EU Risk Management Plan for NPJ5008 (Dantrolene 120 mg powder for solution for injection)

RMP version to be assessed as part of this application:

RMP Version number: 0.4

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Rationale for submitting an updated RMP: N/A – initial marketing application

Summary of significant changes in this RMP: N/A – initial marketing application

Other RMP versions under evaluation: N/A

Details of the currently approved RMP: N/A

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Dantrolene
Pharmacotherapeutic group(s) (ATC Code)	Muscle relaxants, directly acting agents (ATC code: M03CA01)
Marketing Authorisation Applicant	Norgine B.V. Antonio Vivaldistraat 150 1083 HP Amsterdam Netherlands
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Agilus (Project code NPJ5008)
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Dantrolene is classified as a direct-acting skeletal muscle relaxant.
	Summary of mode of action Dantrolene is a skeletal muscle relaxant that binds to the ryanodine receptor-1 (RYR1) suppressing release of calcium from the sarcoplasmic reticulum (SR). RYR1 act as a calcium ion (Ca^{2+}) channel that resides on the SR of skeletal muscle and when activated leads to muscle contraction. Dantrolene can be used in the treatment of malignant hyperthermia (MH), which is an acute hypermetabolic crisis. In MH susceptible individuals RYR1 function is disrupted by triggers such as volatile anaesthetics and/or succinylcholine and does not repolarize, leading to unregulated Ca^{2+} release from the SR. The consequent rise in sarcoplasmic Ca^{2+} causes sustained muscle contraction and excessive stimulation of aerobic and anaerobic metabolism which results in increased oxygen and adenosine triphosphate consumption, metabolic acidosis, and generates heat, which, together establishes a hypermetabolic state and hyperthermia ensues. Dantrolene binds to the RYR1 and stabilises its resting state, thereby suppresses the release of Ca^{2+} from the SR and arrests the metabolic cascade.

	Important information about its composition NPJ5008 is a novel formulation of dantrolene, hydroxypropylbetadex (a beta-cyclodextrin) and Macrogol (E1521) that can deliver a 120 mg dose of dantrolene quickly using a commonly available volume of water for injections (20 mL) for reconstitution, and removes the necessity for use of single-use filtration device.
Hyperlink to the Product Information	
Indication(s) in the EEA	Current (if applicable): In combination with adequate support measures, NPJ5008 is indicated for the treatment of malignant hyperthermia in adults and children of all ages.
	Proposed (if applicable): N/A
Dosage in the EEA	Current (if applicable): Treatment with NPJ5008 should be started as soon as a malignant hyperthermia (MH) crisis is suspected, i.e. characteristically presenting with muscle rigidity, metabolic acidosis and/or rapidly increasing body temperature. NPJ5008 should be administered rapidly by intravenous injection at an initial dose of 2.5 mg/kg body weight for adult and paediatric patients. As long as the main clinical symptoms of tachycardia, hypoventilation, sustained hyperacidity (pH and partial pressure of carbon dioxide (pCO_2) monitoring required) and hyperthermia persist, a bolus injection of 2.5 mg/kg should be repeated every 10 minutes until physiological and metabolic abnormalities improve (see Section 5.1). If a cumulative dose of 10 mg/kg or above is considered, the diagnosis of malignant hyperthermia should be re-examined. **Treatment of recrudescence (recurrence)** It should be noted that the hypermetabolic features of malignant hyperthermia may recur within the first 24 hours after initial resolution. If a recrudescence occurs, NPJ5008 should be re-administered at a dose of 2.5 mg/kg every 10 minutes until the signs of malignant hyperthermia regress once more. The same considerations for monitoring of metabolic abnormalities and the titration of doses in an initial episode apply to the treatment of recrudescence. **Paediatric population** No dose adjustment required.

	Proposed (if applicable): N/A
Pharmaceutical form(s) and strengths	Current (if applicable): NPJ5008 is a powder for solution for injection containing 120 mg of dantrolene sodium [as hemiheptahydrate], intended for intravenous injection. After reconstitution with 20 mL water for injections, each mL of solution contains 5.3 mg dantrolene sodium hemiheptahydrate.
	Proposed (if applicable): N/A
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Malignant Hyperthermia

Malignant hyperthermia (MH) is a fulminant hypermetabolic crisis (FHC) secondary to calcium dysregulation in skeletal muscle triggered by agents such as volatile anaesthetics and/or succinylcholine; characteristically presenting with muscle rigidity, metabolic acidosis and/or rapidly increasing body temperature[1].

This condition is a pharmacogenetic disorder as some subjects that are susceptible to MH have mutations in the ryanodine receptor-1 (RYR1) gene, which is a calcium ion channel (Ca^{2+}) located on the sarcoplasmic reticulum (SR) and plays a key role in excitation-contraction coupling. Mutations in the RYR1 gene can cause unregulated Ca^{2+} release from the SR, via the RYR1 and into the sarcoplasm, which causes sustained muscle contraction and establishes a hypermetabolic state with heat generation and potential hyperthermia[2].

Incidence: The incidence rates of anaesthetic-related MH episodes has been reported to be 1 in 15,000 in children and 1 in 50,000 in adults[3].

Prevalence: Identifying patients who are susceptible to MH can be difficult as it is a silent disorder until triggered, and therefore the true indication of MH susceptibility is unknown[4].

Approximately 50% of patients who experience an MH crisis had previously received a triggering anaesthetic agent without showing any signs or symptoms[4].

Demographics of the population in the proposed indication and risk factors for the disease: NPJ5008 is indicated for the treatment of MH (including suspected cases) in adults and children.

Recommended dosing of dantrolene is based on bodyweight (starting from 2.5 mg/kg). Historical evidence indicates that a significant proportion (as much as 50%) of patients might be expected to be 18 years or younger and the median typical patient bodyweight is likely to be less than the 72 kg mean weight of an adult.

The main existing treatment options: The primary pharmacological treatment for MH is use of dantrolene which prevents the release of calcium into the muscle. Other medications may be administered for metabolic imbalance and to treat any complications.

Further supportive measures may also be used including supplementary oxygen, body cooling with ice packs or chilled intravenous (IV) fluids to help reduce body temperature, additional fluids via an IV line if required, and supportive care to monitor the patient's temperature, blood pressure, breathing and heart rate[5].

Natural history of the indicated condition in the untreated population, including mortality and morbidity: MH is a life-threatening disorder and is fatal if not treated quickly. The clinical presentation of the disorder can be highly variable and can include symptoms such as metabolic and respiratory acidosis, cardiac arrhythmias, rhabdomyolysis and skeletal muscle rigidity[3].

Important co-morbidities: Previous reports have linked MH to several genetic diseases with diagnosis significantly more likely in patients, especially paediatric patients, with diseases of the musculoskeletal system and connective tissue, diseases of the circulatory system and congenital abnormalities[6].

