21 March 2024
EMA/150697/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AGILUS

International non-proprietary name: dantrolene sodium, hemiheptahydrate

Procedure No. EMEA/H/C/006009/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AMRA	Adverse metabolic/ musculoskeletal reaction to anesthesia
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
ATP	Adenosine triphosphate
AUC	Area under the curve
AUC(0-inf)	AUC curve to infinite time.
AUC(0-last)	AUC up to the last measurable concentration
$Ca2^+$	Calcium
CCB	Calcium channel blockers
CHMP	Committee for Medicinal Products for Human Use
CI	CI confidence interval
C_{max}	Maximum (or peak) serum concentration
CQA	Critical Quality Attributes
CV%	CV% coefficient of variation
DIC	Disseminated intravascular coagulation
DMF	Drug Master File
EMHG	European Malignant Hyperthermia Association Group
ESPA	European Society of Paediatric Anaesthesiology
FHC	Fulminant hypermetabolic crisis secondary to calcium dysregulation in skeletal muscle
GC	Gas Chromatography
GMP	Good Manufacturing Practice
GRAS	Generally recognized as safe
HP-β-CD	Hydroxypropyl beta cyclodextrin
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In-Process Control
IR	Infrared
i.v. / IV	Intravenous
K3EDTA	Tripotassium ethylenediaminetetraacetic acid.
MDMA	3,4-methylenedioxy-N-ethylamphetamine, ecstacy
MH	Malignant hyperthermia
MHAUS	Malignant Hyperthermia Association of the United States
MHS	MH-susceptible
MO	Major Objection
MPR	Metabolite to parent ratios
MS	Mass Spectrometry
NAMHR	North American MH Registry
NICE	National Institute for Health and Care Excellence
NMR	Nuclear magnetic resonance
NMS	Neuroleptic malignancy syndrome
NMT	Not More Than

NPC1	Niemann-Pick Disease Type C1
PDE	Permitted Daily Exposure
PEG	Polyethylene glycols
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
QTPP	Quality Target Product Profile
RBC	Red blood cell
RED	Rapid Equilibrium Dialysis
RH	Relative Humidity
RYR1	Ryanodine receptor-1
SBE-β-CD	Sulfobutylether β-cyclodextrin
SERCA	Sarcoplasmic reticulum calcium ATPase
SmPC	Summary of Product Characteristics
SOC	System Organ Classes
SR	Sarcoplasmic reticulum
USP	United States Pharmacopoeia
UV	Ultraviolet
Vss	Predicted volume of distribution at steady state
WFI	Water For Injections
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Norgine B.V. submitted on 24 June 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for AGILUS, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 September 2021.
AGILUS, was designated as an orphan medicinal product EU/3/21/2443 on 20 May 2021 in the following condition: *Treatment of malignant hyperthermia*.

The applicant applied for the following indication:
In combination with adequate support measures, AGILUS is indicated for the treatment of malignant hyperthermia (including suspected cases) in adults and children of all ages.
Malignant hyperthermia is a fulminant hypermetabolic crisis 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to Article 10(3) of Directive 2001/83/EC, as amended– relating to applications for hybrid medicinal product.

The application submitted is composed of administrative information, complete quality data and at least a bioequivalent study with the reference medicinal product *DANTROLEN i.v. 20 mg Pulver zur Herstellung einer Injektions/ Infusionslösung* instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is: DANTROLEN i.v. 20 mg Pulver zur Herstellung einer Injektions-/Infusionslösung

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: DANTROLEN i.v. 20 mg Pulver zur Herstellung einer Injektions-/Infusionslösung, 20 mg, powder for solution for injection/infusion
- Marketing authorisation holder: Norgine B.V.
- Date of authorisation: 1984-03-29
- Marketing authorisation granted by:
  - Member State (EEA): Austria
    - National procedure
- Marketing authorisation number: 17.709

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: DANTROLEN i.v. 20 mg Pulver zur Herstellung einer Injektions-/Infusionslösung, 20 mg, powder for solution for injection/infusion

- Marketing authorisation holder: Norgine B.V.
- Date of authorisation: 1984-03-29
- Marketing authorisation granted by:
  - Member State (EEA): Austria
    - National procedure
- Marketing authorisation number: 17.709

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies and/or in other studies:

- Product name, strength, pharmaceutical form: DANTROLEN i.v. 20 mg Pulver zur Herstellung einer Injektions-/Infusionslösung, 20 mg, powder for solution for injection/infusion
- Marketing authorisation holder: Norgine B.V.
- Date of authorisation: 1984-03-29
- Marketing authorisation granted by:
  - Member State (EEA): Austria
    - National procedure
- Marketing authorisation number: 17.709
- Bioavailability study number: NPJ5008-01/2020

1.3. Information on Paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Frantisek Drafi

The application was received by the EMA on	24 June 2022
The procedure started on	14 July 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 October 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 October 2022

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 October 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	10 November 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 June 2023
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	22 June 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 Dec 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 March 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to AGILUS on	21 March 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Malignant hyperthermia (MH) is a life-threatening hypermetabolic crisis secondary to calcium dysregulation in skeletal muscle. It is triggered by agents such as volatile anaesthetics and/or succinylcholine in genetically susceptible individuals. The first recorded case occurred in 1922 and the syndrome was first described in the literature in 1951 by Guedel (1). The clinical presentation typically includes a disproportionate increase in end-tidal CO2, muscle rigidity, fever/hyperthermia, tachycardia, and signs and symptoms of rhabdomyolysis. Early recognition of an MH reaction and prompt aggressive treatment are essential for the successful management of the reaction. Without prompt recognition and appropriate treatment mortality is high. Dantrolene is an established key component of treatment since 1979 (2).

