ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Mepsevii 2 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 2 mg vestronidase alfa*. Each vial of 5 mL concentrate contains 10 mg vestronidase alfa.

*Vestronidase alfa is a recombinant form of human beta-glucuronidase (rhGUS) and is produced in Chinese Hamster Ovary cell culture by recombinant DNA technology.

Excipient(s) with known effect

Each vial contains 17.8 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).
Colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mepsevii is indicated for the treatment of non-neurological manifestations of Mucopolysaccharidosis VII (MPS VII; Sly syndrome).

4.2 Posology and method of administration

Treatment should be supervised by a healthcare professional experienced in the management of patients with MPS VII or other inherited metabolic disorders. Administration of vestronidase alfa should be carried out by an appropriately trained healthcare professional with the ability to manage medical emergencies.

Posology

The recommended dose of vestronidase alfa is 4 mg/kg of body weight administered by intravenous infusion every two weeks.

To minimise the risk of hypersensitivity reactions, a non-sedating antihistamine with or without an antipyretic medicinal product should be administered 30-60 minutes prior to the start of the infusion (see section 4.4). Infusion should be avoided if the patient has an acute febrile or respiratory illness at the time.

Special populations

Elderly
The safety and efficacy of vestronidase alfa in patients older than 65 years have not been established. No alternative dose regimen is recommended in these patients (see section 5.1).

Renal and hepatic impairment
The safety and efficacy of vestronidase alfa in patients with renal or hepatic impairment have not been evaluated. No alternative dose regimen is recommended in these patients.

Paediatric population
The posology in the paediatric population is the same as in adults. Currently available data are described in section 4.8 and section 5.1.

Method of administration

For intravenous use only.

For instructions on dilution of the medicinal product before administration, see section 6.6.

The total diluted volume of the solution for infusion should be administered with a rate titration regimen over approximately 4 hours.

The rate of infusion should be as follows: in the first hour, 2.5% of the total volume will be infused, with the balance infused over the subsequent three hours. Any dead space in the lines should be accounted for to ensure 2.5% of the total infusion volume is delivered into the patient's bloodstream during the first hour of infusion. The lowest rate administered to a patient in the clinical development program was 0.5 mL/hour during the first 30 minutes of infusion, followed by 1 mL/hour over the next 30 minutes, equalling 0.75 mL as the lowest total volume infused during the first hour.

Do not flush the line containing vestronidase alfa to avoid a rapid bolus of infused enzyme. Due to the low infusion rate, additional sodium chloride 9 mg/mL (0.9%) solution for infusion may be added through a separate line (piggyback or Y tube) to maintain sufficient intravenous flow. After the first hour, the rate can be increased to infuse the remainder of the solution for infusion over 3 hours as tolerated according to the recommended rate guidelines in Table 2.

The infusion rate may be slowed, temporarily interrupted or discontinued in the event of hypersensitivity reactions (see section 4.4).

4.3 Contraindications

Life-threatening hypersensitivity (anaphylactic reaction) to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General

The effects of treatment with vestronidase alfa should be periodically evaluated and discontinuation of treatment should be considered in cases where clear benefits (including stabilisation of disease manifestations) are not observed. Discontinuation of treatment may cause significant worsening of the patient's clinical status.

As end organ damage progresses over time, it is more difficult for the treatment to reverse the damage or to show improvements. It should be considered by the treating physician that the administration of vestronidase alfa does not affect the irreversible complications (e.g. skeletal deformities). Vestronidase alfa, at the exposure observed in humans, is not expected to cross the blood-brain-barrier and therefore it is not likely to impact the neurological manifestations of the disease.

Hypersensitivity reactions including anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been reported with vestronidase alfa; therefore, appropriate medical support should be readily available when vestronidase alfa is administered (see section 4.8).

Infusion should be avoided if the patient has an acute febrile or respiratory illness at the time.

It is recommended that premedication with non-sedating antihistamines with or without antipyretics be administered 30-60 minutes prior to the start of the infusion (see section 4.2).

It is important to administer vestronidase alfa according to the recommended infusion rate schedule (see Table 2 in section 6.6).