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 (from non-clinical studies)	**Relevance to human usage**
Toxicity *Single and repeat dose toxicity:* Data derived from the original development of dantrolene following subacute intravenous administration of dantrolene at doses of up to 20 mg/kg/day, for up to 14 days, the sole observations were reduced body weight gain in rats and hepatic changes in dogs. A GLP compliant 14-day toxicity study has been conducted with NPJ5008. Male and female rats were administered doses of NPJ5008 at 0 (vehicle control formulation), 2.5 or 10 mg/kg/day or DANTRIUM IV at a dose of 2.5 mg/kg/day. The vehicle control formulation in this study was hydroxypropyl beta-cyclodextrin (HP-β-CD) (176.5 mg/mL) and PEG 3350 (20 mg/mL) prepared as a solution in water for injections. The dose levels of NPJ5008 included in this study were 2.5 mg/kg dantrolene (73.5 mg/kg HP-β-CD and 8.3 mg/kg PEG 3350) or 10 mg/kg dantrolene, 294.2 mg/kg HP-β-CD and 33 mg/kg PEG 3350. Following 14-days IV administration to rats toxicity findings were similar for NPJ5008 at 2.5 and 10 mg/kg/day in terms of effects and duration but with a higher incidence and severity at 10 mg/kg/day. There were no major differences in the toxicity profile of dantrolene given at 2.5 mg/kg as NPJ5008 or DANTRIUM IV. The no adverse effect level (NOAEL) for NPJ5008 in the rat was 2.5 mg/kg/day. The 10 mg/kg/day dose level was deemed an effect level due to the effects on the kidneys (vacuolated renal tubular epithelial and Kupffer cells), which was also seen in the vehicle control formulation animals. All other effects were related to dantrolene pharmacology and were similar between both dantrolene formulations. Overall, the toxicity profile of dantrolene was unchanged, no new safety findings were identified, the only effects observed were well known class effects associated with the use of the excipient HP-β-CD (reversible kidney changes), which were similarly seen in	*Single and repeat dose toxicity:* Treatment related findings for NPJ5008 at 10 mg/kg/day were related to the known pharmacology of dantrolene, which were predominantly effects on muscles, including general muscle weakness, ataxia and dulled reflexes. The anticipated minimum therapeutic dose of dantrolene from NPJ5008 is 2.5 mg/kg and is the same as that for DANTRIUM/DANTROLEN IV. In general, both excipients in the formulation of NPJ5008 (HP-β-CD and PEG 3350) are considered to have a low toxicity to humans and are widely used in final pharmaceutical formulations. *Nephrotoxicity* Potential target organ toxicity (kidney) associated with the use of the excipients was identified from the literature, however it is noteworthy that the kidney effects observed with HP-β-CD and high molecular weight PEGs are different (see below): • Betacyclodextrins form vacuoles in both renal proximal tubule epithelium and liver Kupffer cells. The vacuoles are considered to contain beta-cyclodextrin which is slowly excreted via the urine. The vacuoles disappear quickly following cessation of dosing and thus the effect is considered reversible. • PEG does not form vacuoles in renal proximal tubule epithelium, liver Kupffer cells or any other cells. PEG is metabolised to oxalic acid which can accumulate to induce renal proximal tubule epithelium necrosis. In the GLP compliant 14-day toxicity study in rats no indication of PEG-related toxicity, such as proximal tubule epithelium necrosis, were observed microscopically. However, kidney effects were observed on repeated administration in the 10 mg/kg/day treatment group as well as in the

animals dosed with the vehicle control formulation. **Acute toxicity data for the excipients:** **HP-β-CD** Doses of up to 10 g/kg (human equivalent dose 3226 mg/kg) of HP-β-CD administered to the cynomolgus monkey were not lethal following a single IV dose. A single IV dose of up to 2000 mg/kg or 1000 mg/kg were not lethal in mice and rats respectively. **PEG** Acute toxicity of PEG 4000 following a single intravenous administration dose defined the LD50 as 7.5 g/kg (human equivalent dose 1210 mg/kg) in the rat and greater than 10 g/kg (human equivalent dose 3226 mg/kg) in the rabbit. PEG 4000 was administered intravenously to dogs at dosages of 4 to 12 g/kg. There were no deaths even up to 12 g/kg. *Ototoxicity*: Several recent review publications have investigated and summarised the potential for ototoxicity in nonclinical models following dosing with the excipient HP-β-CD via subcutaneous, intrathecal or intracerebroventricular administration. In mice and cats, HP-β-CD has been shown to mainly damage the outer hair cells (OHCs) of the inner ear, while in rats the effects are more severe with damage seen to the OHCs, inner hair cells (IHCs) and spiral ganglion neurones[18]. A single dose of 2000 mg/kg was found to be close to the critical dose for inducing significant hearing loss and cochlear damage following subcutaneous administration in the rat. Doses greater than 2000 mg/kg caused significant hair cell damage and completely abolished distortion product acoustic emissions (DPOAE), whereas lower doses had relatively little effect on functional and structural measures.	vehicle group receiving the same volume of excipients. Thus, the kidney effects were linked to HP-β-CD known toxicity of vacuolated renal tubular epithelial cells in both male and female rats and increased incidence of vacuolated alveolar macrophages in male rats but were of low grade. These effects are consistent with a well-established reversible class effect associated with the use of the excipient HP-β-CD when given chronically to rodents. From the literature reviewed it is noted that the reversibility of vacuolation and lack of kidney damage or functional impairment indicate that the vacuolation observed following treatment with HP-β-CD and other CDs is a physiological adaptation and is unlikely to present a clinical risk or alter the positive benefit/risk of the use of NPJ5008 for the intended indication. The transient nature of the tubular vacuolation found in the kidney was generally observed to have minimal toxicological significance in the literature reviewed. Furthermore, the duration of dose (particularly continuous infusion rather than intermittent dose) was found to be the main factor in determining the presence of changes. Both the transient nature of the vacuolation and the impact of duration of exposure are highly relevant in the assessment of benefit/risk for NPJ5008, given the posology and the intended indication. *Ototoxicity* The relevance of these findings to the acute intravenous use of NPJ5008 in the treatment of MH in humans has not been determined. Clinical studies have been conducted with the HP-β-CD in Niemann-Pick disease Type C[21]. Intravenous doses of 1500-2500 mg/kg every two weeks for 14 weeks resulted in hearing loss at in four out of 13 patients, as observed by audiometric assessment. No functional hearing loss was observed. Hearing loss returned to baseline within 3 months, apart from very mild loss at high frequencies in one patient. All AEs of hearing loss were detected by protocol-mandated audiometry and were not perceived by the subjects themselves or their families. It is important to note that hearing loss is part of the natural history of NPC. There is no experience with NPJ5008 at these dose levels and the