2.1.2. Epidemiology

The incidence of MH events is difficult to estimate but is likely somewhere in the range 1/15 000 to 1/75 000 anaesthetic procedures (3, 4). The true prevalence of MH susceptibility is higher than MH event incidence because of incomplete penetrance of the genetic disorder, variable expression of the

MH susceptibility trait, and differences in trigger characteristics. The prevalence of the MH genetic trait has been estimated between 1/2000 and 1/3000.

During a 6.5 year period in Denmark the incidence of fulminant MH was overall 1 in 250 000 anaesthetic procedures, but 1.6 in 100 000 anaesthetic procedures when a combination of inhalation anaesthetics and succinylcholine was used (4). MH was suspected in 6.2 of 100 000 anaesthetics overall, but in 23.8 of 100 000 anaesthetics with the above-mentioned combination of agents.

Using more recent administrative hospital discharge data from four US states in 2011 or 2012, there were 164 recordings with an MH diagnosis (3). The overall prevalence of MH was estimated to 1.7 (95% CI, 1.4–1.9) per 100 000 hospital discharges and 2.4 (95% CI, 2.0–2.8) per 100 000 surgical discharges. Due to the method used these estimates likely overestimate MH incidence.

In a US study focused on obstetric anaesthesia there were 47 178 322 delivery-related discharges during the 12-year study period, including 15 175 127 (32.2%) caesarean deliveries (5). Of them, 215 recorded a diagnosis of MH, yielding a prevalence of 0.46 per 100 000 [95% CI, 0.40 to 0.52].

Several neuromuscular diseases linked to mutations in ryanodine receptor 1(RYR1) are strongly associated with MH susceptibility, including central core disease, multiminicore myopathy, congenital myopathy with cores and rods, centronuclear myopathy, and possibly also myotonic dystrophy type I (dystrophia myotonia type 1, DM1; Steinert disease) (6).

2.1.3. Biologic features

Experimental evidence has clarified that MH is caused by abnormal intracellular calcium homeostasis within the skeletal muscle. Normally, an action potential activates a specific type of the voltage-gated Ca2+ channels (sarcolemmal L-type Ca2+ channels, or dihydropyridine receptor (DHPR)). Activated DHPR interacts with the ryanodine receptor type 1 (RyR1), a Ca2+ channel located in the membrane of the sarcoplasmic reticulum. RyR1 is activated and opened, and Ca2+ release from the sarcoplasmic reticulum into the cytoplasm leads to muscular contraction.

Out of three known mammalian RYR isoforms, RyR1, RyR2, and RyR3, RyR1 is the one predominantly expressed in skeletal muscle. Genetic mutations in RYR1 can lead to excessive Ca2+ release leading to myofibrillar contraction and muscular rigidity (7). Muscular rigidity results in the rise of oxygen consumption and carbon dioxide production. Heat is generated and the body temperature rapidly rises. When ATP stores become exhausted, lactic acid level rises, the membrane integrity of the skeletal muscle cells is compromised, leading to rhabdomyolysis with associated electrolyte disorders, and potentially renal failure.

The first causative genetic mutation associated with MH was identified in 1990, mapped to chromosome 19q12-13.2, which is the position encoding the RyR1. However, genetic mutations in the RYR1 only induce 50%–86% of individuals associated with MH. Up to 430 mutations of RYR1 associated with MH have been reported. Several mutations responsible for MH have also identified in the CACNA1S gene, which encodes the alpha1 subunit of the DHPR.

2.1.4. Clinical presentation, diagnosis

MH reactions can range from fulminant life-threatening presentations to mild, non-specific symptoms that can go unrecognized. Due to incomplete penetrance of the genetic disorder, MH-susceptible individuals might undergo several anaesthetic procedures that are uneventful (on average three) prior to developing a fulminant MH reaction. Different MH-causative genetic variants may also generate different sensitivities to different triggering anaesthetic agents, further contributing to the variability in MH clinical presentation.

The diagnosis of MH is in the acute phase is purely clinical. A grading score based on the clinical presentation has been used to estimate the likelihood for it to be an MH reaction has been developed (8). The scale lacks sensitivity since not all tests may be performed in an individual episode. Tests to verify the underlying genetic trait are performed after recovery to verify the diagnosis and plan for future anaesthetic management. Genetic counselling and prevention of MH through awareness of the

genetic susceptibility and adequate selection of anaesthetic technique and monitoring are key components for mitigation of future risk for the patient.

