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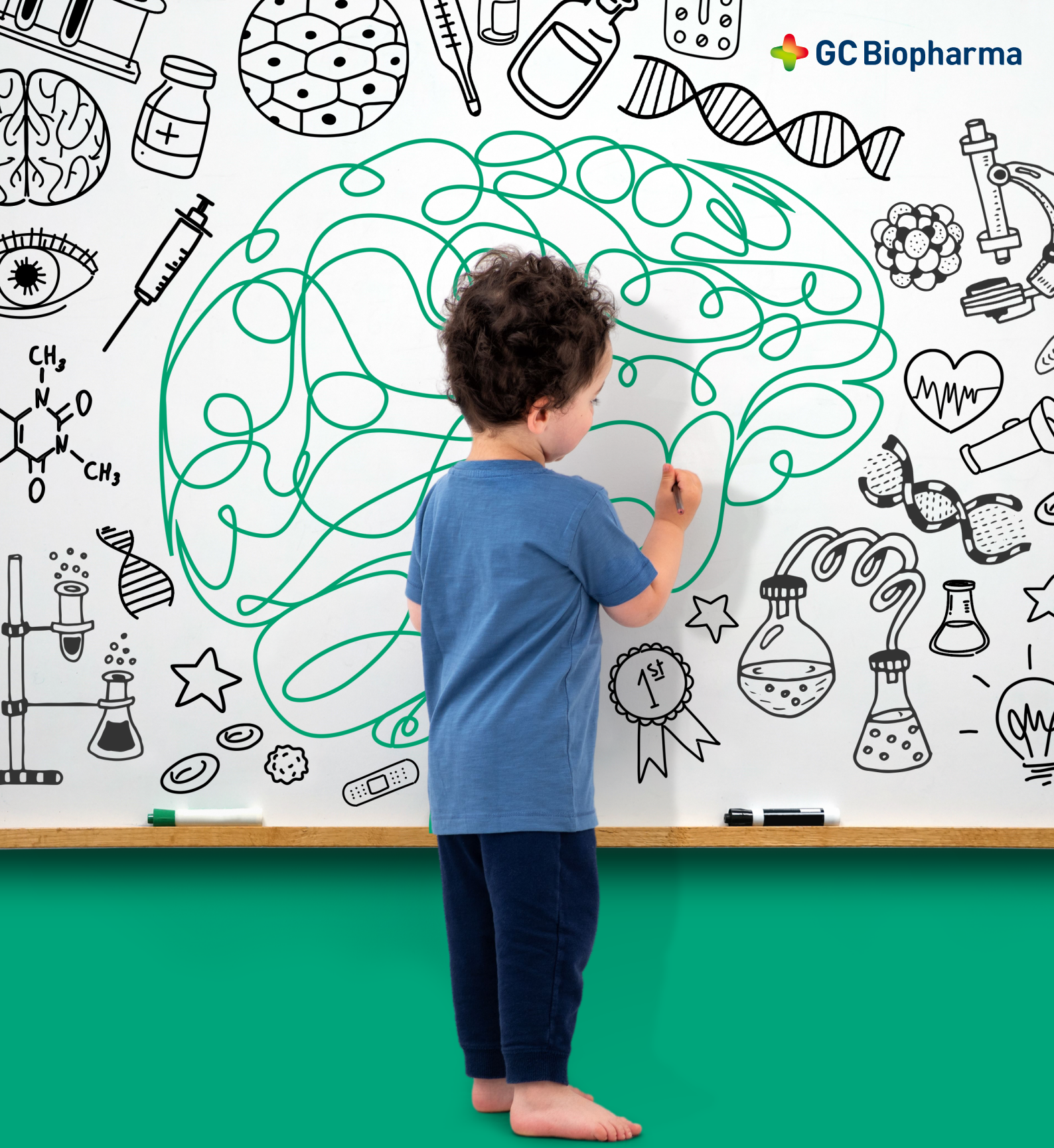


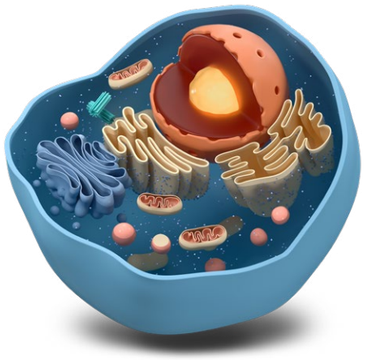
Hunterase

ICV Injection 15 mg

World's 1st approved treatment for Neuronopathic MPS II

About Hunter syndrome (MPS II)