	relevance to NPJ5008 in the acute treatment of MH is not known.
Mutagenicity: Positive. Dantrolene sodium yielded positive results in the Ames *S.typhimurium* test both in the presence and absence of a liver metabolising system[7]. No studies have been conducted with NPJ5008.	*Mutagenicity:* Due to the intended short duration of use of dantrolene for the intended indication (MH), no significant genotoxicity risk is expected.
Carcinogenicity: No studies have been conducted with NPJ5008. Dietary doses of dantrolene sodium in rats at doses of 15, 30 or 60 mg/kg/day for up to 18 months resulted in increases in benign hepatic lymphatic neoplasms at the highest dose level, and in females only, an increase in mammary tumours. In a 30-month study in rats dietary doses of dantrolene sodium resulted in a decrease in the time of onset of mammary neoplasms at the highest dose level and female rats only an increased incidence of hepatic lymphangiomas and hepatic angiosarcomas at the highest dose level. The only dantrolene-related effect seen in a 30-month study in Fischer-344 rats was a dose-related reduction in the time of onset of mammary and testicular tumours. A 24-month study in HaM/ICR mice revealed no evidence of carcinogenic activity[7].	*Carcinogenicity:* The relevance of these oral data for short term clinical use of intravenous dantrolene for the treatment of MH in humans is not known. For the short duration of use for both healthy volunteer clinical trials (up to two single intravenous doses) and the short-term clinical use for the intended indication (MH), no significant carcinogenic risk is expected.
Reproductive toxicity: No studies have been conducted with NPJ5008. In male and female adult rats and female pregnant rabbits, administered oral formulations of dantrolene at doses up to 45 mg/kg/day did not have any adverse effects on rat fertility or general reproductive capability but administration to pregnant rabbits at a dose of 45 mg/kg/day from Gestational Days 6 to 18 led to increased formation of unilateral or bilateral supernumerary ribs in the pups.	*Reproductive toxicity:* There are no data on the effect of dantrolene on human fertility. Dantrolene crosses the placenta and should only be used during pregnancy when the potential benefit outweighs the possible risk to mother and child[8]. Women of childbearing potential were not included in a healthy volunteer clinical trial with NPJ5008 and all women regardless of childbearing potential had a negative highly sensitive pregnancy test prior to their inclusion in the healthy volunteer trial. No information is available on use of dantrolene during breastfeeding. According to its safety profile, risk for a breastfed infant cannot be

	excluded as dantrolene is excreted in breastmilk. Therefore, breastfeeding should be discontinued during administration of NPJ5008. Based on elimination half-life of dantrolene, breastfeeding can be restarted 60 hours after last dose[8]. Women who are breastfeeding were not included in the healthy volunteer clinical trial of NPJ5008.
General safety pharmacology Data derived from the original development of dantrolene looking at safety pharmacology in rodent, dog and sheep demonstrated minimal to no adverse effects on cardiac, gastrointestinal, neuronal/ neurobehavioral activity and respiratory systems or pathways. In toxicity testing, predominantly in the rat and dog, the adverse events (AEs) relating to dantrolene pharmacology were effects on muscles with the major effects in animals composing of general muscle weakness, ataxia and dulled reflexes. These effects were observed at the highest doses administered.	Adverse events after dantrolene administration are commonly reported but are often confounded by underlying illnesses / conditions and co-suspect medication, but are rarely life-threatening. A study of NPJ5008 given to healthy volunteers found the AEs reported were consistent with the known mechanism of action of dantrolene as a skeletal muscle relaxant and with previous literature[8].
Mechanisms for drug interactions Dantrolene is reported to show pharmacodynamic drug interactions with the calcium channel blocker, verapamil. Hence, caution should be advised for the administration of dantrolene sodium with calcium channel blockers. Based on findings in animals[9,10], it has been suggested that calcium channel blockers, such as verapamil, should not be used in combination with IV dantrolene during the management of a MH crisis. The combination of therapeutic doses of intravenous dantrolene and verapamil in halothane/alpha-chloralose anaesthetised swine has resulted in ventricular fibrillation and cardiovascular collapse in association with marked hyperkalaemia.	Isolated case reports and animal studies indicate an interaction between dantrolene and calcium channel blockers, such as verapamil and diltiazem, in the form of heart failure. Concomitant use of NPJ5008 and calcium channel blockers is not recommended. Concomitant administration of NPJ5008 with non-depolarising muscle relaxants such as vecuronium can enhance their effect[8].

Part II: Module SIII - Clinical trial exposure

The clinical safety and efficacy of dantrolene are well established. The proposed dose of NPJ5008 is supported based on the well-established clinical posology of dantrolene from intravenous products marketed since 1984. Intravenous dantrolene is the only available pharmacological treatment for MH[11,12]. Since introduction, it has become the recommended treatment for MH according to several guidelines including those of the European MH Group (EMHG)[13] and of the MH Association of the United States[14]. The type and levels of excipients in NPJ5008 are considered to be acceptable for the acute dosing of an MH crisis.

The pharmacokinetics, safety and efficacy of intravenous dantrolene have long been established for the treatment of MH, e.g. since 1984 in Austria (DANTROLEN IV 20 mg).

Current European guidelines[13] recommend dantrolene is used at a starting dose of 2-2.5 mg/kg (although historically this used to be from 1 mg/kg). The SmPC for NPJ5008 recommends an initial dose of 2.5 mg/kg body to a cumulative dose of 10 mg/kg for the treatment of MH, although higher doses can be given if necessary. In exceptional circumstances some patients have required much more and one documented case has reported as much as 33 mg/kg of dantrolene IV has been required to reverse the crisis. In a patient suffering from a malignant hyperthermic crisis dantrolene has been proven to work rapidly and reduce symptoms when the appropriate amount of dantrolene has been administered, which is dependent on many factors (involvement and extent of muscle and muscle mass). The new product NPJ5008, with its formulation and reconstitution characteristics, enables the optimal dose of dantrolene to be administered more quickly as dictated by the pharmacology for the rapid and direct reversal of symptoms. This is expected to be a significant advance in the treatment of these patients with the active drug component dantrolene.

In comparison with the currently available product: DANTRIUM/DANTROLEN 20 mg powder for solution for injection, NPJ5008 120 mg offers simpler and faster reconstitution of a significantly larger unit dose. For example, depending on the number of staff available to assist with management of a crisis (e.g. one or two operator(s) reconstituting vials and another administering to the patient), preparing a 10 mg/kg dose of the current product for a 70 kg patient could take approximately 2 hours. Whereas, the same dose of NPJ5008 can be prepared within 12 minutes.

Historical evidence indicates that a significant proportion (as much as 50%) of patients might be expected to be 18 years or younger and the median typical patient bodyweight is likely to be less than the 72 kg mean weight of an adult. The improved solubility of NPJ5008 has allowed the choice of a vial unit dose that supports optimal dosing versatility by means of a loading dose throughout a wide range of bodyweights. This loading dose is centred around a target typical patient median bodyweight to support posology across very wide patient demographics of age and weight, from adults to children. For example, an initial dose of two vials (240 mg total) will provide 2.5 mg/kg for a 96 kg adult, a single vial of 120 mg will provide at least a minimum dose of 2.5 mg/kg to children of 6-11 years (up to 48 kg) and half a vial (60 mg) to children less than 6 years (up to 24 kg), respectively. This allows rapid preparation and initial administration to patients experiencing MH and is expected to bring a significant advance in patient care.

The clinical trial (Study QSC204721 or NPJ5008-01/2020), a two part, open-label intravenous (IV) cross-over study in male and female healthy volunteers, was the first clinical study using NPJ5008.

The aim of the study was to compare the relative bioavailability of NPJ5008 in comparison with DANTRIUM/DANTROLEN IV. Bioequivalence in terms of overall exposure (area under the curve) was to be confirmed from the results. It was anticipated that the systemic exposure of dantrolene following administration of NPJ5008 would be equivalent with that from DANTRIUM/DANTROLEN IV.

