EU RISK MANAGEMENT PLAN (RMP)

for

Elaprase (Idursulfase)

RMP Version number: 5.2

Date: 21-May-2025

[redacted]

[redacted]

EU Risk Management Plan for Elaprase (Idursulfase)

RMP version to be assessed as part of this application:

RMP Version number: 5.2

Data lock point (DLP) for this RMP: 28-March-2025.

Date of final sign-off: 21-May-2025

Rationale for submitting an updated RMP: This RMP is being updated to reflect completion of Hunter outcome survey (HOS) study and removal from the Pharmacovigilance plan. Based on Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur's preliminary assessment report (Procedure no.: EMEA/H/C/PSUSA/00001722/202407) and in accordance with Good Pharmacovigilance Practices (GVP) Module V Revision 2, all safety concerns including missing information are being removed from the RMP.

Summary of significant changes from v4.2 to v5.2:

RMP Module:	Significant Changes:
Part I Product Overview	Updated 'Pharmacotherapeutic group and ATC Code'; 'Brief description of the product' and 'Indication' in alignment with the latest summary of product characteristics (SmPC).
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Updated as of DLP of the RMP.
• **Module SII Non-clinical part of the safety specification**	Updated details regarding "Immunogenicity studies" as of DLP.
• **Module SIII Clinical trial exposure**	Updated the exposure with data from ongoing study SHP-ELA-401 as of DLP.
• **Module SIV Populations not studied in clinical trials**	SIV.1: Updated details regarding "Hypersensitivity to the active substance or to any of the excipients" as of DLP. Table SIV.2: Removed details regarding "Due to prolonged exposure" following completion of HOS study.
• **Module SV Post-authorisation experience**	Updated until 28-February-2025.
• **Module SVI Additional EU requirements for the safety specification**	Not applicable
• **Module SVII Identified and potential risks**	SVII.2: Justification provided for the removal of below mentioned safety concerns: Important identified risks • Infusion-related reactions and hypersensitivity • Immunogenicity • Lack of efficacy due to neutralizing antibodies Missing information: • Use among elderly patients • Use among female patients

[redacted]

RMP Module:	Significant Changes:
	• Use among patients with hepatic or renal impairment SVII.3: Updated to 'Not applicable" following removal of above safety concerns.
• **Module SVIII Summary of the safety concerns**	Removal of all safety concerns.
Part III Pharmacovigilance plan	Part III.1: Updated to 'Not applicable' following removal of all safety concerns. Parts III.2 and III.3: HOS study completed and hence was removed from additional pharmacovigilance activities.
Part IV Plans for post-authorisation efficacy studies	HOS study completed and hence was removed.
Part V Risk minimisation measures	Updated as "Not applicable" following removal of all safety concerns.
Part VI Summary of the risk management plan	Part VI.1: Included the European Public Assessment Report (EPAR) link. Part VI II: Updated to align with Part II and Part III.
Part VII Annexes	Annex 2: HOS study was added under completed study table along with the completion date.

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Version number: 4.2

Approved with procedure: PSUSA/1722/201407

Date of approval (opinion date): 12-February-2015

QPPV name: **Jean-Marie Heim, MD**

Please note that e-signature may also be performed by [redacted] Deputy EUQPPV, [redacted] on behalf of the EU QPPV (i.e., 'per procurationem').

QPPV signature: [redacted] RMP signatures are kept on file.

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[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition/Description
6MWT	6-Minute Walk Test
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification system
DLP	Data Lock Point
DNA	Deoxyribonucleic Acid
eCTD	electronic Common Technical Document
ELISA	Enzyme-Linked Immunosorbent Assay
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GAG	Glycosaminoglycans
GVP	Good Pharmacovigilance Practices
HOS	Hunter Outcome Survey
I2S	Iduronate-2-Sulfatase
IgE	Immunoglobulin E
INN	International Non-proprietary Names
IRR	Infusion-Related Reaction
IV	Intravenous
kD	kilodalton
M6P	Mannose-6-Phosphate
MPS II	Mucopolysaccharidosis II
Nab	Neutralizing Antibody
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
uGAG	Urinary GAG

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Elaprase (Idursulfase)
Pharmacotherapeutic group(s) (ATC Code)	Other alimentary tract and metabolism products – enzymes (A16AB09)
Marketing Authorisation Holder	Takeda Pharmaceutical Company Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Elaprase
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Enzyme
	Summary of mode of action: Hunter syndrome is an X-linked recessive disease caused by insufficient levels of the lysosomal enzyme iduronate-2-sulfatase. Iduronate-2-sulfatase (I2S) functions to catabolize the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate by cleavage of oligosaccharide-linked sulfate moieties. Due to the missing or defective I2S enzyme in patients with Hunter syndrome, GAG progressively accumulate in the lysosome of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction.
	Important information about its composition: Idursulfase is a purified form of human I2S and is produced by recombinant deoxyribonucleic acid (DNA) technology in a human cell line. Idursulfase is expressed as a single polypeptide chain of 550 amino acids, which, after removal of a signal peptide, is secreted as a 525 amino acid glycoprotein. The enzyme contains 8 N-linked glycosylation sites that are occupied by complex, hybrid, and high-mannose type oligosaccharide chains. Idursulfase has a molecular weight of approximately 76 kilodalton (kD). Treatment of Hunter syndrome patients with intravenous (IV) idursulfase provides exogenous enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow specific binding of the enzyme to the M6P receptors on the cell surface, leading to cellular internalisation of the enzyme, targeting to intracellular lysosomes and subsequent catabolism of accumulated GAG.
Hyperlink to the Product Information (PI)	Refer to eCTD Module 1.3.1 for proposed PI or latest approved PI.
Indication(s) in the EEA	Current: Elaprase is indicated for the long-term treatment of patients with

[redacted]

	Hunter syndrome (Mucopolysaccharidosis II [MPS II]).
	Proposed: Not applicable
Dosage in the EEA	Current: This treatment should be supervised by a physician or other healthcare professional experienced in the management of patients with MPS II disease or other inherited metabolic disorders. Elaprase is administered at a dose of 0.5 mg/kg body weight every week by Intravenous (IV) infusion over a 3 hour period which may be gradually reduced to 1 hour if no infusion-associated reactions are observed. Infusion at home may be considered for patients who have received several months of treatment in the clinic and who are tolerating their infusions well. Home infusions should be performed under the surveillance of a physician or other healthcare professional. Method of Administration: Elaprase is a concentrated solution for intravenous infusion and must be diluted in 100 mL of 0.9% sodium chloride for IV administration. The total volume of infusion should be delivered using a 0.2 µm in line filter. The total volume of infusion may be administered over a period of 3 hours, which may be gradually reduced to 1 hour if no infusion-related reactions are observed. The duration of the infusion can be temporarily extended if infusion reactions occur. Elaprase should not be infused with other products in the infusion tubing. The compatibility of Elaprase in solution with other products has not been evaluated. Vials are for single use only. Any unused product should be disposed of appropriately.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Concentrate for solution for infusion. It is supplied in a glass vial as a clear to slightly opalescent, colourless solution. Each vial contains 3 ml of concentrate for solution for infusion which contains 6 mg of idursulfase. Each ml contains 2 mg of idursulfase.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