Hunter syndrome is Mucopolysaccharidosis type II (MPS II) which is a rare X-linked genetic lysosomal storage disorder caused by the deficiency of iduronate-2-sulfatase (IDS).[1, 2]



Signs & Symptoms[1, 2]

Neuronopathic (severe) type : CNS involvement

Neurobehavioral symptoms

- Aggression
- Hyperactivity
- Sleep disturbances
- Progressive neurological decline
- Cognitive impairment

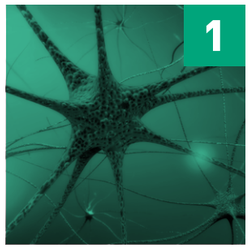
Non-neuronopathic (attenuated) type : Minimal CNS involvement

Common symptoms & signs

- Developmental delay
- Coarse face
- Short stature
- Skeletal abnormalities (dysostosis multiplex)
- Joint contracture
- Hepatosplenomegaly
- Upper airway obstruction
- Valvular heart disease

Early Diagnosis and Prescription are Keys to Better Outcomes

Unmet needs in IV ERT-treated patients



1 Symptoms of CNS involvement[3]

Since conventional intravenous enzyme replacement therapy (ERT) does not reach the brain compartment due to the **Blood brain barrier (BBB)**, the abnormal accumulation of glycosaminoglycans in the brain can lead to degeneration of brain tissue and progressive decline in cognitive function. Cognitive development stops at the age of 3-4 years and regression starts at the age of 4-5 years.

2 Quality of Life[4]

In the neuronopathic type of MPS II, developmental age can be significantly affected by the CNS involvement associated with the disorder. The patients experience **intellectual disabilities and delays in speech and language development**, which can affect their ability to learn, communicate, and function independently. In addition, the progressive nature of MPS II can lead to a decline in physical abilities over time, including difficulties with fine motor skills and mobility. These factors can further affect an individual's developmental age and overall quality of life.

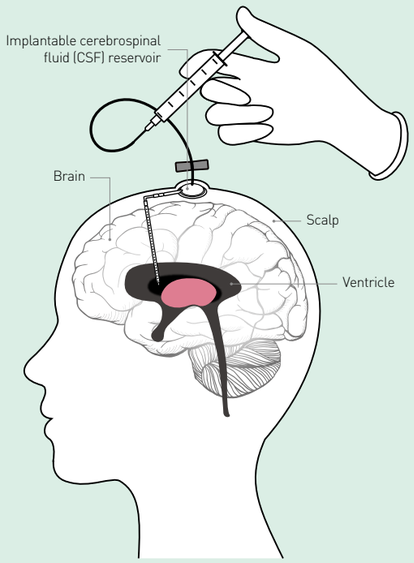
3 Life Expectancy[5, 6]

The life expectancy of MPS II patients can depend on the severity of their condition. In severe cases of MPS II, life expectancy is significantly reduced and **may be limited to the teenage years or early adulthood** compared to a longer the life expectancy until the fifth or sixth decade in the attenuated type. Eearly diagnosis and intervention are indeed critical in prolonging life expectancy and improving the quality of life as well.

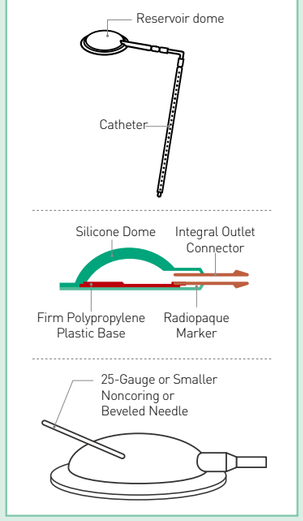
Novel ERT with ICV administration of Hunterase ICV inj.