The study was conducted in two parts:

Part 1 was a randomised, open-label, single-dose, 2-period crossover study, with sentinel dosing in 16 healthy male and female (women of non-childbearing potential [WONCBP]) subjects to enable a safety and pharmacokinetic assessment of NPJ5008 vs DANTRIUM/DANTROLEN IV (marketed reference), using a fixed dose of 60 mg of NPJ5008 (5.3 mg/mL) infused over at least 1 minute (60 mg dantrolene sodium /min) and 60 mg of DANTRIUM/DANTROLEN IV (0.33 mg/mL) infused over at least 5 minutes (12 mg dantrolene sodium /min). Each subject received a single dose of NPJ5008 and DANTRIUM/DANTROLEN IV reference with a minimum washout interval of 5 days.

Part 2 was an open-label, single-dose study in 10 healthy male and female (WONCBP) subjects designed to assess safety and pharmacokinetics of NPJ5008 in a different group of subjects receiving a dose of 120 mg or 240 mg NPJ5008. Each subject received a single dose of NPJ5008 on one occasion.

The study parts, dosing regimens and patient demographics are summarised in Table 1, Table 2 and Table 3 below.

Table 1: Description of Study QSC204721 Parts

Part	Regimen	Product	Dantrolene dose (mg)	Dantrolene dose (mg/mL)	Batch numbers
1	A	NPJ5008	60	5.3	20SP071
1	B	DANTRIUM/DANTROLEN IV	60	0.32	20SP070
2	C	NPJ5008	120	5.3	20SP071
2	D*	NPJ5008	240	5.3	N/A

* Part D was planned but not performed during this study.

Table 2: Patient demographics for Study QSC204721 Part 1

		Treatment Sequence		
		AB (n=8)	**BA (n=8)**	**Overall (n=16)**
Age (years)	N	8	8	16
	Mean	44.3	34.6	39.4
	Min	23	26	23

	Max	55	45	55
Race n (%)	White	8 (100)	8 (100)	16 (100)
Ethnicity n (%)	Not Hispanic or Latino	8 (100)	8 (100)	16 (100)
Sex n (%)	Male	7 (87.5)	8 (100)	15 (93.8)
	Female	1 (12.5)	0	1 (6.3)
Height (cm)	Mean	175.5	182.9	179.2
Weight (kg)	Mean	79.83	82.05	80.94
BMI (kg/m^2)	Mean	25.83	24.58	25.20

Table 3: Patient demographics for Study QSC204721 Part 2

		120 mg, NPJ5008 (n=5)
Age	N	5
	Mean	43.6
	Min	20
	Max	55
Race n (%)	White	5 (100)
Ethnicity n (%)	Not Hispanic or Latino	5 (100)
Sex n (%)	Male	4 (80.0)
	Female	1 (20.0)
Height (cm)	Mean	177.0
Weight (kg)	Mean	86.88
BMI (kg/m^2)	Mean	27.78

The safety objectives in the study; secondary objective for Part I and the primary objective for Part II were met. All subjects reported AEs during the study following dosing with NPJ5008 and DANTRIUM/DANTROLEN IV. The AEs reported, included decreased hand grip strength, were consistent with the known mechanism of action of dantrolene as a skeletal muscle relaxant and with previous literature, indicating that both regimens were performing as expected in a healthy subject, and a similar profile (type and severity) of AEs was reported following dosing with NPJ5008 and DANTRIUM/DANTROLEN IV. No serious AEs were reported and no pre-specified study safety stopping criteria were met.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exposure during pregnancy

Reason for exclusion: Potential safety implications for the patient due to lack of data in this population clinically. The rarity of MH, together with the fulminant nature of the crisis and resultant need for urgent treatment make the prospect of controlled clinical trials unrealistic and unethical.

Is it considered to be included as missing information?: No

Rationale: There are no data from the use of NPJ5008 in pregnant women. Dantrolene crosses the placenta and should only be used during pregnancy when the potential benefit outweighs the possible risk to mother and child.

Intravenous dantrolene has been shown to treat MH in both mothers and their neonates; all reports indicated that the patients responded rapidly to IV dantrolene. Postpartum uterine atony has been reported after IV dantrolene therapy. The risk of floppy child syndrome in neonates has also been described when IV dantrolene was administered to the mother during caesarean section.

Nursing mothers

Reason for exclusion: Potential safety implications for the patient due to lack of data in this population clinically. The rarity of MH, together with the fulminant nature of the crisis and resultant need for urgent treatment make the prospect of controlled clinical trials unrealistic and unethical.

Is it considered to be included as missing information?: No

Rationale: Dantrolene should not be used during the breast-feeding period as it is excreted in the breast milk. If the treatment is necessary, breast feeding should be discontinued and benefit/risk assessment should be made.

Use in the paediatric population

Reason for exclusion: Potential safety and efficacy implications for the patient. The rarity of MH, together with the fulminant nature of the crisis and resultant need for urgent treatment make the prospect of controlled clinical trials unrealistic and unethical.

Is it considered to be included as missing information?: No

Rationale: Paediatric subjects will not be recruited into the healthy volunteer clinical trial. Dantrolene IV is indicated for use in both adults and children. After IV administration, the pharmacokinetic profile of dantrolene in children was found to be similar to adults. Metabolic patterns are similar in adults and children[15].

Use in the geriatric population

Reason for exclusion: Potential safety and efficacy implications for the patient. The rarity of MH, together with the fulminant nature of the crisis and resultant need for urgent treatment make the prospect of controlled clinical trials unrealistic and unethical.

Is it considered to be included as missing information?: No

Rationale: Geriatric subjects will not be recruited into the clinical trial. A similar dosage titration schedule should be used with the elderly[15] .

Use in patients with hepatic dysfunction

Reason for exclusion: Potential safety and efficacy implications for the patient. The rarity of MH, together with the fulminant nature of the crisis and resultant need for urgent treatment make the prospect of controlled clinical trials unrealistic and unethical.

Is it considered to be included as missing information?: No

Rationale: No data are available for NPJ5008 in hepatically impaired subjects. Hepatic dysfunction, including hepatitis and fatal hepatic failure, has been reported with prolonged oral dantrolene sodium therapy[2]. This is dependent on the dosage and duration of therapy[17], however therapy duration is not expected to be prolonged for the treatment of MH.

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.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	

Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment	Not included in the clinical development programme.
Population with relevant different ethnic origin	Not included in the clinical development programme.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable - NPJ5008 is a new drug product for intravenous administration of dantrolene, and therefore there is currently no data concerning post-authorisation exposure.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

In vivo data have shown that dantrolene has limited central nervous system (CNS) penetration following oral dosing. Inhibition of the Blood Brain Barrier (BBB) transport protein, P-glycoprotein breast cancer resistance (P-gp/BCRP), function has been shown to increase the brain/plasma concentration ratios of dantrolene. Following oral administration to mice, the brain:plasma ratio ranged from 10-30% up to 70 minutes after an oral dose[16]. Additional work confirmed no BBB transport via transporter involvement of Mdr1a (P-glycoprotein) in rats (no change in brain to plasma ratio's) in addition to a weak effect of breast cancer resistance protein (BCRP) transport (3.3-fold change) based on Mdr1a and BCRP knockout animals[17].