Outcome of MH has improved notably over time. In a 1970 study that analysed 94 case reports before use of dantrolene, the reported mortality rate was 64% (9). A review of MH cases reported to the NAMHR between January 1, 1987 and December 31, 2006 found that of 291 events, 8 (2.7%) resulted in cardiac arrests and 4 (1.4%) resulted in death (10). Increased risk of cardiac arrest/death was related to a longer time between anaesthetic induction and maximum end-tidal carbon dioxide (216 vs. 87 min).

2.1.5. Management

The key components in successful management of MH are early recognition, discontinuation of triggers, general supportive care, cooling, and treatment with dantrolene. The rarity of this condition and the acute life-threatening presentation mean that well-established consensus guidelines and institutional treatment protocols are essential. The table below lists some international guidelines but is not intended to be exhaustive.

Guideline title	Region	Reference / year
Consensus guidelines on perioperative management of malignant hyperthermia suspected or susceptible patients from the European Malignant Hyperthermia Group	Europe	Rüffert-2021 (11)
Malignant hyperthermia 2020: Guideline from the Association of Anaesthetists	UK	Hopkins-2021 (12)
Availability of dantrolene for the management of malignant hyperthermia crises: European Malignant Hyperthermia Group guidelines	Europe	Glahn-2020 (13)
JSA guideline for the management of malignant hyperthermia crisis 2016	Japan	Safety Committee of JSA-2017 (14)
Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group	Europe	Glahn-2010 (15)
Updated guide for the management of malignant hyperthermia	Canada	Riazi-2018 (16)

Following resolution of the acute reaction, testing to verify the genetic predisposition and functional MH susceptibility is important, along with counselling the patient regarding future exposure to anaesthesia (17).

2.2. About the product

Dantrolene sodium (1-[[[5-(4-nitrophenyl)-2-furanyl]-methylene]amino]-2,4- imidazolidinedione sodium salt) is a highly lipophilic hydantoin derivative poorly soluble in water. Experimental evidence suggests that dantrolene inhibits the release of calcium in skeletal muscle cells by increasing the affinity of the RYR for Mg2+ and that it requires elevated cytoplasmic Mg2+ to adequately close RYR (18, 19). This results in a marked reduction in muscle contraction in response to electrical stimulation or stimulation by pharmacological agents without affecting action potential patterns (20). In vivo studies in MH-susceptible pigs show that dantrolene inhibits abnormal excitation-contraction coupling and reverses and prevents development of MH. However, in vitro studies using isolated skeletal muscle from susceptible animals produced variable results, with inhibition, no effect or potentiation of halothane- and caffeine-induced muscle contraction. Dantrolene appears to have some effects on

smooth muscle and cardiac tissue in vitro, but these are inconsistent and negligible. Dantrolene may affect calcium release from nerve terminals and nerve terminal responses, and appears to have a marked GABAergic effect, but is devoid of anticonvulsant and anaesthetic properties.

The proposed indication for AGILUS is:

In combination with adequate support measures, Agilus is indicated for the treatment of malignant hyperthermia in adults and children of all ages.

The proposed posology is:

Treatment with Agilus should be started as soon as a malignant hyperthermia crisis is suspected, i.e. characteristically presenting with muscle rigidity, metabolic acidosis and/or rapidly increasing body temperature.

Posology

Agilus 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.

The following table provides examples of dosing based on the number of vials needed for the initial 2.5 mg/kg dose, required immediately by rapid injection:

Table 1. Dosing examples

Dosing examples by body weight to achieve a loading dose of 2.5 mg/kg for both adults and children				
Number of vials to be prepared[a]	***Body weight range***	***Example dosing recommendation***		
		Body weight	***Dose to be administered***	***Volume to be administered[a]***
1	*Up to 48 kg*	*3 kg*	*7.5 mg*	*1.4 mL*
		6 kg	*15 mg*	*2.8 mL*
		12 kg	*30 mg*	*5.6 mL*
		24 kg	*60 mg*	*11.3 mL*
		48 kg	*120 mg*	*22.6 mL*
2	*From 49 kg to 96 kg*	*72 kg*	*180 mg*	*33.9 mL*
		96 kg	*240 mg*	*45.2 mL*
3	*From 97 kg*	*120 kg*	*300 mg*	*56.5 mL*
		144 kg	*300 mg[b]*	*56.5 mL*

[a] *Total volume of one reconstituted vial is 22.6 mL*

[b] *For all bodyweights, the initial dose and any repeat doses should not exceed 300 mg, equivalent to 2.5 vials.*

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, Agilus 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.

The key feature of this new product is a new formulation that facilitates the dissolution of dantrolene and allows faster preparation and reduced amount of fluid administration. This has been major issues with currently available formulations (12, 21).

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a powder for solution for injection containing 120 mg of dantrolene sodium (as hemi heptahydrate) as active substance.

Other ingredients are: hydroxypropylbetadex and macrogol (E1521).