[redacted]

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Long-term treatment of patients with Hunter syndrome (MPS II)	
Incidence:	The mutations in the I2S gene responsible for Hunter syndrome occur throughout all ethnicities. Although Hunter syndrome has been documented in a small number of females, due to the X-linked recessive disease, nearly all occurrences are in males [redacted]. The incidence rate of Hunter Syndrome reported from several countries around the world is estimated to range between 0.6 and 2.0 per 100,000 live male births [redacted]. Drawing on data from multiple countries and different time periods, Celik et al. (2021)[redacted] aggregated the incidence (proportion) of Hunter syndrome within the total population of mucopolysaccharidosis (MPS) cases. The findings from the Celik et al study[redacted] showed that the cumulative incidence of Hunter syndrome (%) among all incident MPS cases were lowest in Pakistan (1.11%) and were highest in Japan (55.0%). Overall, Hunter syndrome is a rare congenital metabolic disease globally and represents the most common type of mucopolysaccharidosis disorders in the East Asian countries [redacted].
Prevalence:	The prevalence of Hunter syndrome is more commonly reported as birth prevalence. This metric, birth prevalence, is a ratio of the number of cases and the total number of live births during a specific period, which is typically in a given year or spanning a time period. Drawing on data from published studies, Celik et al. (2021) [redacted] aggregated the birth prevalence of Hunter syndrome across different geographic regions/countries and time periods. Data from this study suggests that the birth prevalence of Hunter syndrome can vary considerably among countries within the same continent and globally. For example, the birth prevalence for Hunter syndrome among individuals in Europe was as low as 0.13 per 100,000 live births in Norway [redacted], 0.27 per 100,000 live births in both Denmark and Sweden, [redacted] but as high as 2.16 per 100,000 live births in Estonia [redacted]. Globally, the birth prevalence for Hunter syndrome is estimated to range between 0.10 and 2.16 per 100,000 live births [redacted].
Demographics of the target population in the indication:	Hunter syndrome is a sex-linked genetic disorder inherited in an X-recessive pattern. As such, Hunter syndrome occurs almost exclusively in males. However, chromosomal rearrangement or inactivation of the normal gene expressing the X-chromosome may infrequently lead to cases occurring in females[redacted]. Two distinct subgroups of Hunter syndrome patients have been described in the published literature. Patients with mild form of the disease have normal cognitive, speech and language, and adaptive functions, whereas patients with severe form of the disease have a dramatic decline in these areas [redacted]. Clinical features of Hunter syndrome is often apparent by two to four years of age in most individuals [redacted]. Several studies have noted a difference between the attenuated and severe forms in terms of age at diagnosis and age at death. In one study, the average age of onset of symptoms for the mild patients and severe patients was 4.3 and 2.5 years of age, respectively ($p<0.02$). The average age at death for the mild patients and

Long-term treatment of patients with Hunter syndrome (MPS II)	
	severe patients was 21.7 and 11.8 years, respectively (p<0.001) [redacted]. An earlier appearance of clinical symptoms generally, but not always, predicts a more severe clinical course [redacted].
Risk factors for the disease:	Family history and sex are two well-known risk factors for developing Hunter syndrome. Hunter syndrome is an X-linked recessive disease; therefore, compared with females, males have increased risk for Hunter syndrome [redacted].
The main existing treatment options:	Prior to marketing approval of idursulfase, treatments for Hunter syndrome were palliative and focused on clinical symptoms. For example, surgery to reduce airway obstruction and continuous positive airway pressure has been used to treat sleep apnoea[redacted]. Although hematopoietic stem cell transplant has been suggested as a way of providing donor cells capable of expressing I2S, long-term results are limited and inadequate to support a recommendation of this procedure for individuals with Hunter syndrome[redacted]. A variety of complications can occur with Hunter syndrome and concomitant medications may be used to treat these complications. Some medications commonly used in Hunter syndrome patients include, but are not limited to, antibiotics (due to chronic and recurrent infections), antihypertensive (due to cardiac complications), antiepileptics, and drugs to improve gastrointestinal symptoms.
Natural history of the indicated condition in the untreated population, including mortality and morbidity:	The clinical manifestations of Hunter syndrome are multi-systemic and vary considerably from patient to patient [redacted]. At the onset, patients appear physically normal at birth. As the disease progresses the phenotypic features typical of the disorder become increasingly apparent. The most common clinical signs and symptoms include coarse facial features, enlarged tongue, hearing loss, abnormal dentition, restrictive lung disease, hepatosplenomegaly, valvular heart disease, ventricular hypertrophy, decreased joint range of motion, skeletal deformities, and severe short stature[redacted]. In addition to their restrictive pulmonary disease, oropharyngeal and respiratory deposition of GAG leads to severe airway obstruction due to macroglossia, supraglottic narrowing, and tracheomalacia, further contributing to impaired pulmonary function and sleep apnoea[redacted]. Over time, the increasing size and protuberance of the tongue causes difficulty with swallowing and also may impair their ability to speak clearly[redacted]. In the latter stages of the disease, continued accumulation of GAG leads to progressive end-organ failure and significantly shortened life span. Perhaps the most devastating aspect of Hunter syndrome, is the impact on quality of life due to progressive physical abnormalities. Individuals with Hunter syndrome suffer from chronic, severely diminished endurance. Early on, this may manifest as an inability to keep up with peers in activities that require physical exertion. Later, their ability to walk even short distances may be lost and ultimately, many patients become wheelchair bound [redacted]. Approximately 60% of Hunter patients also develop global intellectual decline and severe developmental delays[redacted]. Approximately one half of Hunter syndrome patients, as a consequence of their global intellectual impairment, lose much of their ability to perform even simple activities of daily living. In addition, the progressive decrease in joint mobility and their broad, claw-like short fingers may prevent patients from autonomously performing many self-care activities including self-dressing, toilet care, and personal grooming. Hunter syndrome patients become entirely dependent on others at an early

[redacted]

