VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Hunter syndrome is a rare genetic disease which mainly affects males of all ethnicities. The incidence rate ranges from 0.6 to 2.0 per 100,000 male births. This disease causes a shortage of an enzyme (iduronate-2-sulfatase) needed by the body to destroy human glycosaminoglycans (GAGs), which are substances that build up in various body tissues. This build up negatively affects nearly all cell types, tissues, and organs of the body Over time, continued buildup of GAGs leads to a dramatic decline in mental functions and progressive organ failure. Despite the variety in the disease forms, onset of signs and symptoms typically occurs between 2.5 to 4.5 years of age. Death usually occurs in the second or third decade of life, most often from respiratory and/or cardiac failure. Before the coming of enzyme replacement therapy, treatment for Hunter syndrome was palliative and focused on clinical symptoms.

VI.2.2 Summary of Treatment Benefits

In clinical trials, direct treatment by replacement of the missing enzyme with idursulfase has been shown to provide significant therapeutic effect on multiple systems. Idursulfase has been studied in a total of 135 patients from two randomized, double-blind, placebo-controlled studies and their open-label extensions, in one open-label named-patient use study, and one open-label postmarketing study. In controlled studies, administration of intravenous idursulfase weekly and every other week was found to be generally well-tolerated and to provide clinical improvement after treatment of endurance as measured by distance walked with the difference being greatest between the placebo group and the weekly treatment group. One study in young patients with Hunter syndrome (age range at study entry from 1.4 to 7.5 years), with weekly IV idursulfase 0.5 mg/kg also showed a therapeutic response to idursulfase as measured by decreases in urinary glycosaminoglycans levels, and reductions in liver and spleen size.

The approved dose of idursulfase is 0.5 mg/kg once weekly by IV infusion over a 3-hour period, which may be gradually reduced to 1 hour if infusion related reactions are not observed.

VI.2.3 Unknowns Relating to Treatment Benefits

The idursulfase clinical development program was carefully designed in consideration of the clinical complexity and rarity of Hunter syndrome. The limited patient population necessitated a development program that employed broad eligibility criteria and that was also international in scope. The clinical development program did not include children less than 5 years of age but one study (HGT-ELA-038) was conducted in these patients to gather more information in younger children.

VI.2.4 Summary of Safety Concerns

Table 1: Important Identified Risks

Risk	What is Known	Preventability
Allergic reaction (Infusion-related reactions and hypersensitivity)	Up to 70% of patients enrolled in clinical trials had an allergic reaction to idursulfase. Most of the reactions were mild to moderate and were improved by slowing or stopping the medication or by taking certain medications. The more severe infusion related reactions have been reported in patients with severe underlying airway disease where airway may be compromised; however these have all been manageable.	Patients who previously had an allergic reaction to idursulfase can be given certain medication and can be treated with a slower rate of infusion. Special care should be taken when administering an infusion in patients with severe underlying airway disease. These patients should be closely monitored and infused in an appropriate clinical setting. Delaying the infusion in patients who present with an acute febrile respiratory illness should be considered.
Idursulfase is not recognized by the body and produces antibodies in response (Immunogenicity)	Approximately 51% of the patients exposed to weekly idursulfase 0.5mg/kg for 2 years developed an antibody response and 67.9 % of patients less than 5 years of age had at least one sample that tested positive for anti-idursulfase antibodies. The safety risks associated with presence of antibodies appear to be minimal. Patients with particular genotypes were more likely to produce antibodies.	It is unknown if there is any way to prevent this from occurring.
Idursulfase does not work because the body produces antibodies that reduce the effect of idursulfase (Lack of efficacy due to neutralising antibodies)	Approximately 24.3% of patients tested were positive for neutralising antibodies and approximately half (53.6%) of 28 very young children developed neutralising antibodies on at least one assessment.	It is unknown if there is any way to prevent this from occurring.

Table 2: Important Missing Information	
Risk	**What is Known**
Lack of information on use in elderly patients	Hunter syndrome is primarily a pediatric disease, with diagnose and start of treatment in the first years of life. The disease is always severe, progressive, and life-limiting, despite the use of any available therapies. Death usually occurs in the second or third decade of life. Therefore, it is not expected that the elderly population will be exposed to idursulfase in the near future.
Lack of information on use in female patients	Although females were excluded from the clinical trials, some females have been treated with idursulfase in the post-marketing setting but it is not likely that idursulfase will be used to treat a significant number of females in the future since Hunter syndrome is a male dominated disease. Females tend to express a milder form of the disease because some endogenous production of enzyme is expected. Therefore treatment benefits observed in male population are likely to apply to females as well.
Lack of information in patients with hepatic or renal impairment	Impaired liver and kidney function are not expected to affect the pharmacokinetic profile of idursulfase in a clinically significant way, because the enzyme is not eliminated through these organs.