These data suggest that the abuse liability potential of dantrolene is low and non-abuse liability assessments are deemed unnecessary.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The following safety concerns have been identified for NPJ5008:

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Hearing loss
Missing information	• None

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

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

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 by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Hypersensitivity to dantrolene or any of NPJ5008 excipients - Hypersensitivity is followed up via routine pharmacovigilance and it is considered that health care professionals are already aware of the risk of anaphylactic reactions and will have the appropriate measures in place as part of clinical practice. The SmPC lists hypersensitivity and anaphylactic reaction in Section 4.8 with a frequency of unknown. Additionally, Section 4.3 Contraindication states hypersensitivity to the active substance or to any of the excipients.
- Dantrolene-induced hepatic dysfunction – This is included in the RMP v3.2 for the originator product DANTRIUM/DANTROLEN IV as an important identified risk. Liver damage may occur during dantrolene therapy. This has been observed during longer term, oral administration and may run a lethal course. The SmPC lists jaundice, hepatitis, hepatic function abnormal, hepatic failure including fatal outcome, idiosyncratic or hypersensitive liver diseases in Section 4.8 with a frequency of unknown. No data are available for NPJ5008 in hepatically impaired subjects, however, NPJ5008 is intended for short-term use for the treatment of MH and therefore risk of hepatic dysfunction is minimized based on the short-term exposure. This risk is mainly associated with chronic oral dosing and not acute IV dosing.
- Particle formation (of active substance) in reconstituted solution in some batches – This is included in the RMP v3.2 for the originator product DANTRIUM/DANTROLEN IV as an important potential risk. This safety concern was specific to the originator product, however NPJ5008 has a different composition and therefore, this safety concern is not considered applicable. No requirement for single use filtration needle as NPJ5008 pharmaceutical form does not have issues with solubility, unlike with DANTRIUM IV.

- Medication errors – This is included in the RMP v3.2 for the originator product DANTRIUM/DANTROLEN IV as an important potential risk. This was considered an important potential risk for DANTRIUM/DANTROLEN IV due to issues with product solubility during reconstitution, a single use filtration needle was introduced to prevent particle formation during reconstitution of the product. The risk for medication errors was identified due to incorrect use of the filtration device which may lead to an increase in the incidence/severity of skin reactions or thrombophlebitis. Additionally, a large number of vials are required to be made up, in a 70kg male this would be 36 vials.
  Medication errors are followed up via routine pharmacovigilance. There is clear wording in the SmPC for NPJ5008 regarding posology and method of administration. There is no requirement for use of single use filtration needles with NPJ5008 as its pharmaceutical form does not have issues with solubility, unlike DANTRIUM/DANTROLEN IV. Additionally, the number of vials required in treatment of the patients with NPJ5008 is much less than the number of vials used with the originator hence minimising this risk further.
- Lack of efficacy – This is included in the RMP v3.2 for the originator product DANTRIUM/DANTROLEN IV as an important potential risk. Lack of efficacy is followed up via routine pharmacovigilance. The SmPC states that use of NPJ5008 in the management of MH should be used in combination with adequate supportive measures.
- Use in pregnancy and lactation – This is included in the RMP for the originator product DANTRIUM/DANTROLEN v3.2 IV as missing information. There are no data from the use of NPJ5008 in pregnant women. The SmPC states that there are no or limited data for the use of dantrolene in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Postpartum uterine atony has been reported after intravenous dantrolene therapy. The risk of floppy child syndrome in neonates has also been described when intravenous dantrolene was administered to the mother during caesarean section. Dantrolene crosses the placenta and should only be used during pregnancy when the potential benefit outweighs the possible risk to mother and child.
  In relation to breast feeding, it is mentioned in the SmPC that no information is available on the use of dantrolene during breastfeeding. According to its safety profile, a risk to a breastfed infant cannot be excluded as dantrolene is excreted in breastmilk. Therefore, breastfeeding should be discontinued during administration of NPJ5008. Based on elimination half-life of dantrolene, breastfeeding can be restarted 60 hours after the last dose.
- Off label use - This is included in the RMP v3.2 for the originator product DANTRIUM/DANTROLEN IV as missing information. Off label use is followed up via routine pharmacovigilance. There is clear wording in the SmPC for NPJ5008 regarding approved indications which therefore minimizes the risk of off label use.
- Drug interaction with Vecuronium: Drug interactions with vecuronium is not considered a safety concern as there is clear wording in the SmPC for NPJ5008. Section 4.5 of the SmPC notes that the effects of non-depolarising muscle relaxants (vecuronium) can be enhanced in patients who have been administered dantrolene. Drug interactions with vecuronium are followed up via routine pharmacovigilance.
- Drug interactions with calcium channel blockers: Drug interactions with calcium channel blockers is not considered a safety concern as there is clear wording in the SmPC for NPJ5008 to state that concomitant use with calcium channel blockers is not recommended. Section 4.4 states that caution should be exercised if hyperkalaemia symptoms occur (muscular paralysis, electrocardiogram changes, bradycardic arrhythmias) or in cases of pre-existing hyperkalaemia (renal insufficiency, digitalis intoxication, etc.), as an increase in serum potassium has been demonstrated in animal studies as a result of the co-administration of dantrolene with verapamil. Section 4.5 of the SmPC notes that isolated case reports and animal studies indicate an interaction between dantrolene and calcium channel blockers, such as verapamil and diltiazem, in the form of heart failure. Hyperkalaemia and cardiac failure are listed in Section 4.8 with a

frequency of unknown. Drug interactions with calcium channel blockers are followed up via routine pharmacovigilance.

- Serious skin reactions including extravasation: Section 4.4 of the SmPC for NPJ5008 states that the product is only for intravenous use. Due to the high pH value of the solution (pH 9.5), extravascular injection must be avoided as it can lead to tissue necrosis. Due to the risk of vascular occlusion, intraarterial injections must be avoided. There is clear wording in the SmPC on method of administration to be used.