Long-term treatment of patients with Hunter syndrome (MPS II)	
	age for their continued survival[redacted]. Although the disease is heterogenous at initial presentation, Hunter syndrome is always progressive and life-limiting. In the latter stages of the disease, continued accumulation of GAG leads to progressive end organ failure and significantly shortened lifespan[redacted]. For the neuronopathic phenotype, death usually occurs in the second or third decade of life, most often from respiratory and/or cardiac failure. Patients with the non-neuronopathic phenotype usually survive into later adulthood[redacted]. A recent paper describes clinical outcomes for a pair of siblings diagnosed with neuronopathic form of Hunter Syndrome, the older sibling after onset of clinical disease at age 3.7 years, and the younger sibling at 12 months and prior to onset of clinical symptoms. Both initiated enzyme replacement therapy within 1 month of diagnosis. The older sibling demonstrated significant cognitive disability (measurement score <55, normal range 85-115), the younger sibling scored 91 and within the normal range. The older sibling always required assistance with daily activities including toileting, dressing, and washing whereas the younger sibling was fully toilet-trained and required more modest assistance. The older sibling developed significant physical disability and required use of an adaptive stroller by age 11, the younger sibling was able to hike unassisted > 6 miles by age 10.5. Both siblings developed sensory-seeking behaviours, hyperactivity, impulsivity, and sleep difficulties. Although outcomes of this sibling pair cannot be readily generalized to the Hunter Syndrome population, these outcomes are suggestive that pre-symptomatic detection and treatment of Hunter Syndrome may provide opportunity to alter progression and severity of disease[redacted].
Important co-morbidities:	Comorbidities among patients with Hunter syndrome are related to the underlying pathology. The central, underlying pathophysiological process leading to the clinical manifestations of Hunter syndrome is the chronic accumulation of heparan sulfate and dermatan sulfate inside cellular lysosomes, resulting in cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. Accumulation of these GAG species affects nearly all cell types, tissues, and organs of the body including the respiratory tract, heart, liver, spleen, leptomeninges, bones, joints, oropharynx, head, neck, and central nervous system. For example, the accumulation of dermatan and heparan sulfate – important constituents of the heart valves – lead to abnormally thick valves which have been reported to reduce overall cardiac efficiency and predispose individuals with Hunter syndrome to higher risk for valvular heart disease, mitral and aortic regurgitation, left ventricular hypertrophy, and hypertension[redacted]. In a survey of patients with Hunter syndrome, about two-thirds (63%) were reported to have valvular heart disease[redacted]. The clinical manifestations of Hunter syndrome vary considerably from patient to patient with pathology in one organ system presenting the most prominent clinical problem in some patients and impairment in other organ systems presenting the biggest challenge in others [redacted]. As the disease progresses the phenotypic features typical of the disorder become increasingly apparent. The most common clinical signs and symptoms include slow mental development, enlarged tongue, coarse facial features, hearing loss, abnormal dentition, restrictive lung disease, hepatosplenomegaly, valvular heart disease, decreased joint range of motion, skeletal deformities, and severe short stature[redacted]. In addition to their restrictive pulmonary disease, oropharyngeal and respiratory deposition of

[redacted]

Long-term treatment of patients with Hunter syndrome (MPS II)	
	GAG leads to severe airway obstruction due to macroglossia, supraglottic narrowing, and tracheomalacia, further contributing to impaired pulmonary function and sleep apnoea [redacted]. Over time, the increasing size and protuberance of the tongue causes difficulty with swallowing and also may impair their ability to speak clearly [redacted]. In the latter stages of the disease, continued accumulation of GAG leads to progressive end-organ failure and significantly shortened life span.

[redacted]

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Single and repeat-dose toxicity Toxicity studies indicate that acute IV bolus administration of idursulfase presents no acute toxicological risk in either Sprague-Dawley rats or cynomolgus monkeys at doses up to at least 20 mg/kg, a dose that reflects a 40-fold increase in enzyme administration relative to the approved dose of 0.5 mg/kg. Repeat (6 months) IV bolus administration of idursulfase also presents no toxicological risk in cynomolgus monkeys at doses up to at least 12.5 mg/kg.	Nonclinical data indicate repeat-dose toxicity is not considered to be a potential risk in humans.
Reproductive toxicity Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development. Animal studies have shown excretion of idursulfase in breast milk.	Use of idursulfase during pregnancy is not recommended. Idursulfase may get into breast milk and therefore the patient should talk to their doctor or pharmacist before using this medicine before breastfeeding.
Developmental toxicity Studies in juvenile animals have not been performed.	Not applicable.
Nephrotoxicity Idursulfase has not been evaluated in specific nephrotoxicity studies. In general toxicity studies in rat and non-human primate, examination of the kidney does not indicate any adverse effect or potential toxicity.	Nonclinical data does not indicate a potential risk in humans.
Hepatotoxicity Idursulfase has not been evaluated in specific hepatotoxicity studies. In general, toxicity studies in rat and non-human primate did not indicate any adverse effect or potential toxicity upon examination of the liver.	Nonclinical data does not indicate a potential risk in humans.
Genotoxicity Idursulfase has not been evaluated in genotoxicity studies since it is a naturally occurring human protein. Its mechanism of action and site of action (degradation of GAG in cellular lysosomes) do not suggest any genotoxic risk.	None.
Carcinogenicity No carcinogenicity studies have been conducted with idursulfase, although the compound is intended for long-term treatment.	None.

[redacted]

Key Safety Findings	Relevance to human usage
However, no carcinogenic potential would be anticipated with idursulfase based on its structure (a recombinant form of a naturally occurring human glycoprotein) and its impurity profile. The biochemical properties of I2S are well characterised, and there are no known interactions with DNA.	
General safety pharmacology A safety pharmacology study in cynomolgus monkeys showed no treatment related effects on cardiovascular, respiratory, or central nervous system parameters following a single IV administration of idursulfase at dose levels of 5, 10, or 20 mg/kg.	Nonclinical data indicate, cardiovascular, respiratory, or central nervous system safety is not considered to be a potential risk in humans.
Mechanisms for drug interactions No formal drug product interaction studies have been conducted with idursulfase. Based on its metabolism in cellular lysosomes, idursulfase would not be a candidate for cytochrome P450 mediated interactions	None
Local tolerance studies No formal local tolerance studies for idursulfase have been performed. However, in nonclinical toxicity studies, there were no serious adverse findings related to the injection of idursulfase.	Nonclinical data indicate local tolerability is not considered to be a potential risk in humans.
Immunogenicity studies Since idursulfase is a human protein being administered to animals, it would not be unexpected to see the development of anti-idursulfase antibodies following repeat administration of drug. While antibody development was shown to occur following chronic administration of enzyme, no adverse toxicological findings were associated with the presence of anti-idursulfase antibodies.	Immunogenicity and lack of efficacy due to neutralising antibodies (Nab) were previously considered important identified risks in humans but are currently considered as not important risks that require only routine pharmacovigilance and routine risk minimisation.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

All studies included in the tables below are complete except for SHP-ELA-401, which is ongoing and data reflect the complete study period (up to 28-March-2025).