The product is available in type I glass vial with a rubber stopper and a seal as described in section 6.5 of the SmPC.

2.3.2. Active Substance

2.3.2.1. General information

The chemical name of dantrolene sodium is 1-{[5-nitrophenyl) furfurylidene] amino} hydantoin sodium salt hemiheptahydrate corresponding to the molecular formula $C_{14}H_9N_4O_5$. 3.5 H_2O. The relative molecular mass of the hemi heptahydrate is 399.29 g/mol, and that of the anhydrous is 336.24 g/mol, and the following structure:

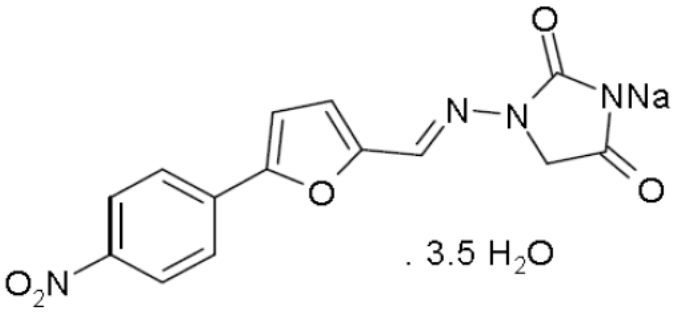


Figure 1: active substance structure

The chemical structure of dantrolene sodium active substance has been elucidated by analysis of data from ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, infrared spectroscopy (IR), mass spectrometry (MS), ultraviolet spectroscopy (UV), and elemental analysis of dantrolene sodium reference standard.

The solid-state properties of the active substance were measured by XRPD analyses.

Polymorphism has been observed for the active substance. Dantrolene is known from the literature to exist in different polymorphic phase: six anhydrous phases (form I, II, III, IV, V, VI), three monohydrate phases (MH-I, MH-II, MH-III), and 18 solvate phases with different solvents. It was confirmed that a single polymorphic form (form I) of the active substance is consistently manufactured by the current manufacturing process conditions. The water content is controlled in the specification of the active substance with an adequate limit corresponding to the hemi heptahydrate form.

The active substance is a yellowish orange to deep-orange crystalline powder that is obtained as a single polymorphic form and is a hemi heptahydrate. The solubility of the active substance has been investigated in various solvents (DMF, ethanol, methanol, isopropanol, acetone) including water at neutral and alkaline pH. The active substance is very slightly soluble in water at neutral pH and sparingly soluble in alkaline solution.

The active substance has a non-chiral molecular structure and has therefore no optical isomer.

The active substance is not described in the Ph. Eur.

2.3.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is supplied by one ASMF holder and manufactured at two manufacturing sites, of which one conducts the last manufacturing step only. The testing of the active substance involves three sites of which two also responsible for the manufacture of the active substance.

The active substance is synthesized using commercially available well defined starting materials with acceptable specifications.

Reprocessing can be used in the manufacture of the active substance for specific cases and is adequately described.

The CHMP initially raised a Major Objection (MO) on the choice of starting materials (SMs) to which the applicant responded by providing sufficient information and justification. Both starting materials are available from many alternative suppliers at a large scale and are supplied to a comparable quality grade. The controls strategy applied for each of the starting materials are considered adequate to ensure the quality of the stating materials. Taking also into consideration that dantrolene sodium containing products have been marketed in Europe since 2010 and that the product is a lifesaving

medicinal product that is administered to a patient over an extremely short period only once in their lifetime, the current starting materials are considered acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Fate of the possible impurities which may arise from the route of synthesis of the starting materials have been presented. The controls strategy applied for each of the starting materials are considered adequate to ensure the quality of the starting materials. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The ASMF holder's justification is acceptable and fully supported by ICH Q11 Questions and Answers.

Class 2 and class 3 residual solvents used or released during the synthesis are controlled within the limits of ICH Q3C.

The manufacturing process was assessed in line with ICHQ3D for elemental impurities which confirmed that there were no elemental impurities of risk present in the active substance. Elemental impurities are therefore not tested on the active substance.

Adequate discussion on possible formation of nitrosamine and elemental impurities have been presented. The omission of a test and limits for possible residue of nitrosamines in the specification for the active substance have been justified by the absence of nitrosamines in 3 commercial batches of active substance.

The active substance is packaged in double polyethylene bag within a stainless-steel drum protecting from light which complies with Commission Regulation (EU) 10/2011, as amended.

2.3.2.3. Specification

The provided active substance specifications include tests for description (visual); Identification A, B, C, and D (IR, HPLC, Na, USP monograph); assay (USP monograph); water content (Karl Fisher); impurities (HPLC); residual solvents (GC); particle size (dispersion); microbiological (Ph. Eur.).**1**

Dantrolene sodium active substance is manufactured and tested by the supplier to ensure compliance with ICH Guidelines Q3A (R2) on impurities in new drug substances and Q3C (R6) on impurities: guideline for Residual Solvents and that the necessary microbiological quality is controlled.