If severe hypersensitivity reactions occur, the infusion of vestronidase alfa should be stopped immediately and appropriate treatment should be initiated. Management of hypersensitivity reactions should be based on the severity of the reaction and include temporary interruption or discontinuation of the infusion and/or administration of additional antihistamines, antipyretics, and/or corticosteroids for mild to moderate reactions. Consider rapid sodium chloride 9 mg/mL (0.9%) solution for infusion for decreased blood pressure and oxygen for hypoxia. Patients should be observed for a minimum of 60 minutes after completing the infusion of vestronidase alfa.

Patients should be informed of the signs and symptoms of hypersensitivity reactions and instructed to seek immediate medical care should such signs and symptoms occur. The risks and benefits of re-administering vestronidase alfa should be considered following a severe hypersensitivity reaction.

Spinal/cervical cord compression

Spinal or cervical cord compression is a known and serious complication of MPS VII. During enzyme replacement therapy, spinal cord injury can occur due to improved neck and spine mobility. Patients with MPS VII receiving vestronidase alfa should be monitored for signs and symptoms of spinal cord compression or neck instability including neck or back pain, weakness of limbs, changes in reflexes or urinary and faecal incontinence. Appropriate clinical treatment should be immediately sought.

Sodium restricted diet

This medicinal product contains 17.8 mg sodium per vial and is administered in sodium chloride 9 mg/mL (0.9%) solution for infusion (see section 6.6). For each vial dosed, including the corresponding diluent volume, the sodium intake is 35.5 mg sodium. This amount is equivalent to 1.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Mepsevii is considered high in sodium. This should be taken into consideration during dilution of the medicinal product for patients on a controlled sodium diet or for those patients with congestive heart failure needing to restrict sodium and total water intake.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Because it is a recombinant human protein and its enzyme action is within the lysosome, vestronidase alfa is not expected to interact with other medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of vetronidase alfa in pregnant women. Animal studies with vestronidase alfa do not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development, or pre- and postnatal development (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Mepsevii during pregnancy, unless the potential benefit to the mother outweighs the potential theoretical risks to the foetus.

Breast-feeding

There are no data from studies in breast-feeding women. It is not known whether vestronidase alfa is excreted in human milk, but systemic exposure via breast-milk is not expected. Due to lack of human data, vestronidase alfa should only be administered to a breast-feeding woman if the potential benefit of vestronidase alfa to the mother and the benefit of breast-feeding to the infant outweighs the potential theoretical risks to the infant.

Fertility

No human data are available on the effect of vestronidase alfa on fertility. Animal studies with vestronidase alfa do not indicate any impact on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Mepsevii has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions from 4 clinical trials in 23 patients treated with vestronidase alfa were rash (17.4%), urticaria (17.4%), infusion site extravasation (17.4%), anaphylactoid reaction (13%), infusion site swelling (8.7%), pruritus (8.7%) and diarrhoea (8.7%). Most adverse reactions were mild to moderate in severity.

Tabulated list of adverse reactions

The assessment of adverse reactions was based on the exposure of 23 patients from 4 clinical trials, aged 5 months to 25 years, who received vestronidase alfa at doses up to 4 mg/kg once every two weeks for up to 187 weeks. Nineteen patients were younger than 18 years of age.

Table 1 lists the adverse reactions reported from 4 clinical trials in 23 patients treated with Mepsevii. Adverse reactions are presented by System Organ Class and frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), and very rare (< 1/10 000).

Table 1 Adverse reactions reported in patients treated with Mepsevii

MedDRA System Organ Class	MedDRA Preferred Term (PT)	Frequency
Immune system disorders	Anaphylactoid reaction	Very common
Nervous system disorders	Febrile convulsion*	Common
Gastrointestinal disorders	Diarrhoea	Common
Skin and subcutaneous tissue disorders	Urticaria Rash** Pruritus	Very common Very common Common
General disorders and administration site conditions	Infusion site extravasation*** Infusion site swelling****	Very common Common