A total of 73 subjects were exposed to idursulfase in the randomized double-blind studies TKT 008 and TKT 024, and 161 subjects in all clinical trial population in table below.

One study SHP-ELA-401 is ongoing and is presented separately.

Study TAK-665-4003 is currently 'ongoing' however, no patient has been enrolled so far.

Table SIII.1: Duration of exposure

Randomized Blinded Trial Population Only (TKT 008, TKT 024)		
Duration of Exposure (At Least)	**Subjects**	**Subject-time (years) [a]**
1 day	73	154.5
1 week	72	154.5
12 weeks (3 months)	72	154.5
24 weeks (6 months)	72	154.5
36 weeks (9 months)	72	154.5
48 weeks (12 months)	72	154.5
96 weeks (24 months)	33	114.6
144 weeks (36 months)	32	112.3
192 weeks (48 months)	9	38.4
240 weeks (60 months)	2	10.5
288 weeks (72 months)	0	0.0
Total subject-time	**73**	**154.5**

[a]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).

All Clinical Trial Populations (TKT 008/018, TKT 024/024EXT, HGT-ELA-038, HGT-ELA-042[b])		
Duration of Exposure (At Least)	**Subjects**	**Subject-time (years) [a]**
1 day	161	403.2
1 week	159	403.2
4 weeks (1 month)	158	403.1
12 weeks (3 months)	158	403.1
24 weeks (6 months)	155	402.1
36 weeks (9 months)	153	400.9
48 weeks (12 months)	152	400.0

[redacted]

All Clinical Trial Populations (TKT 008/018, TKT 024/024EXT, HGT-ELA-038, HGT-ELA-042[b])		
Duration of Exposure (At Least)	**Subjects**	**Subject-time (years) [a]**
96 weeks (24 months)	117	362.7
144 weeks (36 months)	76	275.1
192 weeks (48 months)	28	123.4
240 weeks (60 months)	10	51.5
288 weeks (72 months)	0	0.0
Total subject-time	**161**	**403.2**

[a]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).
[b] 8 subjects in HGT-ELA-042 also participated in TKT 024 study024 and are included in the exposure totals for both.

SHP-ELA-401 study		
Duration of Exposure (At Least)	**Subjects**	**Subject-time (years)***
1 day	21	106.7
1 week	21	106.7
12 weeks (3 months)	21	106.7
24 weeks (6 months)	21	106.7
36 weeks (9 months)	20	106.2
48 weeks (12 months)	20	106.2
96 weeks (24 months)	19	104.7
144 weeks (36 months)	18	101.9
192 weeks (48 months)	17	99.2
240 weeks (60 months)	17	99.2
288 weeks (72 months)	6	43.7
336 weeks (84 months)	5	37.7
384 weeks (96 months)	3	23.5
Total	**21**	**106.7**

*Subject-time is calculated as the total exposure for all subjects within the study, converted to years (total exposure/365.25).

Table SIII.2: Exposure by Dose

Randomized Blinded Trial Population Only (TKT 008, TKT 024)		
Dose	**Subjects**	**Subject-time (years) [a]**
0.15 mg/kg every other week	3	4.2
0.5 mg/kg every other week	35	45.9

[redacted]

Randomized Blinded Trial Population Only (TKT 008, TKT 024)		
0.5 mg/kg weekly	32	101.2
1.5 mg/kg every other week	3	3.2
Total	**73**	**154.5**

[a]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).

All Clinical Trial Populations (TKT 008/018, TKT 024/024EXT, HGT-ELA-038, HGT-ELA-042[b])		
Dose	**Subjects**	**Subject-time (years) [a]**
0.15 mg/kg every other week	4	21.0
0.5 mg/kg every other week	36	122.1
0.5 mg/kg weekly	117	240.2
1.5 mg/kg every other week	4	19.9
Total	**161**	**403.2**

[a]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).
[b]8 subjects in HGT-ELA-042 also participated in TKT 024 study024 and are included in the exposure totals for both.

SHP-ELA-401 study		
Dose	**Subjects**	**Subject-time (years)***
0.5 mg/kg weekly	21	106.7
Total	**21**	**106.7**

*Subject-time is calculated as the total exposure for all subjects within the study, converted to years (total exposure/365.25).

Table SIII.3: Exposure by Age Group and Sex

Randomized Blinded Trial Population Only (TKT 008, TKT 024)				
Age Group	**Subjects**		**Subject-time (years)[a]**	
	Male	Female	Male	Female
<12 years	33	0	65.2	0.0
12-18 years	17	0	32.4	0.0
>18 years	23	0	56.9	0.0
Total	**73**	**0**	**154.5**	**0.0**

[a]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).

[redacted]

All Clinical Trial Populations (TKT 008/018, TKT 024/024EXT, HGT-ELA-038, HGT-ELA-042[b])				
Age Group	**Subjects**		**Subject-time (years) [a]**	
	Male	Female	Male	Female
<12 years	91	0	200.7	0.0
12-18 years	32	0	95.3	0.0
>18 years	38	0	107.3	0.0
Total	**161**	**0**	**403.2**	**0.0**

[a]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).
[b]8 subjects in HGT-ELA-042 also participated in TKT 024 study024 and are included in the exposure totals for both.

SHP-ELA-401 study				
Age Group	**Subjects**		**Subject-time (years)***	
	Male	Female	Male	Female
<12 years	21	0	106.7	0.0
Total	**21**	**0**	**106.7**	**0.0**

*Subject-time is calculated as the total exposure for all subjects within the study, converted to years (total exposure/365.25).

Table SIII.4: Exposure by Ethnic Origin or Racial origin

Randomized Blinded Trial Population Only (TKT 008, TKT 024)		
Ethnic/Racial Origin	**Subjects**	**Subject-time (years) [a]**
Caucasian	64	134.8
African American	3	7.9
Asian	2	2.0
American Indian or Alaska Native	3	6.0
Other	1	3.9
Total	**73**	**154.5**

[a]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).