The manufacturer controls the active substance in line with the provided specification.

Appropriate specifications have been set for impurities. Two related compounds have specification limits higher than the qualification threshold set by ICH Q3A and are considered qualified since they have always had specification limits above the qualification threshold in the countries it was registered (EU since 2010, US since 2006) without any toxicological or safety issues having ever been reported. This deviation from ICH Q3A is appropriately justified.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on process validation batches manufactured using the commercial process and commercial batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.3.2.4. Stability

Stability data from validation and commercial batches of dantrolene sodium from the proposed manufacturers using the commercial manufacturing process and stored in the proposed supplying

container for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The parameters tested on the validation batches are: appearance, assay, related substances, and water content; and on the commercial batches: appearance, assay, related substances, water content, endotoxins, and microbiology. The analytical methods used were the same as for release and were stability indicating.

Dantrolene sodium, as used in the manufacture of AGILUS is chemically and physically stable when stored for up to 36 months at 25°C/60%RH and for up to 3 months at 40°C/75%RH. Additional data at 30°C/65%RH confirms that the dantrolene sodium is stable for up to 12 months at 30°C/65%RH. A time dependent increasing trend in the content of Impurity B can be observed in all batches of dantrolene sodium. An out of specification was observed on one batch of dantrolene sodium in the content of Impurity B at the 6-month timepoint when stored under accelerated conditions (40°C/75%RH).

On this basis, a retest period of 18 months has been assigned to the active substance and the proposed storage temperature is 20 – 25 °C.

Stress testing (heat, light, acid and base, and oxidation conditions) was performed on the active substance to establish the degradation pathway and the intrinsic stability of dantrolene sodium. Forced degradation studies were performed on the reference standard batch.

The impurity profiles for the heat, light, acid and base, and oxidation force-degraded samples showed that the known hydrazine impurity (Related Compound B) at relative retention time of 0.15 was present in all samples. The acid sample exhibited levels comparable to the control, while the remaining conditions were present at levels above 1%. The known furfural impurity (Related Compound C) at relative retention time of 1.44 was present in all conditions but base. The levels for the heat and oxidation samples were comparable to the control, while the light and acid samples were two to four times larger.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 18 months when stored up to 25 °C in the proposed container.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

AGILUS 120 mg powder for solution for injection is a yellow-orange sterile lyophilised powder for solution for injection contained in a clear 50R glass vial, stoppered with a siliconised butyl rubber lyophilisation stopper, and a grey lacquered aluminium polypropylene button.

A vial of AGILUS 120 mg powder for solution for injection is reconstituted prior to use with 20 mL of Water for Injections resulting in a final volume of 22.6 mL and a dantrolene sodium concentration of 5.3 mg/mL.

AGILUS 120 mg powder for solution for injection has been developed as a hybrid medicinal product to address the acknowledged difficulties associated with preparation and administration of DANTRIUM IV 20 mg powder for solution for injection (reference medicinal product). DANTRIUM IV is marketed by the same Company/Applicant.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Hydroxypropylbetadex (Hydroxypropyl – β – cyclodextrin) is generally recognised as safe (GRAS) for use as a food additive when used in accordance with good manufacturing practices. Hydroxypropylbetadex is used as an excipient for oral and parenteral pharmaceutical products and a monograph is available in the European Pharmacopeia (Ph. Eur.).

Macrogol 3350 (Polyethylene glycol 3350) is generally recognised as safe (GRAS) for use as a food additive when used in accordance with good manufacturing practices. Macrogol 3350 is used in pharmaceutical products and a monograph is available in the European Pharmacopeia (Ph. Eur.).

A series of investigations into the physicochemical properties of dantrolene sodium were performed and are described in dossier. Dantrolene sodium critical material attributes were identified after consideration of the Target Product Profile, Quality Target Product Profile and manufacturing process.

AGILUS 120 mg powder for solution for injection has been developed as a lyophilised powder for injection, containing 120 mg of dantrolene sodium. The development of AGILUS 120 mg powder for solution for injection was informed by the Quality Target Product Profile.

Using the Quality Target Product Profile, the product's Critical Quality Attributes were defined.

Initial pre-formulation studies were performed to determine the suitability of a number of components for use in Agilus 120 mg powder for solution for injection.

The final formulation was altered to 6 mg/ml dantrolene sodium and hydroxypropylbetadex to decrease the reconstitution time, whilst also maintaining the QTPP of achieving 120 mg of active substance per vial.

The manufacturing process was developed through consideration of the QTPP requirements, prior knowledge of DANTRIUM IV (a lyophilised 20 mg dantrolene sodium powder for solution for injection administered for the treatment of malignant hyperthermia licenced by the applicant) manufacturing process, dantrolene sodium active substance characteristics, available literature, good manufacturing practices and information generated during development.

The resulting reformulated product produced reconstitution results that met the QTPP requirements. Studies were initiated upon this product to evaluate its physical and chemical stability under ICH storage conditions. The chemical and physical stability of the formulation was confirmed, and the results generated confirmed that a manufacturing process that included lyophilisation could deliver 120 mg in a 50 mL vial.