**Refer to description of selected adverse reactions for details on the febrile convulsion reported in 1 of 23 trial patients.*
*** Rash includes grouped PTs of rash, rash papular, rash pruritic, rash maculo-papular, papule, and macule*
**** Infusion site extravasation includes one PT of extravasation*
***** One adverse reaction of Peripheral swelling is included within the frequency of Infusion site swelling as the event is classified as intravenous catheter issue.*

Description of selected adverse reactions

Febrile convulsion

One patient receiving a vestronidase alfa dose of 4 mg/kg experienced a febrile convulsion during treatment at the week 66, within 3 days of diphtheria, tetanus, pertussis vaccination. The infusion was stopped, the patient received anticonvulsants, antipyretics and antibiotics, and the febrile convulsion resolved. The patient subsequently was re-challenged without recurrence and continued on vestronidase alfa treatment. This event was assessed as possibly related to vestronidase alfa due to the temporal association with the infusion.

Immunogenicity

Eighteen out of 23 patients (78%) from 4 clinical trials developed anti-recombinant human beta-glucuronidase (rhGUS) antibodies (ADA), ten of whom further developed neutralizing antibodies (NAb) on at least one occasion, but not consistently over time. There is no definitive correlation between the antibody titre and neutralizing antibody development. In most patients, a pattern of attenuated immunogenicity with chronic exposure was suggested by declining antibody titres over time on continuous treatment. The presence of ADA (non-NAb and NAb) does not appear to affect reduction in the pharmacodynamic marker, urinary glycosaminoglycans (uGAGs) and development of hypersensitivity reactions including infusion associated reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdoses of vestronidase alfa. For the management of adverse reactions, see sections 4.4 and 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes, ATC code: A16AB18

Mechanism of action

Mucopolysaccharidosis VII is a lysosomal storage disorder characterised by the deficiency of beta-glucuronidase (GUS) that results in glycosaminoglycans (GAGs) accumulation in cells throughout the body leading to multisystem tissue and organ damage.

Vestronidase alfa is a recombinant form of human GUS and is intended to provide exogenous GUS enzyme for uptake into cellular lysosomes and subsequent catabolism of accumulated GAGs in affected tissues.

Clinical efficacy and safety

The clinical program for vestronidase alfa included 23 treatment naïve patients with MPS VII from 4 clinical trials, aged 5 months to 25 years, who received vestronidase alfa at doses up to 4 mg/kg once every two weeks for up to 187 weeks. Nineteen patients were younger than 18 years of age.

Studies 301 and 202

In a multi-centre, randomised, placebo-controlled, blind-start, single-crossover phase 3 trial (study UX003-CL301, referred to as study 301), 12 patients with MPS VII received vestronidase alfa 4 mg/kg every two weeks for 24 to 48 weeks. The patients were randomised in a blinded manner into 4 groups: 3 patients received vestronidase alfa immediately for 48 weeks (Group A), 3 patients received placebo for 8 weeks then vestronidase alfa for 40 weeks (Group B), 3 patients received placebo for 16 weeks then vestronidase alfa for 32 weeks (Group C), and 3 patients received placebo for 24 weeks then vestronidase alfa for 24 weeks (Group D). Patients who were enrolled in study 301 were eligible to roll over to study UX003-CL202 (referred to as study 202), an open-label extension trial in which patients received additional doses of vestronidase alfa at 4 mg/kg intravenously every other week for up to 144 weeks. Ten patients rolled over directly from the end of study 301 to week 0 of study 202 while 2 patients (17%) had gaps in treatment before enrolling in study 202.

Of the 12 patients enrolled in study CL301, 4 were male and 8 were female and ranged in ages from 8 to 25 years (median 14 years). Nine patients were younger than 18 years of age. MPS VII diagnosis was confirmed by GUS enzyme activity assay for 5 patients, by genotyping for 3 patients, and via both enzyme assay and genotyping for 4 patients. Patients with MPS VII who received hematopoietic stem cell transplant therapy were excluded in this study. The extremely small population of patients with MPS VII globally necessitated the enrolment of all patients able to participate in this clinical trial, resulting in a highly variable group. Clinical endpoints were not assessable in some patients due to their extent of disease, age or level of cognition (23 out of 72 assessments [~32%] in 6 domains for 12 patients were non-assessable at baseline).

