralization method and enzyme activity neutralization method were 2 (16.67%) and 5 (41.67%), respectively.

**3. Post-marketing adverse reactions of this product**

The following adverse reactions have been found after the marketing of Hunterase, including hypersensitivity, dizziness, hypersomnia, oedema mouth, vomiting, angioedema, rash, Skin discolouration, skin reaction, urticaria, infusion site rash,

oedema, catheter placement. Because these reactions are reported spontaneously from a population of uncertain sample size, it is not always possible to reliably estimate their frequency of occurrence or establish a causal relationship to drug exposure.

**4. Adverse reaction occurrence condition of the same category**

According to foreign literature reports, the following adverse reactions have been observed in clinical trials and after marketing of similar variety, including: anaphylactoid/anaphylactic reaction, headache, tremor, cyanosis, arrhythmia, tachycardia, flushing, hypertension, hypotension, wheezing, dyspnoea, hypoxia, bronchospasm, tachypnoea, abdominal pain, nausea, diarrhea, swollen tongue, dyspepsia, erythema, pyrexia, chest pain, infusion-site swelling, face oedema, oedema peripheral, infusion related reaction.

**[Contraindications]**

Those who had severe or life-threatening hypersensitivity to the ingredients or any excipients of this product.

**[Precautions]**

**Infusion-related reactions**

Infusion-related reactions may occur in patients administered with Hunterase. The most common infusion-related reactions are mild to moderate, including skin reactions (urticaria, rash, pruritus), fever, headache, hypertension and flushing. Infusion-related reactions can be treated or improved by slowing down the infusion rate, interrupting the infusion, or administering drugs (antihistamines and / or corticosteroids).

**Anaphylactic reations and hypersensitivity reactions**

No life-threatening anaphylactic reactions were observed in clinical trials and application of Hunterase, but life-threatening anaphylactic reactions were observed in some patients during the infusion of similar drugs of Hunterase, including respiratory distress, hypoxia, hypotension, seizure and / or angioedema. As anaphylactic reactions may occur during infusion, appropriate medical support readily available should be prepared at the time of infusion of Hunterase. If a anaphylactic reaction occurs during the infusion, the subsequent infusion should use antihistamines and / or corticosteroids before or during the infusion to slow down the Hunterase infusion rate and/or discontinue Hunterase early (if serious symptoms occur) for management.

**Acute respiratory complications related to drug administration**

Patients with compromised respiratory function or acute respiratory disease may be at higher risk of life-threatening complications due to infusion reactions.

**Acute cardiopulmonary failure risks**

No cases of acute cardiopulmonary failure have been found in Hunterase clinical trials and marketing applications. However, according to foreign literature reports, patients who are susceptible to excessive circulatory load, or patients who suffer from acute potential respiratory diseases or impaired heart and/or respiratory function and have indications of infusion restriction may have the risk of serious deterioration of heart or respiratory state during infusion with similar products. In the process of infusion with Hunterase, appropriate medical support and monitoring measures should be readily available, and the observation time should be extended as needed.

**Patients with complete gene deletion/large fragment gene rearrangement**

There is no definite conclusion about the correlation between Hunterase and gene. According to foreign literature reports, pediatric patients with complete gene deletion/large fragment gene rearrangement have a higher probability of antibody (including neutralizing antibody) after being exposed to the same variety. Compared with patients with missense mutation genotype, patients with this genotype have a higher probability of transfusion-related adverse events, and tend to show no significant curative effect (evaluated by the decrease of glycosaminoglycan amount in urine, liver size and spleen volume).

**Injection with caution**

Patients with serious recurrent reactions related to injection after infusion of Hunterase.

Patients with a history of anaphylaxis to anaphylaxis of Hunterase.

Patients with a history of shock due to ingredients of Hunterase.

**[Medicine for pregnant women and nursing women]**

**Gestation period**

At present, clinical trials have not been carried out in female patients with mucopolysaccharide storage Type II, and the potential risks to human body are unclear. Therefore, it is not recommended to use this product during pregnancy unless there is a clear necessity.

**Lactation period**

It is not clear whether this product can be secreted by human milk, and this product should be used with caution in lactating women.

**[Pediatric Use]**

Clinical trials have included children and adolescents aged 38 months and above, and the results show that the response to Hunterase treatment is similar to that of adults. The dosage and administration is not required adjusting.

**[Geriatric Use]**

Clinical trials of this drug have not been carried out in elderly patients.

**[Drug Interactions]**

No drug interaction trial of this product has been conducted.

**[Overdose]**

There is no experience of Hunterase overdose.

**[Clinical trials]**

Up to now, two clinical trials of Hunterase have been completed, including one Phase I/II trial and one Phase IIIb trial. There is also an ongoing Phase III trial.