Compatibility of the reconstituted product with dosing devices was studied. The results presented confirm that, the reconstituted solution is compatible with different dosing devices.

Bioequivalence study was performed showing bioequivalence between the clinical formulation and the reference product DANTRIUM IV. The AGILUS development programme has focused on the change (compared to the reference product DANTRIUM IV) in the formulation, where HP-β-CD and Macrogol are substituted for mannitol and sodium hydroxide. No further clinical study was considered required as explained in the clinical part.

Sterile Manufacturing Development

The manufacturing process was designed to ensure that the finished product critical quality attribute of sterility was attained. An initial assessment for the choice of sterilisation was carried out as per EMA/CHMP/CVMP/QWP/850374/2015. During the procedure, the Applicant was asked to further justify the choice of aseptic process in an MO raised by the CHMP. The Applicant provided an acceptable justification in line with the decision tree of EMA/CHMP/CVMP/QWP/850374/2015 guideline. The primary packaging is type I glass vial with a rubber stopper and a seal. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The finished product is manufactured at one site that showed GMP compliance for the intended manufacturing activities.

The manufacturing process consists of 5 main steps: compounding of solutions, bioburden and sterile filtrations, aseptic filling into vials, lyophilisation, and vials stoppering and sealing.

The process includes aseptic processing and lyophilisation and is therefore considered to be a non-standard manufacturing process.

1
Satisfactory details and conditions regarding the sterilisation of primary packaging (glass vials with rubber stoppers) was provided.

A representative batch formula is provided that will be used for manufacture of the medicinal product.

Major steps of the manufacturing process have been validated by a number of studies. The manufacturing process has been validated using consecutive full production scale commercial batches. Sufficient information has been presented regarding the performed media fill runs, demonstrating that aseptic conditions are maintained during the filling process. Hold times for the manufacturing process have been also evaluated and were suitably defined. Process validation batches have been produced by the proposed finished product manufacturing site. Based on validation data and adequacy of in-process controls as well as experience gained on dantrolene IV, it is considered that the manufacture is sufficiently robust to provide assurance that the process produces the finished product (Dantrolene 120 mg lyophilised powder for injection) of consistent quality, complying within the designated specification.

Control of critical manufacturing process is accomplished by the establishment of optimum process parameters to control the critical quality attributes (CQAs) of AGILUS 120 mg powder for solution for injection and through the use of in-process tests. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.3.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: **on the powder for injection:** appearance (visual), reconstitution time (in-house), water content (Karl-Fisher); **on reconstituted solution:** identification (HPLC, PDA), particulate contamination (Ph. Eur.), appearance (visual), pH (Ph. Eur.), assay (HPLC), uniformity of dosage units (Ph. Eur.), impurities (HPLC), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.).

The specifications used for the control of Agilus 120 mg lyophilised powder for injection were set on the basis of the available manufacturing and testing experience, manufacturing process capabilities, regulatory guidance, and the stability characteristics.

It should be noted that the finished product is a lifesaving product that is administered to a patient over an extremely short time period only once in their lifetime. Taking into consideration that dantrolene sodium containing products have been marketed in the USA and in European member states for over 35 years, the proposed limits for related compounds are considered acceptable. The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 4 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

It is considered that there is sufficient control over the manufacturing process to ensure consistent osmolality. The analytical methods used have been adequately described and appropriately validated in

accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for commercial validation batches along with one engineering and one clinical batch confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.3.3.4. Stability of the product

Stability data from commercial and clinical batches of finished product manufactured by the proposed manufacturer and stored for up to 24 months under long term conditions (25 ºC / 60% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Stability data on the same batches were also provided under intermediate conditions (30 ºC / 75% RH) for up to 24 months.

Samples were tested for appearance of the lyophilizate and solution, pH, reconstitution time, moisture content, osmolality, dantrolene sodium assay, related substances content (compound B), unknown impurities, total unknown impurities, sterility, and bacterial endotoxins. The analytical procedures used are stability indicating.

The data obtained from these primary stability studies demonstrate that NPJ5008 displays no significant changes nor trends in any of the measured parameters. All tested parameters remained within the specification. The primary stability studies under long-term and intermediate conditions will continue until 36 months.

In-use stability studies were conducted on clinical and commercial process validation batches for which stability data under long term conditions (25 ºC / 60% RH) are available at the following timepoints: 3, 6, 12, and 24 months. The reconstituted solutions from studied batches at each timepoint available were stored for up to 48 hours at 25 ºC / 60% RH. The results generated confirmed that there were no significant changes observed in any of the parameters measured during the in-use study that would influence the performance or impurity profile of the product. Therefore, it can be considered that the data supports a 24 hour in-use shelf life (SmPC section 6.3). In-use stability studies will continue until 36 months.