All Clinical Trial Populations (TKT 008/018, TKT 024/024EXT, HGT-ELA-038, HGT-ELA-042[b])		
Ethnic/Racial Origin	**Subjects**	**Subject-time (years)[a]**
Caucasian	132	342.9
African American	10	23.1
Asian	11	14.6
American Indian or Alaska Native	3	11.9

[redacted]

All Clinical Trial Populations (TKT 008/018, TKT 024/024EXT, HGT-ELA-038, HGT-ELA-042[b])		
Ethnic/Racial Origin	**Subjects**	**Subject-time (years)[a]**
Other	5	10.8
Total	**161**	**403.2**

[a]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).
[b] 8 subjects in HGT-ELA-042 also participated in TKT 024 study024 and are included in the exposure totals for both.

SHP-ELA-401 study		
Ethnic/Racial Origin	**Subjects**	**Subject-time (years)***
White	4	18.3
Asian	15	80.6
Other	2	7.7
Total	**21**	**106.7**

*Subject-time is calculated as the total exposure for all subjects within the study, converted to years (total exposure/365.25).

Table SIII.5: Exposure by Genotype

Randomized Blinded Trial Population Only (TKT 008, TKT 024)		
	Subjects	**Subject-time (years) [a]**
Complete Deletion/Large Rearrangement	0	0.0
Frameshift	7	11.1
MisSense	35	73.7
Unclassified/Unclassifiable	31	69.6
Total	**73**	**154.5**

[a]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).

All Clinical Trial Populations (TKT 008/018, TKT 024/024EXT, HGT-ELA-038, HGT-ELA-042[b])		
	Subjects	**Subject-time (years) [a]**
Complete Deletion/Large Rearrangement	10	9.3
Frameshift	19	30.6
MisSense	75	183.9
Unclassified/Unclassifiable	57	179.4
Total	**161**	**403.2**

[a]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25.
[b] 8 subjects in HGT-ELA-042 also participated in TKT 024 study024 and are included in the exposure totals for both.

[redacted]

SHP-ELA-401 study		
	Subjects	**Subject-time (years)***
Inversion	5	25.5
Indel	1	7.8
MisSense	8	34.2
Deletion	4	24.2
Nonsense	2	10
Splicing	1	5
Total	**21**	**106.7**

*Subject-time is calculated as the total exposure for all subjects within the study, converted to years (total exposure/365.25).

[redacted]

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Hypersensitivity to the active substance or to any of the excipients.	
Reason for exclusion:	True type I hypersensitivity has not been observed in the clinical program. In a non-company-sponsored post-marketing study, Kim et al. reported that 3/34 (8.8%) of patients treated with idursulfase, experienced anaphylaxis and a positive IgE antibody detected by skin prick test or Enzyme-Linked Immunosorbent Assay (ELISA) [redacted]. The duration of ERT was 154±34 weeks (range of 13-180 weeks), and the first reaction was found at 67±46 weeks (range, 3-109 weeks). No deaths occurred during the study period. If a patient is allergic to the active substance or to any of the excipients, administration of the drug should be stopped.
Is it considered to be included as missing information?	No
Rationale:	Previously considered as an important identified risk; subsequently re-classified to a non-important risk subject to routine pharmacovigilance and routine risk minimisation.

Patient had a tracheostomy	
Reason for exclusion:	Pulmonary function tests cannot be performed on patients who had a tracheostomy which was a primary endpoint in the registration trial. This was not an exclusion criterion in phase I-II clinical trials.
Is it considered to be included as missing information?	No
Rationale:	Evaluation of disease progression and therapeutic benefits can be carried out using other clinical methods (e.g., 6-minute walk test [6MWT], etc.). It may also not be a contraindication if patients have no severe underlying respiratory disease.

Patient had received a bone marrow or cord blood transplant	
Reason for exclusion:	This could introduce bias in assessment of efficacy as bone marrow or cord blood transplant are potential alternative therapies for Hunter syndrome.
Is it considered to be included as missing information?	No
Rationale:	Idursulfase can be used if the patient had a bone marrow or cord blood transplant, and it was not efficacious.

[redacted]

Females	
Reason for exclusion:	Because of the X-linked inheritance, very few female patients with Hunter syndrome have been reported.
Is it considered to be included as missing information?	Yes
Rationale:	Due to preserved (albeit insufficient) production of I2S from normal cells, females typically manifest a milder disease compared to their male counterparts.

SIV.2. LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Because Hunter syndrome is a rare disease with an estimated incidence of 1 in approximately 162,000 live births, very few patients across the world are available for evaluation in clinical studies [redacted]. The patients participating in the studies of the idursulfase clinical development program presented a broad spectrum of disease manifestations quite similar to the wide heterogeneity present in the general population of patients with Hunter syndrome. This degree of heterogeneity naturally presents a challenge to demonstrating a clear drug benefit that rises above the intra-patient variability in complex disease signs and symptoms of the underlying disease. Due to the limited number of Hunter syndrome patients available for clinical studies, broad admission criteria were applied, including range of patients' ages (children, adolescent, and adult patients) and few limits on the extent of disease.

Table SIV.2: Limitations of Adverse Drug Reaction Detection to Clinical Study Development Programmes

Ability to Detect Adverse Reactions	Limitation of Study Programme	Discussion of Implications for Target Population
Which are rare	The idursulfase clinical development program includes data from 153 male patients receiving the clinically recommended dose of idursulfase.	Adverse drug reactions with a frequency greater than 1 in 51 could be detected if there was no background incidence.

SIV.3. LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table SIV.3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Children	Idursulfase has been shown to be safe in children and adolescents 16 months to 18 years of age. Due to the nature of the primary endpoints, patient recruitment in the pivotal study (TKT024) was limited to those able to perform pulmonary function tests and the 6MWT, which is a sub-maximal exercise tolerance test that reflects the physical activities of daily living. Therefore, children less than 5 years old were excluded from this study.

