Drug for the treatment of mucopolysaccharidosis type II
Idursulfase beta (genetic recombination) for
intracerebroventricular administration

Hunterase ICV Injection 15 mg

Note) Caution – Use only pursuant to the prescription of a physician, etc.

1. WARNINGS

Administration of HUNTERASE may cause serious anaphylaxis and shock. Administration of this product should be started after adequate facilities for the treatment of emergencies being prepared, and the patient should be continued to be adequately monitored after completing administration. (see Section 8.2.)

2. CONTRAINDICATIONS (HUNTERASE is contraindicated in the following patients.)

Patients with a history of anaphylactic shock due to any of the ingredients of HUNTERASE. (see Sections 8.2 and 9.1.2.)

3. DESCRIPTION

3.1 Composition

Brand name	Hunterase ICV Injection 15 mg	
Active ingredient (Content per milliliter in a vial)	Idursulfase beta (genetic recombination)Note) 15 mg	
Inactive ingredient	Sodium chloride	8.766 mg
	Polysorbate 20	0.05 mg

Note) Manufactured in Chinese hamster ovary cells.

3.2 Product Description

Brand name	Hunterase ICV Injection 15 mg
Color/description	Clear to slightly opalescent, colorless solution in a transparent and colorless glass vial
pH	5.5 to 6.5

4. INDICATIONS

Mucopolysaccharidosis type II (MPS II)

5. PRECAUTIONS CONCERNING INDICATIONS

Administration of HUNTERASE should be considered for patients with MPS II for which improvement of central nervous system symptoms is necessary.

6. DOSAGE AND ADMINISTRATION

The usual dosage is 30 mg of idursulfase beta (genetic recombination) administered intracerebroventricularly (ICV) once every 4 weeks.

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

7.1 HUNTERASE should be administered to patients who have received idursulfase (genetic recombination) intravenously and have been confirmed to tolerate it well. (see Section 14.1.1.)

7.2 To prevent fluctuations in intraventricular pressure, collect cerebrospinal fluid (CSF; 2 mL) of the same volume with HUNTERASE to be injected in advance and administer HUNTERASE without dilution over at least 1 min.

7.3 HUNTERASE should be administered by a physician with knowledge and experience of intracerebroventricular administration.

8. IMPORTANT PRECAUTIONS

8.1 As device-related complications, infections that include cerebral ventriculitis and cerebral meningitis, central nervous system events such as excessive intracranial hypotension or hypertension, device failure, etc., may occur. Pay attention to the following. (see Sections 9.1.1, 11.3.2–11.3.3.)

- Establish a system to take appropriate actions for device failure etc.
- To reduce the risk of infection, HUNTERASE should be administered aseptically.
- Confirm that there is no abnormality in the skin around the site of implantation before every administration of HUNTERASE to check the signs of device failure and infection.
- Take appropriate actions if device-related complication is noted. See also the package inserts of the relevant medical device for device failure etc.

8.2 Because HUNTERASE is a protein product, the possibility of causing anaphylactic shock cannot be ruled out. Therefore, the patient should be adequately monitored, and if any abnormality is noted, treatment with this product should be discontinued, and appropriate therapeutic measures should be taken. In addition, facilities for the treatment of emergencies should be prepared in case of the development of such a symptom. (see Sections 1, 2, 9.1.2)

8.3 Periodic testing of IgG antibodies against idursulfase beta (genetic recombination) is recommended, because IgG antibody production is predicted.

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

9.1 Patients with Complication/Medical History

9.1.1 Patients on ventriculoperitoneal shunt or ventriculoatrial shunt
Intracerebral HUNTERASE exposure decreases, and efficacy cannot be expected. (see Section 8.1.)

9.1.2 Patients with a past history of hypersensitivity to the compounds of HUNTERASE (see Sections 2, 8.2.)

9.2 Use during Pregnancy
HUNTERASE should be used in pregnant women or women who may possibly be pregnant only if it is considered that the expected therapeutic benefits outweigh the possible risks associated with treatment. Impact on pregnancy of dams, embryos, fetuses, and neonates has not been investigated.

9.3 Use during Lactation
Consider therapeutic benefits and the benefit of breast-feeding to decide on whether to continue or discontinue breast-feeding. No study on the excretion of HUNTERASE in breast milk has been conducted.