The primary endpoint was the percent reduction in urinary GAG excretion (dermatan sulfate, DS) before and after 24 weeks of treatment with vestronidase alfa. The key secondary endpoint was the multi-domain clinical responder index (MDRI) score consisting of six domains [six-minute walk test (6MWT), forced vital capacity (FVC), shoulder flexion, visual acuity, Bruininks-Oseretsky test of motor proficiency (BOT-2) fine motor and gross motor function] after 24 weeks of treatment and fatigue total score as measured by the Pediatric Quality of Life Multidimensional Fatigue Scale (PedsQL).

Minimal important differences (MIDs) were pre-specified for the six MDRI domains plus fatigue, which are: 6MWT ($\geqslant$23 meters and $\geqslant$10% change from baseline), FVC (5% absolute change or 10%

relative change from baseline in FVC%pred), shoulder flexion (20 degree change of both shoulder range of motion), visual acuity (3 lines (corrected, both eyes)), BOT-2 fine motor (fine motor precision: change of 0.72, and manual dexterity: change of 1.47), BOT-2 gross motor (balance: 0.57, and running speed and agility: 0.59), and fatigue (10 points of total score).

Primary endpoint: uGAG reduction
After 24 weeks of treatment with vestronidase alfa, a rapid and sustained, highly significant reduction in uGAG (DS) excretion was achieved with a LS mean (±SE) percentage change of -64.82% (±2.468%) ($p<0.0001$). All 12 patients were responders, pre-specified as ≥ 50% reduction in uGAG on at least one visit during the first 24 weeks of treatment. In addition, uGAG response (% change from study week 0) shows a similar magnitude of reduction in uGAG in all groups after crossover to active treatment. The reductions in uGAG DS that were observed in study 301 were sustained when patients (n=12) rolled over into the extension Study 202 and received vestronidase alfa for up to 3.6 years total between the 2 studies. Reduction in uGAG DS excretion was achieved with LS mean (SE) percentage changes of -62% (4.9%) at study 202 week 0 and -58% (7.2%) at week 48 (n=10). In patients who continued beyond study 202 week 48, the mean percentage reduction in uGAG DS was greater than 70% at all subsequent assessment visits through study 202 week 144 (n=4).

Key secondary endpoints: multi-domain clinical responder index (MDRI) and 6-minute walk test (6MWT)
For the clinical (secondary) endpoints, beneficial responses were observed although not in all patients. After 24 weeks of vestronidase alfa treatment in study 301, the overall MDRI results, both pre-specified and post-hoc (6 MDRI domains plus fatigue domain) analyses, were positive with an increase of +0.5 domains ($p=0.0527$) and +0.8 domains ($p=0.0433$) including fatigue, respectively (t-test). For patients who continued into study 202, a mean (SD) improvement in MDRI was observed at week 24 (+0.7 [1.01] domains) and at week 48 (+0.9 [1.30] domains).

For 6MWT, the distance increased from baseline to treatment week 24 in study 301 by a LS mean (±SE) of 20.8 m (±16.75 m) in 9 patients who were able to perform the assessment at baseline and at least one post-baseline visit. 6 patients had 6MWT results at treatment week 24. Three of these (50%) met the pre-defined MID at treatment week 24 and had sustained walking improvements of 65 meters, 80 meters and 83 meters. For patients who continued into study 202, 8 patients were able to perform the 6MWT at week 48. Sustained 6MWT results were observed with a mean distance of 308.4 m (range: 80-556), for a mean (SE) increase from study 301 baseline of 19.0 m (16.4 m).

Other investigations

Study UX003-CL201 (referred to as study 201) was a single arm, open-label, dose exploration trial that enrolled three MPS VII patients, ranging in age from 5 years to 25 years. After 120 weeks of exposure to vestronidase alfa, one patient demonstrated a 21% improvement over baseline in forced vital capacity (FVC% predicted) on pulmonary function testing in addition to a 105 meter improvement in the 6MWT. Two other patients with baseline hepatosplenomegaly had reduction in liver volume (24% and 53%) and spleen volume (28% and 47%) after 36 weeks of treatment.