Trial 1 was a Phase I/II single-blind, randomized clinical trial of the MPS II subjects with the similar variety Elaprase as the active control. It is administered by intravenous infusion once a week for 24 weeks. Thirty-one Korean male subjects aged 6 to 35 years who had received enzyme replacement therapy were recruited and randomly assigned to three experimental groups (Hunterase 0.5 mg/kg, once a week: 10 subjects; Hunterase 1.0 mg/kg, once a week: 10 subjects; and active control drug 0.5 mg/kg, once a week: 11 subjects). The main purpose of this trial was to evaluate the efficacy of Hunterase based on the pharmacodynamic measurement index of the percent change of the urine GAG from baseline to the 24th week. The secondary therapeutic objectives included urine GAG changes from baseline to the 24th week, 6-minute walking test (6-MWT) change and percent change, liver volume change and percent change, heart size change and percent change, heart function changes, joint mobility changes and percent change, and lung function change. The main observational endpoints are as shown in Table 1.

**Table 1 Main trial endpoint results of Phase I/II clinical trial**

| **Observational endpoints (Mean ± SD)** | **24-Week treatment (ITT population)** | | |
|---|---|---|---|
| | **Hunterase group 0.5 mg/kg, once a week** | **Hunterase group 1.0 mg/kg, once a week** | **Active control group 0.5 mg/kg, once a** |

| | | | week |
|---|---|---|---|
| Urine GAG change % | -29.5 (±15.5) | -41.1 (±10.2) | -15.3 (±18.9) |
| Change % in 6-MWT | 19 (±18.4) | 15.1 (±13.8) | 0.8 (±10.9) |
| Change % in FVC | 7.9 (±11.3) | 15.8 (±7) | 1.7 (±7.6) |
| Change % in liver volume | -5 (±18.4) | -5.9 (±25.1) | -11.4 (±19.8) |

Trial 2 was a Phase IIIb, single-arm, non-controlled, open-label trial for MPS II pediatric patients under 6 years old. In this trial, 6 Korean children who had received enzyme replacement therapy were enrolled and given Hunterase 0.5 mg/kg intravenously once a week for 52 weeks. The main purpose of this trial was to conduct safety evaluation by collecting information about adverse events (including infusion-related adverse events). The secondary purposes included reviewing the changes of ECG, vital signs, laboratory and physical examination results, immunogenicity evaluation, and urine GAG changes after 52 weeks of treatment.

After 52 weeks of Hunterase treatment, the main therapeutic results are shown in Table 2.

**Table 2 Main efficacy endpoint results of Phase IIIB clinical trial**

| **Observational endpoints (Mean ± SD)** | **52-Week treatment (ITT population)** | | | |
|---|---|---|---|---|
| | **0.5mg/kg for the Hunterase group, once a week** | | | **P value from baseline** |
| | **Baseline value** | **Last visit value** | **Changes compared to the baseline** | |
| Urine GAG change | 169.00 ± 30.98 | 133.88 ± 37.74 | -35.12±30.64 mg GAG/gcreatinine | p=0.0377 |
| Urine GAG change % | / | / | -20.62±20.67% | p=0.0584 |

Trial 3 was a randomized, double-blind, Phase III trial with Elaprase as the active control (Part 1) and open-label, historical placebo control (Part 2) to evaluate the efficacy and safety of Hunterase in patients with Hunter's syndrome (mucopolysaccharide storage Type II). The trial included all newly diagnosed patients in China. In the completed Part 1, 20 newly diagnosed male MPS II patients aged 5 to

53 years were randomly assigned to two treatment groups (Hunterase 0.5 mg/kg, once a week, 12 subjects; active drug 0.5 mg/kg, once a week, 8 subjects). The exploratory efficacy outcome of the Stage 1 trial showed that the changes of 6-MWT from baseline in the 53rd week were 52.33 ± 34.49 m in the Hunterase group and 44.71 ± 49.30 m in the active drug group respectively. At the 53rd week, the changes of urine GAG from baseline were -203.55 ± 152.39 mg GAG/g creatinine in the Hunterase group and -166.15 ± 90.21 mg GAG/g creatinine in the active drug group. In addition, the volume of liver and spleen was measured by abdominal MRI, and it was found that the volume of liver and spleen decreased in the subjects in both the Hunterase group and active drug group.

**[Pharmacology & Toxicology]**

**1 Mechanism of Action**

MPS II is a rare X-linked recessive disease caused by deletion or mutation of lysosomal enzyme iduronidase-2-sulfatase (IDS) gene, which leads to insufficient expression level. The enzyme cuts the terminal 2-O-sulfate part from GAG dermatan sulfate and heparan sulfate as the first step of glycosaminoglycan degradation. GAG gradually accumulates in lysosomes of various cells due to the deletion or defect of iduronidase-2-sulfatase in patients with mucopolysaccharidosis, which leads to the destruction of tissue structure, organ enlargement and system dysfunction. Hunterase enzyme replacement therapy (ERT) can provide exogenous iduronidase-2-sulfatase for MPS II patients with deletion or mutation of iduronidase-2-sulfatase gene. The mannose-6-phosphate (M6P) residue on the oligosaccharide chain of glycoprotease makes Idursulfase β bind specifically with the M6P receptor on the cell surface, causing it to enter cells and target into lysosomes, thus causing the catabolism of accumulated glycosaminoglycans. Thereby it achieves the purpose of exogenous enzyme replacement therapy.