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

Important Potential Risk: Hearing loss

Risk-benefit impact:

NPJ5008 contains hydroxypropylbetadex (a cyclodextrin) as an excipient. In animals, via subcutaneous, intrathecal or intracerebroventricular administration, hydroxypropyl beta cyclodextrin (HP-ß-CD) was found to damage the outer hair cells (OHCs) of the inner ear in mice and cats, while in rats the effects were more severe with damage seen to the OHCs, inner hair cells (IHCs) and spiral ganglion neurons (SGNs).[18]

HP-β-CD has been administered as a potential therapeutic agent both intrathecally and intravenously to patients with Niemann-Pick Type C (NPC) disease in clinical investigations since approximately 2009. From the published data, it is clear that there is a difference in ototoxicity in humans depending on whether HP-β-CD is administered intrathecally or intravenously. Significant hearing loss is noted following intrathecal administration, compared to either an absence or transient effects on hearing in subjects receiving HP-β-CD intravenously or via intravenous infusion, even at doses up to 2500 mg/kg three times per week in adults[19], as well as in infants under six months of age at 1000 mg/kg, twice per week.[20]

Hastings et al[21] investigated intravenous HP-β-CD in NPC. Of the ten subjects completing the study, the most common treatment emergent adverse effect was hearing loss/reduction (deafness) occurring in six (46%) subjects, one subject (16.7%) in the 1500 mg/kg group and five subjects (71.4%) in the 2500 mg/kg dose group. Two subjects in the 2500 mg/kg group experienced a Grade 3 hearing loss (change from Baseline of 25 dB averaged over 3 contiguous frequencies) that was temporally related to the study drug infusion; the loss resolved within two weeks post-infusion in both subjects. After two further doses in both subjects, Grade 3 hearing loss was observed again, both of which improved significantly within two weeks. It is important to note that hearing loss is part of the natural history of NPC, and that 11 of the 13 subjects who enrolled into the study, had hearing loss of some degree at baseline. All AEs of hearing loss were detected by protocol-mandated audiometry and were not perceived by the subjects themselves or their families.[21]

Sharma et al[23] conducted a Phase I/II, randomised, double-blind, parallel-group study, to compare the pharmacokinetics of three different single IV doses of HP-β-CD in patients with NPC1 and to evaluate the efficacy and tolerability of the different dosages after 48 weeks of treatment. Twelve patients aged at least 2 years (2–39 years of age) were randomised to receive one of three IV doses of HP-β-CD (1500 mg/kg, 2000 mg/kg, or 2500 mg/kg) every 2 weeks for 48 weeks. As part of the safety measure outcomes, patients underwent audiology testing across a range of frequencies from 0.5 to 8 kHz at screening, baseline and at weeks 12, 24, 36, and 48 using either pure tone audiometry or auditory brainstem response (ABR). No safety signals or trends were noted apart from audiometry changes with no perceptible changes in hearing. Slight-to-mild hearing loss in two cases (one each in the 1500 mg/kg and 2500 mg/kg group) and transient hearing change in three cases (one in the 1500 mg/kg and two in the 2000 mg/kg group) were reported. Of the changes in hearing noted, none were reported by either

the patient or caregiver as a noticeable change. The authors conclude that given no hearing change was noted by patients or carers, the benefit/risk of continuing treatment with HP-β-CD was considered to be acceptable.

Given that the total dose of HP-β-CD (2500 mg/kg) administered to a 70 kg subject (175,000 mg) is 8.5-fold higher than the dose of HP-β-CD that would be administered to a 70 kg subject with NPJ5008 over a 24-hour period using the proposed posology, it is considered unlikely that HP-β-CD exposure would pose a significant risk to subject hearing.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable – this is an initial marketing authorisation application.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk: Hearing loss

Potential mechanisms:

Based on the actions of β-cyclodextrins, these compounds could target different aspects of OHC physiology. HP-β-CD entry into the cochlear duct could induce one or more events that lead to the selective injury of OHCs. These targets include intracellular organelles that govern a variety of cell stress pathways, membrane resident proteins, and cell-cell junctions that regulate ion flux between fluid compartments surrounding the OHCs. Oxidative stress is a major effector of hair cell death in acquired forms of hearing loss. It should be noted that HP-β-CD effects on other structures within the inner ear could indirectly affect OHC health or modulate their susceptibility to direct influence of the drug. One possibility is altered ion homeostasis within the cochlear duct.[22]

Evidence source(s) and strength of evidence:

NPJ5008 contains hydroxypropylbetadex (a cyclodextrin) as an excipient. In animals, via subcutaneous, intrathecal or intracerebroventricular administration, HP-β-CD was found to damage the OHCs in mice and cats, while in rats the effects were more severe with damage seen to the OHCs, IHCs and SGNs.[18]

HP-β-CD has been administered as a potential therapeutic agent both intrathecally and intravenously to patients with NPC disease in clinical investigations since approximately 2009. From the published data, it is clear that there is a difference in ototoxicity in humans depending on whether HP-β-CD is administered intrathecally or intravenously. Significant hearing loss is noted following intrathecal administration, compared to either an absence or transient effects on hearing in subjects receiving HP-β-CD intravenously or via intravenous infusion, even at doses up to 2500 mg/kg three times per week in adults[19], as well as in infants under six months of age at 1000 mg/kg, twice per week.[20]

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the study drug infusion; the loss resolved within two weeks post-infusion in both subjects. After two further doses in both subjects, Grade 3 hearing loss was observed again, both of which improved significantly within two weeks. It is important to note that hearing loss is part of the natural history of NPC, and that 11 of the 13 subjects who enrolled into the study, had hearing loss of some degree at baseline. All AEs of hearing loss were detected by protocol-mandated audiometry and were not perceived by the subjects themselves or their families.[21]

Sharma et al[23] conducted a Phase I/II, randomised, double-blind, parallel-group study, to compare the pharmacokinetics of three different single IV doses of HP-β-CD in patients with NPC1 and to evaluate the efficacy and tolerability of the different dosages after 48 weeks of treatment. Twelve patients aged at least 2 years (2–39 years of age) were randomised to receive one of three IV doses of HP-β-CD (1500 mg/kg, 2000 mg/kg, or 2500 mg/kg) every 2 weeks for 48 weeks. As part of the safety measure outcomes, patients underwent audiology testing across a range of frequencies from 0.5 to 8 kHz at screening, baseline and at weeks 12, 24, 36, and 48 using either pure tone audiometry or auditory brainstem response (ABR). No safety signals or trends were noted apart from audiometry changes with no perceptible changes in hearing. Slight-to-mild hearing loss in two cases (one each in the 1500 mg/kg and 2500 mg/kg group) and transient hearing change in three cases (one in the 1500 mg/kg and two in the 2000 mg/kg group) were reported. Of the changes in hearing noted, none were reported by either the patient or caregiver as a noticeable change. The authors conclude that given no hearing change was noted by patients or carers, the benefit/risk of continuing treatment with HP-β-CD was considered to be acceptable.

Given that the total dose of HP-β-CD (2500 mg/kg) administered to a 70 kg subject (175,000 mg) is 8.5-fold higher than the dose of HP-β-CD that would be administered to a 70 kg subject with NPJ5008 over a 24-hour period using the proposed posology, it is considered unlikely that HP-β-CD exposure would pose a significant risk to subject hearing.

Risk factors and risk groups:

The risk to hearing only became apparent when highly concentrated doses of cyclodextrin were being evaluated as a treatment for NPC.[22] Significant hearing loss is noted following intrathecal administration, compared to either an absence or transient effects on hearing in subjects receiving HP-β-CD intravenously or via intravenous infusion.[19] Exposure to hydroxypropylbetadex from NPJ5008 is expected to be higher in patients with renal impairment. The potential risks associated with hydroxypropylbetadex may be higher in these patients.

Preventability:

Given that only one treatment episode should be required per lifetime for the treatment of MH, as potential triggering agents will be avoided during future anaesthetic administration, there is negligible risk of treatment being required for future episodes of MH.