Study UX003-CL203 (referred to as study 203) was an open-label, uncontrolled single arm study that enrolled eight patients less than 5 years of age who received vestronidase alfa at a dose of 4 mg/kg every two weeks for 48 weeks of treatment period and additional up to 240 weeks during optional continuation period. The study evaluated reduction of urinary GAG excretion, growth velocity and hepatosplenomegaly.

uGAG reduction
Treatment with vestronidase alfa resulted in a rapid and sustained, significant ($p<0.0001$) reduction in uGAG DS excretion with an LS mean (SE) percent change of -60% (6.6) at week 4 which was sustained at -61% (6.4) at Week 48. Patients who entered the continuation period up to week 132 experienced further reduction in uGAG DS.

Growth
At baseline, all 8 patients had impaired growth. The mean (SD) standing height z-score improved from baseline by +0.196 (0.30) at week 48. A non-significant trend toward increased growth velocity was observed after vestronidase alfa treatment, from a mean (SD) z-score of -2.59 (1.49) at baseline to --0.392 (2.10) post-baseline (p=0.27).

Hepatomegaly
All patients with hepatomegaly assessed by ultrasound examination at baseline (n=3/8) had decreased liver size to within normal range for age and sex prior to study termination.

Exceptional circumstances

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease, it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of vestronidase alfa were evaluated in a total of 23 MPS VII patients including 19 paediatric patients and 4 adults from 3 clinical trials. After repeated dosing of 4 mg/kg every other week, the maximal serum concentration (C_{max}) was 17.3 ± 9.6 mcg/mL (mean ± s.d.; range: 4.7 to 35.7 mcg/mL) and the area under the concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}) was 50.9 ± 32.2 mcg*h/mL (mean ± s.d.; range: 17.4 to 153 mcg*h/mL). The pharmacokinetics of vestronidase alfa are time independent with repeat dosing. The limited pharmacokinetic data at steady state suggest dose proportional increase in exposure of vestronidase alfa over the dose range of 1 - 4 mg/kg every other week.

Distribution

After repeated dosing of 4 mg/kg every other week in MPS VII patients, the mean ± standard deviation the total volume of distribution (V_{ss}) was 0.26 ± 0.13 L/kg (range: 0.10 to 0.60 L/kg).

Biotransformation

Vestronidase alfa is a recombinant human enzyme and is therefore eliminated by proteolytic degradation into small peptides and amino acids.

Elimination

After repeated dosing of 4 mg/kg every other week in MPS VII patients, the mean ± standard deviation of the total clearance (CL) was 0.079 ± 0.045 L/h/kg (range: 0.038 to 0.20 L/h/kg); the mean ± standard deviation of the elimination half-life ($t_{1/2}$) was 2.6 ± 0.6 hours (range: 0.9 to 3.6 hours).

Excretion

No excretion studies have been conducted in humans. Vestronidase alfa is not expected to be eliminated through renal or faecal excretion.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single-dose toxicity in rats, repeated dose toxicity in MPS VII mice and juvenile

monkeys, fertility and embryo-foetal development in rats or rabbits, and pre- and postnatal development in rats.

Genotoxicity studies and carcinogenicity studies have not been performed with vestronidase alfa. Based on mechanism of action, rhGUS is not expected to be tumorigenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate
Sodium chloride
Histidine
Polysorbate 20
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

After dilution

Chemical and physical in-use stability of the diluted medicinal product has been demonstrated for up to 36 hours under refrigeration at 2 °C – 8 °C followed by up to 6 hours at room temperature up to a maximum of 25 °C.

From a microbiological safety point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, but should normally not be longer than 36 hours at 2 °C – 8 °C followed by up to 6 hours at room temperature up to a maximum of 25 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless glass vial (Type I) with a rubber stopper with fluoro-resin coating, and an aluminium over seal with a plastic flip-off cap.

Pack size: 1 vial containing 5 mL of concentrate for solution for infusion.

6.6 Special precautions for disposal and other handling

Each vial of Mepsevii is intended for single use only. Mepsevii must be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection using aseptic technique according to the steps described below. The diluted solution for infusion should be administered to patients using a low-protein binding

infusion bag and set (a non di (2-ethylhexyl) phthalate [DEHP] bag could be used) and the application of an infusion set equipped with an in-line, low-protein binding 0.2 µm filter is recommended.