[redacted]

Type of special population	Exposure
	In the pivotal study (TKT024), there were no apparent differences in the types and severity of adverse events (AEs), including infusion-related AEs, when the safety data were reviewed by patient-age category defined as children (5 to 11 years), adolescents (12 to 18 years) and adults (≥19 years). The rates of infusion-related AEs tended to be higher in older patients (21/29; 72.4% in adolescents and 18/24; 75.0% in adults) as compared to younger patients (26/43; 60.5% in children). These 26 children reported a total of 172 events (comprising 10.6% of all AEs in that age group) while the 21 adolescents reported 126 events (15.7% of all AEs in that age group) and the 18 adults reported 177 events (or 22.2% of all AEs in that age group). Very young children (i.e., less than 5 years) with early and pronounced clinical manifestations of Hunter syndrome are potentially more likely to have a large deletion in the I2S gene compared to patients with later onset of clinical symptoms. In cases of large gene deletions, there may be essentially no I2S protein present in the patients that is immunologically similar to idursulfase. Therefore, in the pre-authorisation phase, there was a theoretical concern that such patients may be at increased risk of an immune reaction to idursulfase administration. To address this concern, a safety study of patients under 5 years of age was conducted. This study commenced in December-2007 and completed in July-2011. In this study, patients with the Missense genotype have more benign safety profiles and a larger magnitude in efficacy responses compared to the patients with the Complete deletion/Large rearrangement genotype. The final study report is available (HGT-ELA-038).
Elderly	Although the disease is heterogeneous with regard to initial presentation, Hunter syndrome 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, most often from respiratory and/or cardiac failure [redacted]. Therefore, the elderly were not included in the clinical development program though they have been treated with idursulfase in the post-marketing setting.
Females	Hunter syndrome is a recessive, X-linked disease and very few female patients have been described worldwide [redacted]. Although females were excluded from the clinical trials, some females have been treated with idursulfase in the post-marketing setting.
Patients with Hepatic or Renal Impairment	Patients with Hunter syndrome have liver involvement with major organomegaly but usually minor functional consequences. Furthermore, as metabolism of idursulfase is expected to occur by peptide hydrolysis and renal elimination is considered to be a minor pathway for clearance, impaired liver and kidney function are not expected to affect the pharmacokinetic profile of idursulfase in a clinically significant way. In clinical trials, there is a clinically significant reduction in liver size across all age groups, most likely due to reduction of GAG deposits in the visceral organs.
Patients with a Disease	Patients unable to perform the clinical tests required in the clinical

[redacted]

Type of special population	Exposure
Severity Different from the Inclusion Criteria in the Clinical Study Population	trials due to substantial psychomotor impairment were not enrolled in clinical studies. However, patients with a wide range of pulmonary involvement, including severe restrictive and/or obstructive syndrome, were recruited. In addition, these patients showed a wide range of cardiac pathology, mainly cardiac valvular disease, cardiomyopathy, and congestive heart failure. Only patients with normal pulmonary function were excluded, but in view of the type of adverse drug reactions reported in clinical trials, such patients are likely to exhibit a safety profile that is no worse, and perhaps better than patients with impaired pulmonary function.
Subpopulations Carrying Known and Relevant Polymorphisms	Hunter syndrome is caused by a mutation in the gene for I2S, which results in either an enzyme with deficient activity or a complete lack of expression of an enzyme. In either case, the mutation causes a clear disease state. Therefore, the alterations in the I2S gene that underlie Hunter syndrome are not considered polymorphisms. Patients with the complete deletion/large rearrangement genotype are more likely to manifest a severe form of Hunter syndrome disease compared to other known genotypes. Pediatric patients with the complete deletion/large rearrangement genotype have a high probability of developing antibodies, including Nabs, in response to exposure to idursulfase. Patients with this genotype have a higher probability of developing IRAEs and tend to show a muted response assessed by decrease in urinary GAG (uGAG) levels, liver size and spleen volume compared to the patients with the missense genotype. In general, patients with the frameshift/splice site mutation genotype develop antibody responses between those seen in patients with complete deletion/large rearrangement or missense genotypes. However, individual patients with a complete deletion genotype and high titer antibodies experienced therapeutic responses similar or better than some patients with a missense mutation genotype and no antibody response.
Patients of Different Racial and/or Ethnic Origin	The pivotal study (TKT024) was conducted at 9 sites in the United States, South America, and Europe. This covered a wide sample of diverse ethnic origin including 4 subjects from Japan; however, 82% of the patients were Caucasian. The mutations in the I2S gene responsible for Hunter syndrome occur throughout all races and geographical regions. Therefore, no formal analyses of safety data by ethnic origin were conducted, but race or ethnic-specific toxicity is not expected.

[redacted]

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1. Post-authorisation exposure

SV.1.1. Method used to calculate exposure

Based on an average patient weight of 32 to 36 kg and a dose of 16 to 18 mg per week (3 vials per patient), patient years (PYs) exposure is calculated using the following formula:

$$\text{PY of exposure} = \frac{\text{Number of vials sold}}{52 \text{ weeks} \times 3 \text{ vials}}$$

SV.1.2. Exposure

Cumulatively, the estimated worldwide patient exposure to idursulfase as of 28-February-2025 is 26,203 PYs.

[redacted]

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

There is no evidence that abuse or dependence occurs with idursulfase therapy. Idursulfase is a recombinant human protein that is used solely to replace the missing or defective enzyme iduronate-2-sulfatase in patients with Hunter syndrome. There are no components of the drug substance or formulation that present potential for misuse for illegal purposes.

[redacted]

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

None.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

None.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

None.

Known risks that do not impact the risk-benefit profile

None.

Other reasons for considering the risks not important:

None.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks	Risk-benefit impact
Infusion-related reaction and hypersensitivity	Infusion of any protein-based drug may be associated with systemic body reactions that could, on rare occasions, lead to severe and/or life-threatening conditions.
Immunogenicity	Idursulfase is a recombinant enzyme produced via a genetically engineered human cell line and therefore has the potential for immunogenicity in susceptible patients, similar to other therapeutic recombinant protein therapies administered via the intravenous route. Since Hunter syndrome is caused by a deficiency/very low levels or abnormality of the endogenous iduronate-2-sulfatase, a potential immune response is likely
Lack of efficacy due to neutralizing antibodies	The protein load may be perceived by the body as foreign, despite the enzyme being humanized. Immunogenicity, with Nab, may lead to lack of efficacy.

[redacted]

Important Potential Risks	Risk-benefit impact
None	

Missing Information	Risk-benefit impact
Use among elderly patients	It is not expected that the elderly population will be exposed to IV idursulfase.
Use among female patients	It is not likely that IV idursulfase will be used to treat a significant number of females, 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 the male population are likely to apply to females as well.
Use among patients with hepatic or renal impairment	Impaired liver and kidney function are not expected to affect the pharmacokinetic profile of IV idursulfase in a clinically significant way, because the enzyme is metabolized intracellularly and not eliminated through the liver or kidney.

SVII.2. NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Justification for the removal of safety concerns:

According to GVP Module V (Rev 2), all safety concerns are being removed from the RMP as they are well characterised or no additional information is anticipated. No safety signal has been identified in over 10 years of post-marketing experience; and these risks are currently being monitored via routine pharmacovigilance activities.