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for idursulfase can be found in the Elaprase's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post Authorisation Development Plan

Table 3: List of Studies in Post-authorisation Development Plan				
Study/Activity (including study number)	**Objectives**	**Safety Concerns/Efficacy Issue Addressed**	**Status**	**Planned Date for Submission of (Interim and) Final Results**
Hunter Outcome Survey: A Global, Multi-Center,	To monitor the safety and	Infusion-related reactions and	Ongoing	Annually

Long-Term, Observational Survey of Patients with Hunter Syndrome	effectiveness of idursulfase	hypersensitivity Immunogenicity Lack of efficacy due to neutralising antibodies Use among elderly patients Use among female patients Effectiveness in all patients		Final report: 2023 (estimated)

VI.2.6.1 Studies which are a Condition of the Marketing Authorisation.

The Hunter Outcome Survey (ongoing) are conditions of the marketing authorization.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Table 4: Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
4.2	29 Jan 2015	Deletion of 1-hour infusion as important missing information	Version 4.1 was modified based on PRAC assessment
4.1	10 Sep 2014	Not applicable	Version 4.0 was changed to comply with requests from PRAC final assessment reports. Other changes include revision of information and search terms (preferred terms) for safety concerns.
4.0	19- July 2013	Not applicable	The Risk Management Plan v3.2.1 was reformatted to the new European Union template and updated with results form study HGT-ELA-042 (CSR in Annex 9)
3.2.1	01 November 2012	Infusion related reactions and hypersensitivity reactions Immunogenicity	Based on the completion of the post-hoc TKT024/TKT024EXT immunogenicity analysis, this pharmacovigilance

Table 4: Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
		Lack of efficacy due to neutralising antibodies	action was removed.
		Immunogenicity	Safety data monitoring via the Hunter Outcome Survey was added as a pharmacovigilance activity.
		Lack of efficacy due to neutralising antibodies	Updated labeling text.
3.1.1	2 Oct 2012	Immunogenicity	Safety data monitoring via the Hunter Outcome Survey was added as pharmacovigilance activity.
		Lack of efficacy due to neutralising antibodies	Updated labeling text.
3.2	23 July 2012	Infusion related reactions and hypersensitivity reactions Immunogenicity Lack of effect due to neutralising antibodies	Based on the completion of the post-hoc TKT024/TKT024EXT immunogenicity analysis, this pharmacovigilance action was removed.
3.1	13 July 2012	Immunogenicity	Added as a separate identified risk.
		Lack of efficacy due to neutralising antibodies	This was changed from a potential risk to an identified risk.
		Lack of efficacy due to neutralising antibodies	Post-hoc TKT024/TKT024EXT immunogenicity analysis and the Hunter Outcome Survey Immunogenicity sub-study (HGT-ELA-042) were added as a milestones.
3.0	22 November 2011	Infusion-related reactions	The identified risk “respiratory infusion-related reactions” was expanded to “infusion-

Table 4: Major Changes to the Risk Management Plan Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
			related reactions and hypersensitivity reactions".
		Lack of efficacy due to neutralising antibodies	Added as a potential risk.
		Infusion-related reactions and hypersensitivity and Immunogenicity	Immunogenicity and anaphylactoid/anaphylactic reactions were removed as potential risks. Anaphylactoid/anaphylactic reactions were included as part of the identified risk "infusion-related reactions and hypersensitivity reactions". Immunogenicity is discussed as part of 'infusion-related reactions and hypersensitivity reactions".
		Children under 5 years	Removed as important missing information.
		Safety in home therapy	Removed as important missing information.
		Infusion-related reactions and hypersensitivity	Post-hoc TKT024/TKT024EXT immunogenicity analysis was added as a milestone.
		Safety among patients with hepatic or renal impairment	Analysis of safety and efficacy data from patients with particular laboratory values (ie, Modification of Diet in Renal Disease, Alanine transaminase and Aspartate aminotransferase) collected as part of the Hunter Outcome Survey was removed from the action plan.
2.0	Undated	Not applicable.	Shire's routine pharmacovigilance

Table 4: Major Changes to the Risk Management Plan Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
			activities were added.