9.4 Pediatric Use
No clinical study in pediatric patients under 1 year old has been conducted.

9.5 Use in the Elderly
HUNTERASE should be administered with care while observing the patients' condition. Elderly patients have generally reduced physiological function.

10. ADVERSE REACTIONS

The following adverse reactions may occur. Therefore, the patients' conditions should be adequately monitored, and if any abnormality is noted, appropriate therapeutic measures such as discontinuing the treatment should be taken.

10.1 Other adverse reactions

	≥10%
Gastroenterology	Vomiting, nausea
Skin	Urticaria
Metabolic abnormality	Blood bilirubin increased
Psychoneurotic system	Restlessness
Other	Pyrexia

11. PRECAUTIONS CONCERNING USE

11.1 General Precautions
Check with the administration guide for detailed usage of HUNTERASE.

11.2 Precaution(s) in Preparation of the Drug

11.2.1 Use up promptly once the package is opened. If the drug should be stored out of necessity, store at 25°C or lower, and administer within 8 hours.

11.2.2 Do not shake vigorously.

11.3 Precautions Concerning Administration of the Drug

11.3.1 HUNTERASE should be administered aseptically.

11.3.2 Use a surgically placed implantable CSF reservoir to administer HUNTERASE (Figure 1). Read carefully the package inserts and instructions for use of the relevant medical device, and respond properly to these precautions. (see Section 8.1.)

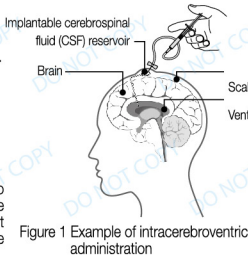

Figure 1 Example of intracerebroventricular administration

11.3.3 To administer HUNTERASE, use an implantable CSF reservoir, which is confirmed to be compatible

with HUNTERASE. (see Section 8.1.)

12. OTHER PRECAUTIONS

12.1 Information based on Clinical Use

MPS II is an X-linked recessive disorder, but female patients are reported rarely. No female patients participated in the clinical study, and the safety of HUNTERASE in female patients has not been established.

13. PHARMACOKINETICS

13.1 Blood Concentrations

When HUNTERASE 3, 10, and 30 mg were increased from low dose in severe MPS II patients, then 30 mg was repeatedly administered ICV over at least 1 min every 4 weeks, the mean human idursulfase concentration in serum* was 45.9 ng/mL at baseline, 42.6 ng/mL at Week 8, 39.3 ng/mL at Week 24, 56.3 ng/mL at Week 52, and 48.8 ng/mL at Week 100. Idursulfase (genetic recombination) was also administered intravenously. Human idursulfase concentration in CSF* after administration of HUNTERASE was below the lower detection limit at all measurement points (Weeks 8, 24, 52, and 100) in 6 patients.

*: Measurement using the specimen collected immediately before administration of HUNTERASE

When a single dose of HUNTERASE 3, 10, and 30 mg was administered ICV to monkeys, pharmacokinetic parameters in CSF and serum are as shown in Table 1.

Table 1 Pharmacokinetic parameters in CSF and serum when a single dose of HUNTERASE was administered ICV

Target	Dose	N	$t_{1/2}$ (h)	t_{max} (h)	C_{max} (μg/mL)	$AUC_{0\text{-}t}$ (μg·h/mL)
CSF	3 mg	4	9.90 ± 10.19	0.313 ± 0.125	461 ± 285	980 ± 226
	10 mg	4	6.04 ± 0.82	0.313 ± 0.125	1490 ± 590	3530 ± 940
	30 mg	3	7.12 ± 3.48	0.333 ± 0.144	2410 ± 670	11200 ± 8000
Serum	3 mg	4	8.08 ± 4.20	4.50 ± 1.00	0.40 ± 0.32	3.03 ± 2.24
	10 mg	4	8.59 ± 2.64	4.00 ± 0.00	1.16 ± 0.41	13.10 ± 3.10
	30 mg	3	16.4 ± 7.3	4.67 ± 1.15	3.77 ± 1.93	51.8 ± 18.4

Mean ± SD

13.2 Distribution

When a single dose of 125I-labeled HUNTERASE 30 mg was administered ICV to monkeys, the radioactive concentration in tissue reached the highest in CSF 0.25 hours after administration, and 1–2 hours after administration in most brain tissues and the spinal cord.