The following safety concerns have been removed from the RMP:

Important identified risks:

- Infusion-related reactions and hypersensitivity
- Immunogenicity
- Lack of efficacy due to neutralizing antibodies

Missing information:

- Use among elderly patients
- Use among female patients
- Use among patients with hepatic or renal impairment

SVII.3. DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

Not applicable

[redacted]

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

[redacted]

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Not applicable

Specific adverse reaction follow-up questionnaires:

Not applicable

Other forms of routine pharmacovigilance activities for:

Not applicable

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable

[redacted]

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable

[redacted]

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Not applicable

V.2. Additional Risk Minimisation Measures

Not applicable

V.3. Summary of risk minimisation measures

Not applicable

[redacted]

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Elaprase (Idursulfase)

This is a summary of the risk management plan (RMP) for Elaprase. The RMP details important risks of Elaprase, how these risks can be minimised, and how more information will be obtained about Elaprase's risks and uncertainties (missing information).

Elaprase's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Elaprase should be used.

This summary of the RMP for Elaprase should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Elaprase RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Elaprase is authorised for long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II [MPS II]) (see SmPC for the full indication). It contains Idursulfase as the active substance and it is given by intravenous infusion route.

Further information about the evaluation of Elaprase's benefits can be found in Elaprase EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

Elaprase | European Medicines Agency (EMA)

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Elaprase, together with measures to minimise such risks and the proposed studies for learning more about Elaprase's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Elaprase are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Elaprase. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

[redacted]

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Elaprase.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for Elaprase.

[redacted]

PART VII: ANNEXES

Table of contents

[redacted]

Annex 4: Specific adverse drug reaction follow-up forms

[redacted]

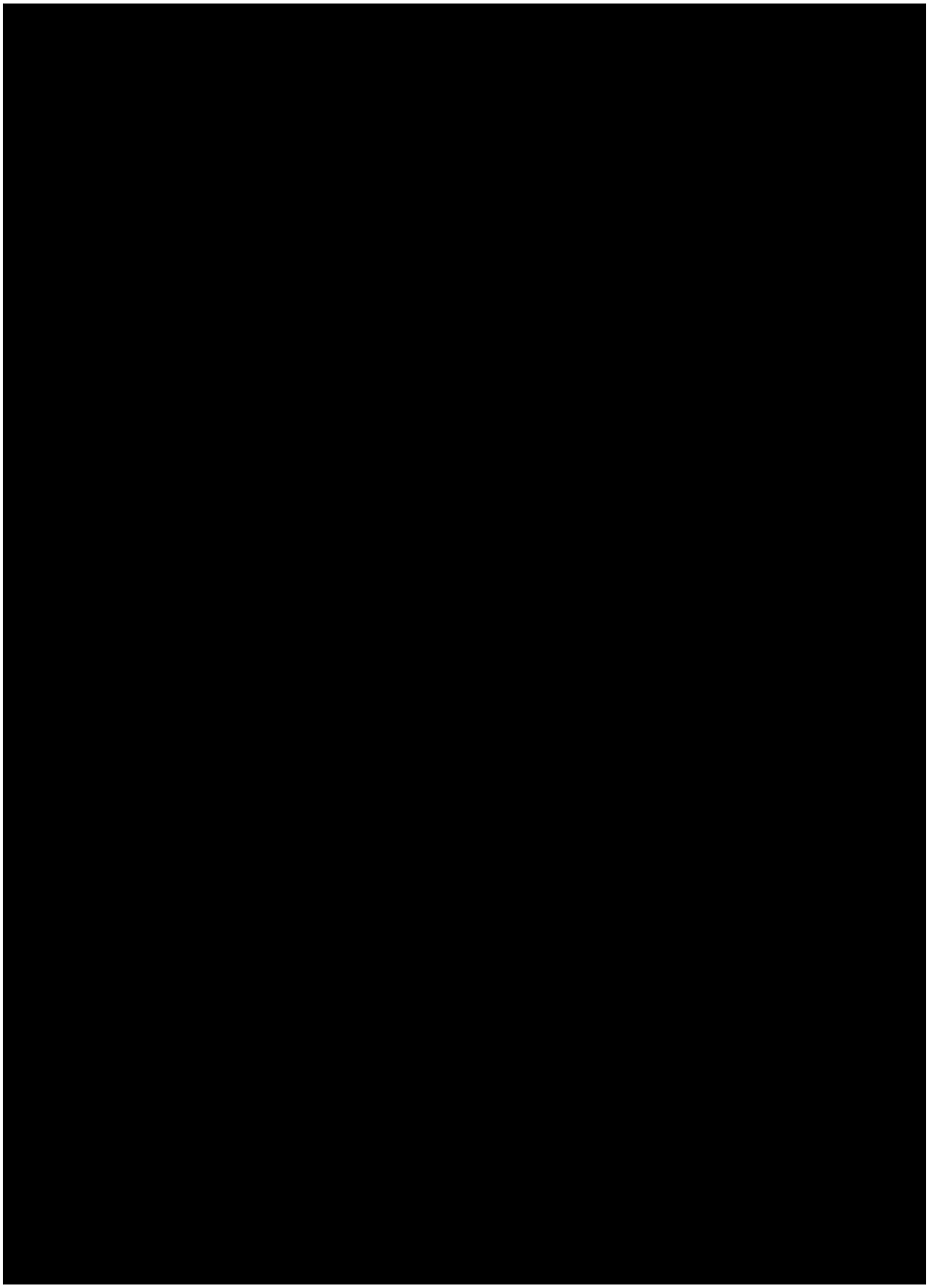
Annex 6: Details of proposed additional risk minimisation activities (if applicable)

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable

[redacted]