1. Determine the number of vials to be diluted based on the patient's actual weight and the recommended dose of 4 mg/kg, using the following calculations (a-b):
    a. Total dose (mg) = Patient's weight (kg) x 4 mg/kg (recommended dose)
    b. Total number of vials = Total dose (mg) divided by 10 mg/vial
2. Round to the next whole vial and remove the required number of vials (refer to Table 2) from the refrigerator to allow them to reach room temperature up to a maximum of 25 °C. Do not heat, microwave or shake vials.
    a. Volume (mL) of calculated dose = Total dose (mg) divided by the 2 mg/mL concentration
3. Dilute the calculated dose 1:1 using equal volume of sodium chloride 9 mg/mL (0.9%) solution for injection for intravenous infusion. The total infusion volume is based on the total Mepsevii dose and volume (refer to Table 2). The above calculated dose diluted 1:1 in sodium chloride 9 mg/mL (0.9%) solution for injection should be added to a new empty infusion bag. Dilution preparation should be done at room temperature.
4. Prior to withdrawing Mepsevii from the vial, visually inspect for particulate matter and discolouration. The Mepsevii concentrate solution for infusion should be colourless to slightly yellow. Do not use if the solution is discoloured or if there is particulate matter in the solution.
5. Slowly withdraw Mepsevii from the appropriate number of vials using caution to avoid excessive agitation and any air or frothing. A sufficiently large needle (18 gauge) should be used to minimise bubbles in the solution.
6. Slowly add Mepsevii to the infusion bag using care to avoid agitation, ensuring liquid to liquid contact without generating bubbles or turbulence.
7. Gently rock the infusion bag to ensure proper distribution of Mepsevii. Do not shake the solution.

Table 2. Recommended infusion rate schedule by patient weight for administration of Mepsevii at recommended dose of 4 mg/kg

Patient weight range (kg)	Total Mepsevii dose range (mg)	Total Mepsevii volume (rounded) (mL)	Total number of Mepsevii vials	Total infusion volume (infused over 4 hours) (mL)	Infusion rate for 1st hour (2.5%) (mL/h)	Infusion rate for subsequent 3 hours (97.5%/3) (mL/h)
3.5-5.9	14-23.6	10	2	20	0.5	6.5
6-8.4	24-33.6	15	3	30	0.75	9.75
8.5-10.9	34-43.6	20	4	40	1	13
11-13.4	44-53.6	25	5	50	1.25	16.25
13.5-15.9	54-63.6	30	6	60	1.5	19.5
16-18.4	64-73.6	35	7	70	1.75	22.75
18.5-20.9	74-83.6	40	8	80	2	26
21-23.4	84-93.6	45	9	90	2.25	29.25
23.5-25.9	94-103.6	50	10	100	2.5	32.5
26-28.4	104-113.6	55	11	110	2.75	35.75
28.5-30.9	114-123.6	60	12	120	3	39
31-33.4	124-133.6	65	13	130	3.25	42.25
33.5-35.9	134-143.6	70	14	140	3.5	45.5
36-38.4	144-153.6	75	15	150	3.75	48.75
38.5-40.9	154-163.6	80	16	160	4	52
41-43.4	164-173.6	85	17	170	4.25	55.25
43.5-45.9	174-183.6	90	18	180	4.5	58.5
46-48.4	184-193.6	95	19	190	4.75	61.75
48.5-50.9	194-203.6	100	20	200	5	65
51-53.4	204-213.6	105	21	210	5.25	68.25
53.5-55.9	214-223.6	110	22	220	5.5	71.5
56-58.4	224-233.6	115	23	230	5.75	74.75
58.5-60.9	234-243.6	120	24	240	6	78
61-63.4	244-253.6	125	25	250	6.25	81.25
63.5-65.9	254-263.6	130	26	260	6.5	84.5
66-68.4	264-273.6	135	27	270	6.75	87.75
68.5-70.9	274-283.6	140	28	280	7	91