In addition, batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The first batch was exposed to controlled lighting conditions in the primary container as an untouched vial sample, reconstituted solution and fragmented powder, whereas the second batch was packaged in the secondary packaging. The data generated during the photostability study of the product in the primary container demonstrated that the finished product in its lyophilised and reconstituted form is photosensitive. The results indicate that whilst the finished product demonstrates photosensitivity, the secondary container carton provides the finished product with protection from photodegradation and should be used for long term storage of the finished product. Consideration of the results generated during the photostability studies the finished product label should include a direction to protect from light.

Based on available stability data, the proposed shelf-life of 36 months for the unopened vials protected from light, and of 24 hours for the reconstituted solution protected from light and stored up to 25 °C, as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.3.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure, one major objection was raised on the restricted part of the ASMF of dantrolene sodium regarding the choice of the starting material for the AS synthesis and one major objection was raised on the finished product part where the applicant was requested to further justify the choice of aseptic filling.

The ASMF holder and the Applicant adequately addressed the issues raised and all quality issues were resolved at the time of opinion.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Description of post-authorisation measure(s)
The MAH should undertake additional development work for a new formulation of the medicinal product that does not contain the excipient HP-β-CD. The development will include a detailed feasibility analysis of available alternatives, which will involve formulation work and could require additional non-clinical and clinical studies. This attempt to develop an alternative formulation of the medicinal product that does not contain the excipient HP-β-CD should be finalised within five years. The Applicant is required to submit annual progress reports to the EMA during the development programme.

2.4. Non-clinical aspects

2.4.1. Introduction

In the non-clinical program, the Applicant has mainly focused on the impact the change in formulation has with regard to safety usage, which includes the change in the vial concentration of dantrolene sodium as well as the excipients used for increasing the solubility.

One single GLP compliant toxicological report conducted in rat for comparison of NPJ5008 with the already approved product, Dantrium IV 20 mg, has been submitted.

Toxicokinetics were conducted on Day 1 and Day 14. The NPJ5008 formulation's haemolytic potential and protein binding (see also: Clinical Pharmacology) have been compared to that of DANTRIUM IV. A review of published literature has also been provided.

2.4.2. Pharmacology

The mode of action of dantrolene has been extensively described in various in vitro and in vivo models. Dantrolene sodium is a direct-acting muscle relaxant used to treat MH, a hypermetabolic crisis in skeletal muscle driven by calcium dysregulation; it depresses excitation-contraction coupling in skeletal muscle by binding to ryanodine receptor isoform 1 (RYR1) and decreasing intracellular calcium concentrations. Dantrolene requires the presence of Mg^{2+} to properly close the Ca^{2+} channel. The RYR1 mutations that reduce Mg^{2+} affinity result in RYR1 variations that are more prone to opening and more sensitive to RYR agonists, which is the main cause of the genetic susceptibility to MH. As the muscle attempts to clear itself of the elevated cytoplasmic Ca^{2+}, the abnormal Ca^{2+} release that takes place in RYR variations during an MH event causes excessive heat production. Dantrolene sodium is the only approved substance in the treatment of MH with successful outcomes in adults and children.

NPJ5008 has been developed to improve the formulation of dantrolene sodium by increasing the solubility and the vial concentration. The reduced injection volume required would speed up time from diagnosis to pharmacological effect, which is crucial for this acute medical condition. The concentration in DANTRIUM IV is 20 mg dantrolene /vial, with the excipients of mannitol and sodium hydroxide. The concentration in NPJ5008 is 120 mg dantrolene/ vial and the new excipients are HP-β-CD and Macrogol (PEG) 3350 (see table 2.1 and 2.2 below for comparison of composition and injection time between the two products).

Table 2.1 NPJ5008 versus DANTRIUM IV composition (final product for IV administration)

NPJ5008 120 mg						DANTRIUM IV 20 mg	
Composition	Per vial (mg)	mg/mL*	Composition	Per vial (mg)	mg/mL*		
Dantrolene Sodium	120	5.31	Dantrolene Sodium	20	0.32		
Hydroxypropylbetadex	3530	156.2	Mannitol	3030	48.9		
PEG3350	400	17.7	Sodium Hydroxide	0.8-1.2	0.013-0.019		
Diluent (not supplied)						Diluent (not supplied)	
Water for Injections (WFI)					20 mL	Water for Injections (WFI)	60 mL
Final Reconstituted Volume					22.6 mL	Final Reconstituted Volume	62 mL

*after reconstitution

Table 2.2 Treatment of a 70 kg adult with an initial 2.5 mg/kg and higher 10 mg/kg

	NPJ5008 120 mg vial		DANTRIUM IV 20 mg vial	
Dose	2.5 mg/kg	10 mg/kg	2.5 mg/kg	10 mg/kg
No. of vials required for 70 kg patient	2	6	9	35
Total volume of WFI for reconstitution	40 mL	120 mL	540 mL	2100 mL
Time required to prepare and administer vials[1, 2]	3 min 46 sec	11 min 18 sec	27 min	105 min

[1]Data from Technical Report TR21/025
[2]For a single operator to prepare and administer vials sequentially

The non-clinical development programme of NPJ5008 has focused on reviewing the current literature and evaluating the impact of the change in the strength of the formulation and the excipients in the new formulation of dantrolene sodium. To compare the toxicological profile of dantrolene sodium in the reference product (DANTRIUM IV) with the improved product NPJ5008 formulation, the Applicant has conducted a single Good Laboratory Practice (GLP) compliant study, following daily IV administration to rat for 14 consecutive days. The Applicant has also submitted a validation report (non-GLP) from the toxicokinetic investigation included in this GLP toxicity study. In addition, the haemolytic potential and plasma protein binding have been investigated.