14. CLINICAL STUDIES

14.1 Clinical Studies for Efficacy and Safety

14.1.1 Japanese clinical study

An open-label, non-controlled study (BHP001 Study) was conducted in patients with severe MPS II (n = 6, 23–64 months. The patients underwent implantable CSF reservoir placement in the head beforehand and received idursulfase beta ICV over at least 1 min once every 4 weeks. It was administered at a dose of 1, 10, or 30 mg, starting from the lowest dose. After each dose level was given two, two, and three doses, respectively, the dose was selected for patients individually based on CSF heparan sulfate (HS) concentrations and safety assessment results, and 30 mg was continued for all the patients. The study targeted patients to whom idursulfase (genetic recombination) had been administered intravenously at least 24 weeks before the start of the study. Intravenous administration of idursulfase (genetic recombination) was to continue after the start of HUNTERASE administration, keeping at least a 24-hour interval between the administration of HUNTERASE and idursulfase (genetic recombination). Table 2 shows CSF HS concentrations by subjects after the administration of HUNTERASE for at least 100 weeks.

Table 2 Change over time in CSF HS concentration after the administration of HUNTERASE

Subject	CSF HS concentration (μg/mL)							
	At start	Week 4	Week 8	Week 12	Week 24	Week 52	Week 76	Week 100
1	15.0	20.0	17.0	10.0	7.0	6.5	5.7	4.5
2	7.9	8.4	7.0	4.6	2.9	2.1	3.2	1.9
3	9.7	8.5	9.5	6.3	3.4	3.2	3.7	2.3
4	6.1	5.7	4.7	3.1	2.2	2.2	1.6	1.2
5	2.5	3.8	2.8	2.1	1.6	1.6	2.4	1.5
6	5.3	4.0	4.2	3.1	3.3	1.8	1.1	2.0

The incidence of adverse reactions was 100% (6/6 subjects). The adverse reactions were vomiting in 100% (6/6 subjects), pyrexia in 50.0% (3/6 subjects), nausea in 33.3% (2/6 subjects), urticaria in 16.7% (1/6 subjects), and blood bilirubin increased (1/6 subjects). (see Section 7.1.)

15. PHARMACOLOGY

15.1 Mechanism of Action

MPS II is an X-linked recessive genetic disease caused by a lack of iduronate-2-sulfatase (IDS), a lysosomal enzyme. This enzyme hydrolyzes glycosaminoglycans (GAGs), namely, dermatan sulfate and HS. In MPS II, because of a defect or deficiency of IDS, GAGs result in their accumulation in various organs and tissues, leading to symptoms such as intellectual disability, unusual facial features, short stature, skeletal deformities, and joint stiffness in severe patients.

Administration of HUNTERASE, a recombinant IDS product, to MPS II patients allows enzyme to specifically bind to mannose 6-phosphate (M6P) receptors on the cell surface via M6P on oligosaccharides, leading to uptake into cells and the degradation of accumulated GAGs. HUNTERASE, when administered ICV, also distributes in the brain and spinal cord and decomposes GAGs accumulated in the cranial nerves.

15.2 Intracerebral HS Degradation Effects

When HUNTERASE 30 μg was repeatedly ICV administered to iduronate-2-sulfatase knockout (IKO) mice once a month for 6 months, cerebral and CSF HS concentrations decreased. An open field study showed that HUNTERASE administration improved the hyperactivity and reduced danger sensing of the IKO mice.

16. PHYSICOCHEMISTRY

Nonproprietary name: Idursulfase beta (genetic recombination)

Descriptive definition: Idursulfase beta is a recombinant human IDS and is produced in Chinese hamster ovary cells. Idursulfase beta is a 525-amino acid glycoprotein (molecular weight: about 77,000).

17. PRECAUTIONS FOR HANDLING

Do not freeze.

18. STORAGE AND SHELF-LIFE

Store at 2 °C to 8 °C.

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

19. PACKAGING

<Hunterase ICV Injection 15 mg>

1 mL [1 vial]

GC Pharma

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