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ultragenyx Germany GmbH
Rahel-Hirsch-Str. 10
10557 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1301/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2018
Date of latest renewal: 28 July 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Rentschler Biopharma SE
Erwin-Rentschler-Strasse 21
88471 Laupheim
Germany

Name and address of the manufacturer(s) responsible for batch release

Ultragenyx Netherlands B. V.
Evert van de Beekstraat 1, Unit 104
1118 CL Schiphol
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being a marketing authorisation under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to obtain long-term data on effectiveness and safety of treatment with Mepsevii and to characterise the entire mucopolysaccharidosis VII, including variability of clinical manifestation, progression and natural history, the MAH is requested to submit the results of a study based on adequate source of data deriving from a disease monitoring program of patients with mucopolysaccharidosis VII.	Reports to be submitted as part of the annual re-assessment

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Mepsevii 2 mg/mL concentrate for solution for infusion
vestronidase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of sterile concentrate contains 2 mg vestronidase alfa. Each vial of 5 mL concentrate contains 10 mg vestronidase alfa (10 mg/5 mL).

3. LIST OF EXCIPIENTS

Excipients:
Sodium dihydrogen phosphate dihydrate
Sodium chloride
Histidine
Polysorbate 20
Water for injections
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

10 mg/5 mL

1 vial (5 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ultragenyx Germany GmbH
Rahel-Hirsch-Str. 10
10557 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1301/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mepsevii 2 mg/mL sterile concentrate
vestronidase alfa
IV use after dilution

2. METHOD OF ADMINISTRATION

For single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg/5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Mepsevii 2 mg/mL concentrate for solution for infusion
vestronidase alfa

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet

1. What Mepsevii is and what it is used for

What Mepsevii is
Mepsevii contains an enzyme called vestronidase alfa. This belongs to a group of medicines called enzyme replacement therapies. It is used in adults and children of all ages with MPS VII to treat non-neurological manifestations of the disease (mucopolysaccharidosis VII, also known as Sly Syndrome).

What is MPS VII
MPS VII is an illness that runs in families, where the body does not produce enough of an enzyme called beta–glucuronidase.
- This enzyme helps to break down sugars in the body called mucopolysaccharides.
- Mucopolysaccharides are made in the body and they help build bones, cartilage, skin, and tendons.
- These sugars are re-cycled all the time – new ones are made and old ones are broken down.
- Without enough beta–glucuronidase, parts of these sugars build up in cells, leading to damage in the body.

How Mepsevii works
This medicine replaces beta-glucuronidase – this helps to break down the sugars that collect in the tissues of people with MPS VII.
- Treatment may improve various signs and symptoms of illness, like walking difficulties and tiredness.

Starting treatment early in children may stop the illness getting worse and reduce permanent damage.

2. What you need to know before you are given Mepsevii

You must not be given Mepsevii
- If you have ever had a severe allergic reaction to vestronidase alfa or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before you are given Mepsevii.

The effects of treatment with vestronidase alfa should be periodically evaluated and discontinuation of treatment should be considered in cases where clear benefits (including stabilisation of disease manifestations) are not observed. Discontinuation of treatment may cause significant worsening of clinical status.

It should be considered that the administration of vestronidase alfa does not affect the irreversible complications (e.g. skeletal deformities).

Look out for side effects during or shortly after Mepsevii infusion

- You may have side effects while you are being given Mepsevii or for up to a day afterwards. These side effects are called infusion reactions because they are caused by the infusion (drip) of the medicine. They may include an allergic reaction (see section 4). If you have an infusion reaction, **tell your doctor straight away.**
- If you have an allergic reaction during your infusion your doctor may slow down, or stop your infusion. Your doctor may also give (or have given) you other medicines to manage the allergic reaction such as an antihistamine or corticosteroid or an antipyretic, a medicine to reduce fever.

Other symptoms to look out for

- If you have neck or back pain, feel numb in your arms or legs, or experience lack of control over passing water (urine) or stools, **tell your doctor straight away**. These problems can be signs of the illness and may be caused by pressure on your spinal cord.