- **World's 1st product developed for Neuronopathic MPS II**
- **Approved by PMDA, Japan (2021)**
- **High-dosage formulation (15 mg/ml) and with a long dosing interval (1q4W)**
- **Administered over at least 1 minute**
- **Generally well tolerated for the neuronopathic MPS II**
- **Reduces GAG concentrations in the CSF and prevents and stabilizes developmental decline**
- **4+ years of experience in Japan including clinical trials**

"Hunterase ICV inj. is directly delivered to the cerebral ventricle using an implanted CSF reservoir"



Reservoir Details



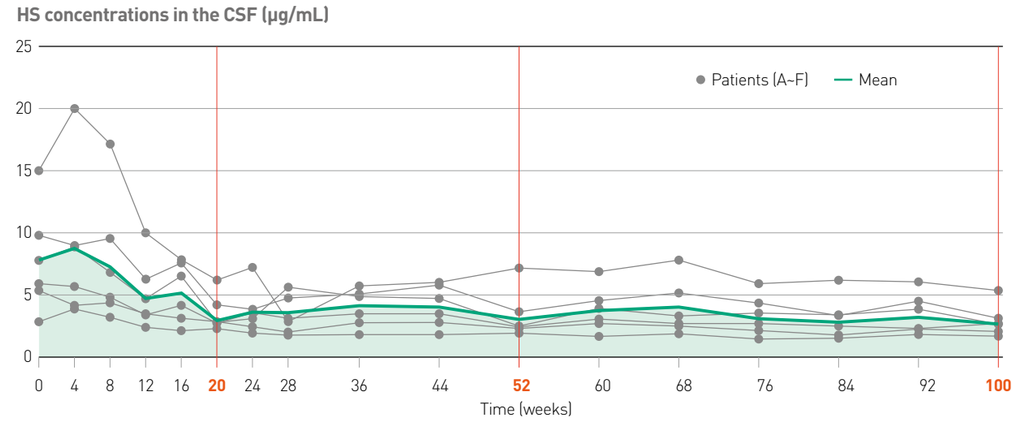
Clinical trial

Study design & objectives
A multicenter, open-label, phase 1/2 clinical study was conducted to evaluate the efficacy and safety of ICV idursulfase-β in patients with MPS II.
ICV Idursulfase-β (increasing from 1 to 30 mg between weeks 0 and 24, followed by a 30-mg final dose) was administered intracerebroventricularly once every 4 weeks using an implanted cerebrospinal fluid (CSF) reservoir; intravenous (IV) administration of idursulfase was also continued throughout the study.

Primary endpoint
Heparan sulfate (HS) concentration in the CSF.

Results
Intracerebroventricular (ICV) administration of idursulfase-β decreased HS concentrations in the CSF by 40% - 80% from baseline to week 100 in all six patients.

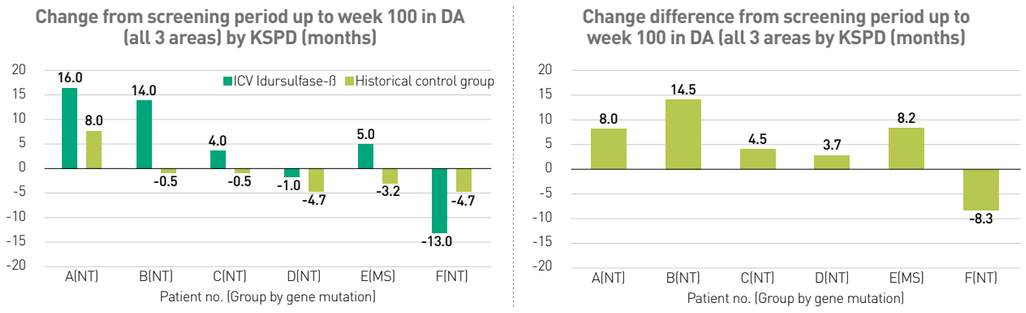
Change in HS in the CSF of patients with MPS II from the start of ICV idursulfase-β treatment up to week 100[2)]



Secondary endpoints
Developmental age (DA) determined by the Kyoto Scale of Psychological Development 2001 (KSPD) in the following three areas: postural-motor, cognitive-adaptive and language-social

Results
Monthly ICV administration of idursulfase-β maintained or increased DA in five of six patients compared with the historical control group receiving IV idursulfase. At 100 weeks (about 2 years) after starting this study, six patients who received ICV idursulfase-β had a 5.1-month increase in mean DA compared with 13 historical control patients who received only IV idursulfase.

