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Galsulfase (Naglazyme)

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Clinical Trials Experience

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

NAGLAZYME was studied in a randomized, double-blind, placebo-controlled trial in which 19 patients received weekly infusions of 1 mg/kg NAGLAZYME and 20 patients received placebo; of the 39 patients 66% were female, and 62% were White, non-Hispanic. Patients were aged 5 years to 29 years. NAGLAZYME-treated patients were approximately 3 years older than placebo-treated patients (mean age 13.7 years versus 10.7 years, respectively).

Serious adverse reactions experienced in this trial include apnea, pyrexia, and respiratory distress. Severe adverse reactions include chest pain, dyspnea, laryngeal edema, and conjunctivitis. The most common adverse reactions requiring interventions were infusion reactions.

Table 1 summarizes the adverse reactions that occurred in the placebo-controlled trial in at least 2 patients more in the NAGLAZYME-treated group than in the placebo-treated group.

Table 1: Adverse Reactions that Occurred in the Placebo-Controlled Trial in at least 2 Patients More in the NAGLAZYME Group than in the Placebo Group

Placebo (n = 20*) No. Patients (%)	NAGLAZYME (n = 19) No. Patients (%)	MedDRA Preferred Term
20 (100)	19 (100)	All
7 (35)	9 (47)	Abdominal Pain
4 (20)	8 (42)	Ear Pain
5 (25)	8 (42)	Arthralgia
1 (5)	6 (32)	Pain
0	4 (21)	Conjunctivitis
2 (10)	4 (21)	Dyspnea
2 (10)	4 (21)	Rash
0	4 (21)	Chills
1 (5)	3 (16)	Chest Pain
0	2 (11)	Pharyngitis
0	2 (11)	Areflexia
0	2 (11)	Corneal Opacity
0	2 (11)	Gastroenteritis
0	2 (11)	Hypertension
0	2 (11)	Malaise
0	2 (11)	Nasal Congestion
0	2 (11)	Umbilical Hernia
0	2 (11)	Hearing Impairment
*One of the 20 patients in the placebo group dropped out after Week 4 infusion		

Four open-label clinical trials were conducted in MPS VI patients aged 3 months to 29 years with NAGLAZYME administered at doses of 0.2 mg/kg (n = 2), 1 mg/kg (n = 55), and 2 mg/kg (n = 2). The mean exposure to the recommended dose of NAGLAZYME (1 mg/kg) was 138 weeks (range = 54 to 261 weeks). Two infants (12.1 months and 12.7 months) were exposed to 2 mg/kg of NAGLAZYME for 105 and 81 weeks, respectively.

In addition to those listed in Table 1, common adverse reactions observed in the open-label trials include pruritus, urticaria, pyrexia, headache, nausea, and vomiting. The most common adverse reactions requiring interventions were infusion reactions. Serious adverse reactions included laryngeal edema, urticaria, angioedema, and other allergic reactions. Severe adverse reactions included urticaria, rash, and abdominal pain.

Observed adverse events in four open-label studies (up to 261 weeks treatment) were not different in nature or severity to those observed in the placebo-controlled study. No patients discontinued during open-label treatment with NAGLAZYME due to adverse events.

Immunogenicity

Ninety-eight percent (53/54) of patients treated with NAGLAZYME and evaluable for the presence of antibodies to galsulfase developed anti-galsulfase IgG antibodies within 4 to 8 weeks of treatment (in four clinical studies). In 19 patients treated with NAGLAZYME from the placebo-controlled study, serum samples were evaluated for a potential relationship of anti-galsulfase antibody development to clinical outcome measures. All 19 patients treated with NAGLAZYME developed antibodies specific to galsulfase; however, the analysis revealed no consistent predictive relationship between total antibody titer, neutralizing or IgE antibodies, and infusion-associated reactions, urinary glycosaminoglycan (GAG) levels, or endurance measures. Antibodies were assessed for the ability to inhibit enzymatic activity but not cellular uptake.

The data reflect the percentage of patients whose test results were considered positive for antibodies to galsulfase using specific assays and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to galsulfase with the incidence of antibodies to other products may be misleading.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of NAGLAZYME. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In addition to infusion reactions reported in clinical trials, serious reactions which occurred during NAGLAZYME infusion in the worldwide marketing experience include anaphylaxis, shock, hypotension, bronchospasm, and respiratory failure.

Additional infusion reactions included pyrexia, erythema, pallor, bradycardia, tachycardia, hypoxia, cyanosis, tachypnea, and paresthesia.

During postmarketing surveillance, there has been a single case of membranous nephropathy and rare cases of thrombocytopenia reported. In the case of membranous nephropathy, renal biopsy revealed galsulfase-immunoglobulin complexes in the glomeruli. With both membranous nephropathy and thrombocytopenia, patients have been successfully rechallenged and have continued to receive NAGLAZYME.