Other medicines and Mepsevii
Tell your doctor if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

You will not be given Mepsevii if you are pregnant unless treatment is clearly necessary. Discuss with your doctor if the benefits of using Mepsevii are greater than the possible risks to your unborn baby. This is because there is no experience on the use of Mepsevii during pregnancy.

It is not known whether Mepsevii passes into breast milk, but transfer of the medication to your baby is not expected. Discuss with your doctor if the benefits of using Mepsevii are greater than the potential risk to your baby while breast-feeding.

Driving and using machines
Mepsevii is not likely to affect you being able to drive or use machines.

Mepsevii contains sodium
This medicine contains 17.8 mg sodium (main component of cooking/table salt) in each 5-mL vial, and is administered with sodium chloride 9 mg/mL as a diluent. Each vial dosed is therefore equivalent to 1.8% of the recommended maximum daily dietary intake of sodium for an adult. Take this into account if you are on a controlled sodium diet.

3. How Mepsevii is given

Treatment with Mepsevii should be started and monitored by your doctor.
- Your doctor or nurse will give Mepsevii to you by an infusion (drip) into a vein.
- The medicine has to be diluted before being given.
- Your doctor may give (or have given) you some medicines to manage the allergic reaction such as an antihistamine or corticosteroid or an antipyretic, a medicine to reduce fever.

Dose
The dose you will receive is based on how much you weigh.
- The recommended dose is 4 mg for each kg of body weight.
- The dose is given every two weeks through a drip into a vein (intravenous infusion).
- Each infusion will be given over about 4 hours.

If you are given more Mepsevii than you should
Mepsevii is given to you and monitored by your doctor. He or she will check that the correct dose has been given and take action as needed.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects were mainly seen while patients were being given the medicine or within a day after the infusion (infusion reactions).

Serious side effects
Severe allergic reaction (Very common: may affect more than 1 in 10 people):
Tell your doctor or nurse immediately if you get any of the following symptoms of a severe allergic reaction (anaphylactoid reaction). The infusion will be stopped immediately and your doctor may give (or have given) you other medicines to manage the allergic reaction such as an antihistamine or corticosteroid or an antipyretic, a medicine to reduce fever. Symptoms of severe allergic reaction may include shortness of breath, wheezing, difficulty breathing, and swelling of the face and tongue.

Other side effects
Tell your doctor straight away if you notice any of the following side effects – you may need urgent medical treatment:

Very common side effects (may affect more than 1 in 10 people):
- Hives (urticaria)
- Rash
- Swelling at the infusion site including leaking into the tissue around the vein (infusion site swelling or infusion site extravasation)

Common side effects (may affect up to 1 in 10 people):
- Itching of the skin (pruritus)
- Loose stools (diarrhoea)
- Fever with involuntary contractions of muscles of face or limbs (febrile convulsion)
- Swelling around the infusion site

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Mepsevii

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after 'EXP'. The expiry date refers to the last day of that month.

Unopened vials:
- Store in a refrigerator (2 °C to 8 °C).
- Do not freeze.
- Store in the original package in order to protect from light.
- Do not use this medicine if you notice particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Mepsevii contains
- The active substance is vestronidase alfa. Each mL of concentrate contains 2 mg vestronidase alfa. Each vial of 5 mL concentrate contains 10 mg vestronidase alfa.
- The other ingredients are: sodium dihydrogen phosphate dihydrate, sodium chloride, histidine, polysorbate 20, and water for injections (for sodium, see section 2 under "Mepsevii contains sodium").

What Mepsevii looks like and contents of the pack
Mepsevii is supplied as a concentrate for solution for infusion (sterile concentrate). The colourless to slightly yellow concentrate must be free of visible particles. It is supplied in a clear glass vial with a rubber stopper and an aluminium seal with a plastic cap.

Pack size: 1 vial of 5 mL

Marketing Authorisation Holder
Ultragenyx Germany GmbH
Rahel-Hirsch-Str. 10
10557 Berlin
Germany

Manufacturer
Ultragenyx Netherlands B. V.
Evert van de Beekstraat 1, Unit 104
1118 CL Schiphol
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {Month YYYY}

This medicine has been authorised under 'exceptional circumstances'. This means that because of the rarity of this disease, it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.