Comparison with the historical control data in patients with MPS II[2)]



Group MS: characterized by missense mutations and presumed to have slight residual enzyme activity
Group NT: considered to have null type mutations, such as deletions, recombination with pseudogene, and nonsense mutations

Characteristics of Hunterase ICV inj.

API	Idursulfase beta
Composition (1 ml/vial)	15 mg/mL of idursulfase beta in 150 mM of sodium chloride and 0.05% of polysorbate 20
Indication	MPS II. Administration of Hunterase ICV Injection should be considered for patients with MPS II for which improvement of central nervous system symptoms is necessary.
Dosage and Administration	The usual dosage is 30 mg of idursulfase beta (genetic recombination) administered intracerebroventricularly (ICV) once every 4 weeks. Administer Hunterase ICV inj. without dilution over at least 1 min.

Serum-Free Production Process

Reduced risk of pathogen contamination (Mycoplasmas, Viruses, Prions, etc.)[1, 7]

Effective Viral Inactivation and Removal Steps

(Low pH Inactivation & Nanofiltration - Dual Clearance)
Improved safety against potential enveloped and non-enveloped virus contamination[8]

High Proportion of Active-Form Enzymes

High level of formylglycine-form peptides (79.40±0.92%)[9]

References

1. Orphanet J Rare Dis. 2013;8:42
2. Mol Ther Methods Clin Dev. 2021;21:67-75
3. Genet Mol Biol. 2014;37(2):315–329.
4. Mol Genet Metab. 2017;122S:1-7.
5. Eur J Pediatr. 2008;167:267–277.
6. J Inherit Metab Dis.2009;32:534-43.
7. ALTEX 2010;27(1):53-62. doi: 10.14573
8. J Chromatogr B, 2007 Mar 15;848(1):28-39.
9. Glycoconj J. 2014;31(4):309-15

Safety Information

Precautions

- **Precautions concerning indications**

  Administration of Hunterase (ICV Injection 15 mg) should be considered for patients with MPS II for which improvement of central nervous system symptoms is necessary.

- **Precautions concerning dosage and administration**

  1. Hunterase ICV 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. of the package insert)
  2. To prevent fluctuations in intraventricular pressure, collect cerebrospinal fluid (CSF, 2 mL) in the same volume as Hunterase ICV to be injected in advance and administer Hunterase ICV without dilution over at least 1 min.
  3. Hunterase ICV should be administered by a physician with knowledge and experience of intracerebroventricular administration.

- **Important precautions**

  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. of the package insert)
     - Establish a system to take appropriate actions for device failure etc.
     - To reduce the risk of infection, Hunterase ICV should be administered aseptically.
     - Confirm that there is no abnormality in the skin around the site of implantation before every administration of Hunterase ICV 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.
  2. Because Hunterase ICV 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 of the package insert)
  3. Periodic testing of IgG antibodies against idursulfase-ß (genetic recombination) is recommended, because IgG antibody production is predicted.

- **Precautions concerning patients with specific backgrounds**

  1. Patients with Complication/Medical History
     - Patients on ventriculoperitoneal shunt or ventriculoatrial shunt
       Intracerebral Hunterase ICV exposure decreases, and efficacy cannot be expected. (see Section 8.1. of the package insert)
     - Patients with a past history of hypersensitivity to the compounds of Hunterase ICV. (see Sections 2, 8.2. of the package insert)
  2. Use during Pregnancy
     Hunterase ICV 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.
  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 ICV in breast milk has been conducted.
  4. Pediatric Use
     No clinical study in pediatric patients under 1 year old has been conducted.
  5. Use in the Elderly
     Hunterase ICV should be administered with care while observing the patients' condition. Elderly patients have generally reduced physiological function.

- **Storage and Shelf-life**
  - Store at 2 °C to 8 °C in a hermetic container.
  - The shelf-life of this product is 24 months from the date of manufacture.

For more information,
Please Scan the QR codes below.

(Phase I/II) Impact of intracerebroventricular enzyme replacement therapy in patients with neuronopathic mucopolysaccharidosis type II, 2021

The efficacy of intracerebroventricular idursulfase-beta enzyme replacement therapy in mucopolysaccharidosis II murine model, 2018

GC Biopharma

107 Ihyeon-ro 30-beongil, Giheung-gu, Yongin-si, Gyeonggi-do, Korea I www.gcbiopharma.com
Tel: +82-31-260-9300 I Fax: +82-31-260-9413

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