**2 Nonclinical Toxicology**

2.1 Carcinogenicity, mutagenicity and fertility damage

The carcinogenic or mutagenic potential of this product has not been evaluated.

No reproductive toxicity was observed in the non-clinical study of fertility toxicity in male animals, which did not suggest potential special harm to human body.

2.2 Animal Toxicology and/or Pharmacology

**Toxicology**

| Species | Route of administration and dose | Administration period | Result |
|---|---|---|---|
| Rats | Intravenous injection 0, 5, 10 or 20 mg/kg | Single dose | No toxic results related to this product were observed |
| Cynomologus monkey | Intravenous injection 0, 5, 10 or 20 mg/kg | Once a week for 4 weeks | No toxic results related to this product were observed |
| Cynomologus monkey | Intravenous injection 0, 0.5, 2.5 or 12.5 mg/kg | Once a week for 26 weeks | No toxic results related to this product were observed. At the 13th week, the anti-drug antibody (ADA) was detected in one animal in the 0.5mg/kg dose group and the 2.5mg/kg dose group respectively, but noADA was detected in any animals at the 26th week and at the end of the recovery period. The formation of ADA did not lead to the increase of the clearance rate of this product. |

**Pharmacology**

In the pharmacological study of single intravenous injection, repeated intravenous injection once a week for 4 weeks, and intravenous injection once a week for 26 weeks on IDS knockout mice, it was observed that this product could effectively reduce the level of glycosaminoglycan (GAG) in urine and tissues to the level of wild-type mice, and significantly relieve hepatosplenomegaly caused by GAG accumulation. There was no change in the cardiovascular system, respiratory system and central nervous system related to this product in safety pharmacology.

**[Pharmacokinetics]**

In the Phase III study, a double-blind, randomized, active controlled trial was conducted on patients with Hunter's syndrome who had not received ERT before, and pharmacokinetic data of Hunterase were collected from the test group (Hunterase) made up of 12 patients. Hunterase (0.5 mg/kg) was given intravenously once a week for 52 weeks (13 cycles in total), and blood was collected immediately before the administration of Visit 2 (cycle 1D1) and Visit 26 (cycle 7D1), 5 minutes, 1, 2, 6, 8, 12, 24 and 48 hours after the start of infusion to evaluate pharmacokinetics (9 blood sampling points in total) The serum concentration of Idursulfase β was quantitatively

determined by antigen-specific ELISA. The main pharmacokinetic parameters are as follows:

**Table 3 Table of pharmacokinetic parameters of Hunterase in Phase III clinical study**

| PK Parameters | Cycle 1 Day 1[2] (n= 12[3]) | Cycle 7 Day 1[2] (n= 11[4]) |
|---|---|---|
| | Mean ± SD | Mean ± SD |
| $AUC_{last}$ (hr*ng/mL) | 7630.25±2181.50 | 7214.24 ±3196.28 |
| $AUC_{inf}$ (hr*ng/mL) | 8600.31±2610.73 | 7893.92 ± 3644.12 |
| $C_{max}$ (ng/mL) | 718.463±175.74 | 743.69 ±295.67 |
| $T_{max}$ (hr)[1] | 2.03 (1.92-8.07) | 1.97 (1.35-6.02) |
| $t_{1/2}$ (hr) | 14.13±4.14 | 11.70 ± 4.89 |
| CL (mL/hr/kg) | 63.93±21.50 | 126.55 ± 208.41 |
| $V_d$ (mL/kg) | 1217.78±282.44 | 1630.97 ± 2080.95 |
| $MRT_{last}$ (hr) | 10.28±1.93 | 8.97 ±2.99 |
| $MRT_{inf}$ (hr) | 15.70±4.00 | 13.00 ± 4.99 |

1） Tmax: median (range).
2） 4 weeks a cycle.
3） The slope-related evaluation parameters of one subject could not be obtained.
4） One subject was not included in the PK analysis because the parameter was below the lower limit of quantification.

The kinetics related to drug milk secretion, placental barrier and blood-brain barrier were not studied. Pharmacokinetic studies were not conducted in special populations.

**[Storage]**

This product is stored under refrigeration at 2℃ to 8℃.

Protect from light, do not freeze or shake.

Do not use this product after the expiration date on the vial.

This product does not contain preservatives, and the diluted solution should be used immediately. If it can not be used immediately, the diluted solution can be stored under refrigeration at 2℃ to 8℃ for up to 48 hours. If it is stored at room temperature, it must be administered within 8 hours.

**[Package]**

6 mL transparent type I glass vial for injection with a gray Teflon-coated chlorobutyl stopper and violet flip-off plastic cap. 1 vial/box.

**[Shelf Life]**

30 months.

**[Specification Executed]**

**[Approval No.]**

**[Marketing Authorization Holder]**

| | |
|---|---|
| Enterprise Name: | Green Cross, Green Cross Corporation |
| Registered Address: | 586 Gwahaksaneop 2-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea |

**[Manufacturer]**

| | |
|---|---|
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