The following wording is proposed in Section 4.4 of the SmPC to allow the prescribing physician to make an informed decision based on the benefits and risks of the clinical situation:

'Agilus contains 3530 mg hydroxypropylbetadex (a cyclodextrin) in each vial, which is equivalent to 156.2 mg/mL in the reconstituted solution. Hydroxypropylbetadex increases solubility of dantrolene and thereby reduces preparation time and fluid volume.

Hydroxypropylbetadex has been associated with ototoxicity in animal studies (see Section 5.3), and cases of hearing impairment have been observed in other clinical settings. Cases of hearing impairment have been observed at hydroxypropylbetadex exposure levels comparable to the higher range of recommended Agilus doses. In most cases the hearing impairment has been transient and of slight to mild severity. For patients requiring high Agilus doses (above 10 mg/kg) the diagnosis should be re-evaluated (see Section 4.2).

The potential risk for hearing impairment may be of particular concern in patients with increased risk for hearing loss, e.g. recurring/chronic ear infections.

Exposure to hydroxypropylbetadex from NPJ5008 is expected to be higher in patients with renal impairment. The potential risks associated with hydroxypropylbetadex may be higher in these patients.'

Addition of information to Section 5.3 on pre-clinical studies is proposed as follows: 'There is evidence of hydroxypropylbetadex-induced ototoxicity in several nonclinical species following single and repeat sub-cutaneous (SC) dosing. In rats (the most sensitive species to hydroxypropylbetadex ototoxicity), a dose of 2000 mg/kg is close to the critical dose for inducing significant hearing loss and cochlear damage following SC administration. Doses greater than 2000 mg/kg cause significant hair cell damage and completely abolish distortion product otoacoustic emissions, whereas lower doses have relatively little effect on functional and structural measures. In literature studies, no ototoxicity from 500 to 1000 mg/kg has been reported in rats. The relevance of these findings for human exposure to hydroxypropylbetadex is not clear.'

Impact on the benefit-risk balance of the product:

The impact of hearing loss on the quality of life is considered to be significant, however the NPJ5008 doses and resultant HP-β-CD doses proposed in the SmPC do not pose a significant risk to subject hearing.

Public health impact:

Unknown

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	• Hearing loss
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for NPJ5008:

Norgine is using a specific adverse reaction follow up questionnaire for NPJ5008 for the following important potential risk (included in Annex 4):

- Hearing loss

Other forms of routine pharmacovigilance activities for NPJ5008:

No other forms of routine pharmacovigilance activities are considered necessary.

III.2 Additional pharmacovigilance activities

Additional pharmacovigilance activities are not necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None planned	N/A	N/A	N/A	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None planned	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities				
None planned	N/A	N/A	N/A	N/A

Part IV: Plans for post-authorisation efficacy studies

No PAES studies have been conducted and none are considered required.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Potential Risk: Hearing loss	Routine risk communication: SmPC Sections 4.4 and 5.3. Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning added in Section 4.4 to allow the prescribing physician to make an informed decision based on the benefits and risks of the clinical situation: 'Agilus contains 3530 mg hydroxypropylbetadex (a cyclodextrin) in each vial, which is equivalent to 156.2 mg/mL in the reconstituted solution. Hydroxypropylbetadex increases solubility of dantrolene and thereby reduces preparation time and fluid volume. Hydroxypropylbetadex has been associated with ototoxicity in animal studies (see Section 5.3), and cases of hearing impairment have been observed in other clinical settings. Cases of hearing impairment have been observed at hydroxypropylbetadex exposure levels comparable to the higher range of recommended Agilus doses. In most cases the hearing impairment has been transient and of slight to mild severity. For patients requiring high Agilus doses (above 10 mg/kg) the diagnosis should be re-evaluated (see Section 4.2). The potential risk for hearing impairment may be of particular concern in patients with increased risk for hearing loss, e.g. recurring/chronic ear infections. Exposure to hydroxypropylbetadex from NPJ5008 is expected to be higher in patients with renal impairment. The potential risks associated with hydroxypropylbetadex may be higher in these patients.' Section 5.3 mentions: 'There is evidence of hydroxypropylbetadex-induced ototoxicity in several nonclinical species following single and repeat sub-cutaneous (SC) dosing. In rats (the most sensitive species to hydroxypropylbetadex ototoxicity), a dose of 2000 mg/kg is close to the critical dose for inducing significant hearing loss and cochlear damage following SC administration. Doses greater than 2000 mg/kg cause significant hair cell damage and completely abolish distortion product otoacoustic emissions, whereas lower doses have relatively little effect on functional and structural measures. In literature studies, no ototoxicity from 500 to 1000 mg/kg has been reported in rats. The relevance of these findings for human exposure to hydroxypropylbetadex is not clear.'

	Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risk: Hearing loss	**Routine risk minimisation measures:** SmPC Section 4.4 states that cases of hearing impairment have been observed at hydroxypropylbetadex exposure levels comparable to the higher range of recommended Agilus doses. In most cases the hearing impairment has been transient and of slight to mild severity. For patients requiring high Agilus doses (above 10 mg/kg) the diagnosis should be re-evaluated. Section 5.3 has additional wording to help the physician have more information regarding the important potential risk. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse event follow-up questionnaire **Additional pharmacovigilance activities:** None

Part VI: Summary of the risk management plan

Summary of risk management plan for NPJ5008 (dantrolene sodium 120 mg)

This is a summary of the risk management plan (RMP) for NPJ5008. The RMP details important risks of NPJ5008, how these risks can be minimised, and how more information will be obtained about NPJ5008's risks and uncertainties (missing information).

NPJ5008's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how NPJ5008 should be used.

This summary of the RMP for NPJ5008 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 NPJ5008's RMP.

I. The medicine and what it is used for

NPJ5008 is authorised, in combination with adequate support measures, for the treatment of malignant hyperthermia in adults and children of all ages. It contains dantrolene as the active substance and it is given intravenously.

Further information about the evaluation of NPJ5008's benefits can be found in NPJ5008's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of NPJ5008, together with measures to minimise such risks and the proposed studies for learning more about NPJ5008'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, including PSUR assessment, 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 NPJ5008 are those 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 NPJ5008. 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);

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

II.B Summary of important risks

Important potential risk: Hearing loss	
Evidence for linking the risk to the medicine	NPJ5008 contains hydroxypropylbetadex (a cyclodextrin) as an excipient. In animals, via subcutaneous, intrathecal or intracerebroventricular administration, hydroxypropyl beta cyclodextrin (HP-ß-CD) was found to damage the outer hair cells (OHCs) in mice and cats, while in rats the effects were more severe with damage seen to the OHCs, inner hair cells (IHCs) and spiral ganglion neurons (SGNs).[18] HP-β-CD has been administered as a potential therapeutic agent both intrathecally and intravenously to patients with Niemann-Pick Type C (NPC) disease in clinical investigations since approximately 2009. From the published data, it is clear that there is a difference in ototoxicity in humans depending on whether HP-β-CD is administered intrathecally or intravenously. Significant hearing loss is noted following intrathecal administration, compared to either an absence or transient effects on hearing in subjects receiving HP-β-CD intravenously or via intravenous infusion, even at doses up to 2500 mg/kg three times per week in adults[19], as well as in infants under six months of age at 1000 mg/kg, twice per week.[20]