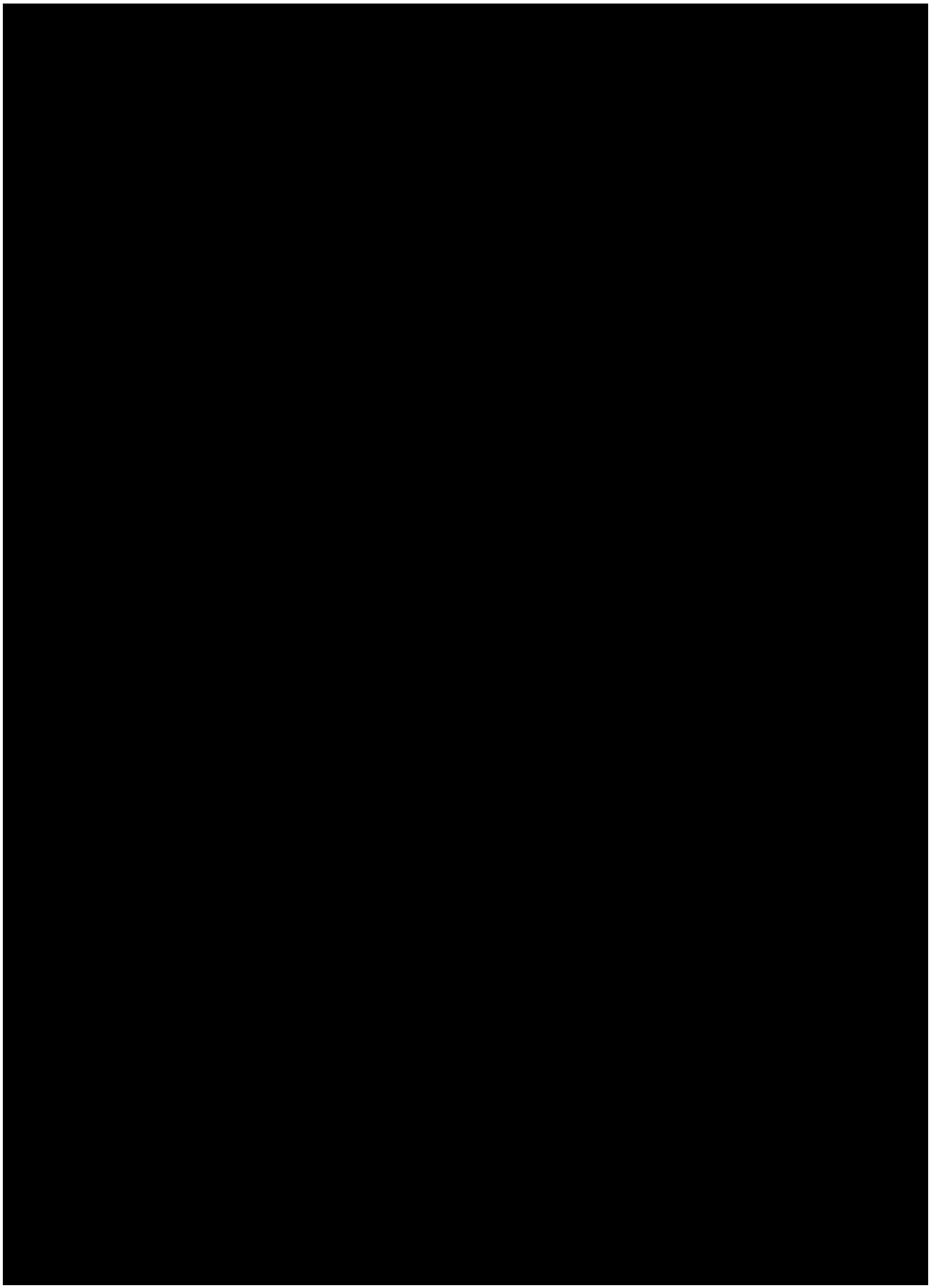
[redacted]

[redacted]

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable

[redacted]



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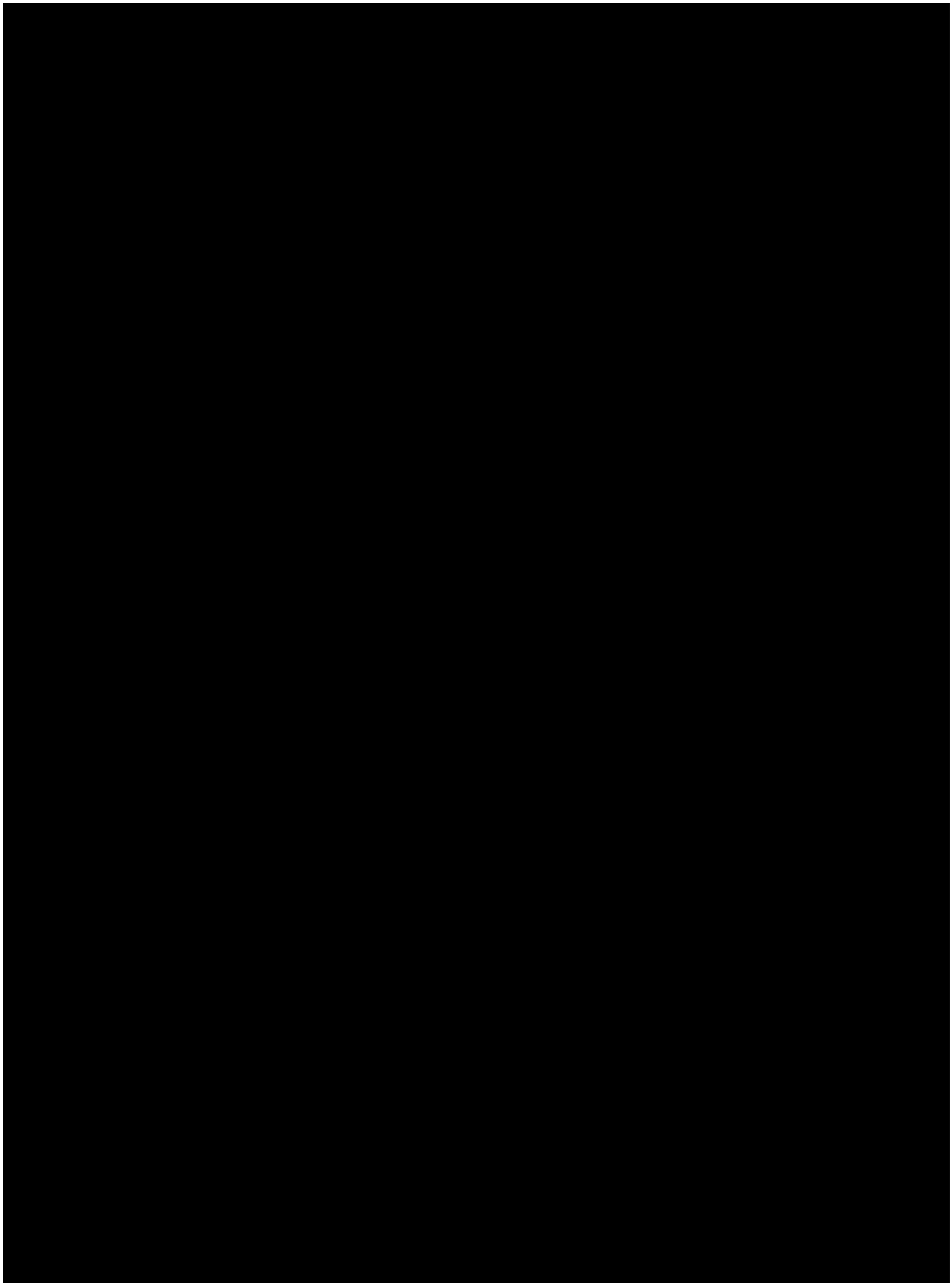

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