	Hastings et al investigated intravenous HP-β-CD in NPC. Of the ten subjects completing the study, the most common treatment emergent adverse effect was hearing loss/reduction (deafness) occurring in 6 (46%) subjects, one subject (16.7%) in the 1500 mg/kg group and five subjects (71.4%) in the 2500 mg/kg dose group. Two subjects in the 2500 mg/kg group experienced a Grade 3 hearing loss (change from Baseline of 25 dB averaged over 3 contiguous frequencies) that was temporally related to the study drug infusion; the loss resolved within two weeks post-infusion in both subjects. After two further doses in both subjects, Grade 3 hearing loss was observed again, both of which improved significantly within two weeks. It is important to note that hearing loss is part of the natural history of NPC, and that 11 of the 13 subjects who enrolled into the study, had hearing loss of some degree at baseline.[21] Sharma et al[23] conducted a Phase I/II, randomised, double-blind, parallel-group study, to compare the pharmacokinetics of three different single IV doses of HP-β-CD in patients with NPC1 and to evaluate the efficacy and tolerability of the different dosages after 48 weeks of treatment. Twelve patients aged at least 2 years (2–39 years of age) were randomised to receive one of three IV doses of HP-β-CD (1500 mg/kg, 2000 mg/kg, or 2500 mg/kg) every 2 weeks for 48 weeks. As part of the safety measure outcomes, patients underwent audiology testing across a range of frequencies from 0.5 to 8 kHz at screening, baseline and at weeks 12, 24, 36, and 48 using either pure tone audiometry or auditory brainstem response (ABR). No safety signals or trends were noted apart from audiometry changes with no perceptible changes in hearing. Slight-to-mild hearing loss in two cases (one each in the 1500 mg/kg and 2500 mg/kg group) and transient hearing change in three cases (one in the 1500 mg/kg and two in the 2000 mg/kg group) were reported. Of the changes in hearing noted, none were reported by either the patient or caregiver as a noticeable change. The authors conclude that given no hearing change was noted by patients or carers, the benefit/risk of continuing treatment with HP-β-CD was considered to be acceptable. Given that the total dose of HP-β-CD (2500 mg/kg) administered to a 70 kg subject (175,000 mg) is 8.5-fold higher than the dose of HP-β-CD that would be administered to a 70 kg subject with NPJ5008 over a 24-hour period using the proposed posology, it is considered unlikely that HP-β-CD exposure would pose a significant risk to subject hearing.
Risk factors and risk groups	The risk to hearing only became apparent when highly concentrated doses of cyclodextrin were being evaluated as a treatment for NPC.[22] Significant hearing loss is noted

	following intrathecal administration, compared to either an absence or transient effects on hearing in subjects receiving HP-β-CD intravenously or via intravenous infusion.[19] Exposure to hydroxypropylbetadex from NPJ5008 is expected to be higher in patients with renal impairment. The potential risks associated with hydroxypropylbetadex may be higher in these patients.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 states that cases of hearing impairment have been observed at hydroxypropylbetadex exposure levels comparable to the higher range of recommended Agilus doses. In most cases the hearing impairment has been transient and of slight to mild severity. For patients requiring high Agilus doses (above 10 mg/kg) the diagnosis should be re-evaluated. Sections 5.3 is added to help the physician have more information regarding the important potential risk. **Additional risk minimisation measures:** None

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 NPJ5008.

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

There are no studies required for NPJ5008.

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

- This annex contains the specific adverse event follow-up questionnaire used to collect additional data for the following Important Potential Risk: Hearing loss

SPECIFIC ADVERSE EVENT FOLLOW-UP QUESTIONNAIRE FOR NPJ5008 120 mg POWDER FOR SOLUTION FOR INJECTION

Hearing loss

Norgine Reference No: .....

1. PATIENT DETAILS

Please tell us more about the person who had the suspected adverse event (AE).

Patient Initials:		
Weight (kg):	Height (cm):	
Age (at the time of report):		
Male ☐	Female ☐	Unknown ☐

2. INFORMATION REGARDING NPJ5008 120 mg POWDER FOR SOLUTION FOR INJECTION

Brand name	Lot/batch number, if known	Dose	Date started	Date stopped	Indication

3. INFORMATION REGARDING THE HEARING LOSS

a. Adverse event description:

Which of the following describes the hearing loss?

☐ Unilateral hearing loss	☐ Sensorineural hearing loss
☐ Bilateral hearing loss	☐ Conductive hearing loss

Degree of hearing loss (measured):

(Grades of hearing impairment as recommended by the Global Burden of Disease Expert Group on Hearing Loss)*

Category	**Pure-tone audiometry**[a,b]	**Result** (including frequency range where the hearing loss occurs)
Normal hearing	-10.0 to 19.9 dB	
Mild hearing loss	20.0 to 34.9 dB	
Moderate hearing loss	35.0 to 49.9 dB	
Moderately severe hearing loss	50.0 to 64.9 dB	
Severe hearing loss	65.0 to 79.9 dB	
Profound hearing loss	80.0 to 94.9 dB	
Complete or total hearing loss	95.0 dB or greater	
Unilateral	<20.0 dB in the better ear, 35.0 dB or greater in the worse ear	

[a] In the better ear

[b] Average frequency of 500, 1000, 2000 and 4000 Hertz (Hz)

∗Olusanya BO, Davis AC, Hoffman HJ. Hearing loss grades and the International classification of functioning, disability and health. Bull World Health Organ. 2019 Oct 1;97(10):725-728..

Degree of hearing loss (subjective/not measured):

☐ Mild	☐ Severe
☐ Moderate	☐ Profound

Was the hearing loss transient: ☐ Yes ☐ No

Further description of the hearing loss and associated symptoms including details on the course (including potential reversibility)":

Date adverse event started (DD MM YY):

Date adverse event stopped (DD MM YY):

Do you consider the reaction to be serious? ☐ Yes ☐ No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

☐ Patient died due to reaction	☐ Involved or prolonged inpatient hospitalization	☐ Life threatening
☐ Involved persistent or significant disability or incapacity	☐ Medically significant (please give details)	

What was the adverse event outcome?:

☐ Recovered	☐ Not recovered	☐ Recovering
☐ Other (please provide detail)		

b. Relevant investigations

Were any relevant investigations performed (e.g. audiometry testing or reports from specialists if consulted)?

Investigation	Date	Results

If no details are available on the relevant investigations, please provide consent to request these details from the health care professional (HCP).

Patient/caregiver consent:

☐ Yes ☐ No Date:

HCP's contact information:

Occupation:

Contact details:

c. Concurrent events or diseases (please detail)

d. Relevant past history

Does the patient have a history of ear or hearing problems prior to the start of the suspect drug?

☐ Yes ☐ No

If yes, please specify:

e. Treatment provided and follow-up recommendations (provide detail)

4. CONCOMITANT DRUG(S)

Please list other medications at the time of the adverse event (including self-medication & herbal remedies)

Give brand name of drug and batch number if known	Route	Dosee	Date started	Date stopped	Indication

5. REPORTER DETAILS

Initials

Occupation:

Country:

Contact details: email/ telephone number:

Date:

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

Not applicable