No new pharmacology studies have been conducted for this Hybrid application. Since the pharmacological properties of dantrolene sodium are well known, further studies are not required. A pharmacological overview based on literature review is thus appropriate.

In the repeat dose toxicity study (Study 8418863), the test item (NPJ5008) formulation contained 176.5 mg/mL of HP-β-CD and 20 mg/mL of PEG 3350.

The values for the final reconstituted product are 156.2 mg/mL for HP-β-CD and 17.7 mg/mL for PEG 3350. The concentrations of the product´s excipients and also the dantrolene concentration (6 mg/mL) used in the RD study were higher than those in the intended marketed product. As the dose used in this study (2.5 mg/kg and 10 mg/kg), the total volume of the administered product was lower (20 mL) than in the proposed marketed product (22.6 mL). Since the difference is minimal, it had little to no impact on the findings' applicability.

2.4.2.1. Primary pharmacodynamic studies

Pharmacodynamic effects of dantrolene were observed in various pig models (e.g., Landrace pigs, Poland China pigs, and Pietrain pigs). Dantrolene both promptly reversed MH symptoms after MH was initiated and prevented the development of MH after succinylcholine and volatile anaesthetics. In a study, the 150 times more concentrated dantrolene (50 mg/mL) suspension resulted in an equally effective pharmacodynamics response compared to the response following the original formulation of dantrolene (0.33 mg/mL). These results may imply that a formulation's efficacy is unaffected by concentration.

2.4.2.2. Secondary pharmacodynamic studies

Based on published literature, off-target pharmacodynamics revealed reversible inhibition of human erythrocyte derived acetylcholinesterase and absence of dantrolene related antagonism on asparagine-valine-angiotensin II or calcium-induced contractions in isolated rabbit aortic strips.

2.4.2.3. Safety pharmacology programme

Studies in safety pharmacology that focused on the effects on the cardiovascular system were based on published literature.

The myotoxicity caused by bupivacaine in cultured mouse (BALB/c) primary muscle cells was reduced by dantrolene. In another study, in aged mouse left ventricular cardiomyocytes but not in younger mouse left ventricular cardiomyocytes, dantrolene enhanced sarcoplasmic reticulum calcium ion content and Ca2+ wave amplitude. According to studies done on isolated regional ischemia-reperfusion rabbit hearts, dantrolene exhibits both proarrhythmic and antiarrhythmic effects.

The Applicant claims in the clinical evidence that no signs of cardiotoxicity have been identified up to and including the dose of 42 mg/kg. This maximal total dose, as stated in posology, was administered to a 6-year-old child, who received dantrolene at 11.5 mg/kg within 3 hours of the episode and for a total dose of more than 42 mg/kg. Furthermore, no subject in the clinical study (Study NPJ5008-01/2020 (QSC204721) - Part 1 and Part 2) experienced clinically significant post-dose changes in any of the parameters measured for vital signs (including respiratory rate and peripheral oxygen saturation), ECGs, spirometry, clinical chemistry, haematology or urinalysis parameters. Thus, according to the available data, dantrolene is not anticipated to pose a cardiovascular risk to patients when used within therapeutic dose ranges.

The safety pharmacology evidence regarding effects on the central nervous system and respiratory system as core battery systems was not presented nor discussed. This is, however, acceptable.

To conclude, the cardiovascular safety is not expected to be decreased in comparison with the reference medicinal product.

2.4.2.4. Pharmacodynamic drug interactions

Dantrolene in combination with verapamil induced hyperkalaemia and cardiovascular collapse in anaesthetised porcine models, affected atrioventricular conduction and cardiovascular performance in dogs, and enhanced the myocardial depressant effects of each other. The pharmacodynamic interaction of dantrolene and verapamil and also diltiazem (non-dihydropyridines calcium channel blockers) is included in section 4.5 of the SmPC and the concomitant use of these drugs is not recommended.

2.4.3. Pharmacokinetics

In the ADME program, the change in formulation of dantrolene in NPJ5008 and the substitution of mannitol and sodium hydroxide with the excipients HP-β-CD and PEG 3350 was investigated. A toxicokinetic study was performed as a part of a 14-day GLP toxicity study in rats for comparison of dantrolene and the metabolite, 5-hydroxydantrolene concentrations in plasma (toxicokinetic report 8418863). Studies comparing plasma protein binding between the NPJ5008 formulation and DANTRIUM IV (Report CLS4_0069_0001) have been also performed (See also: Clinical Pharmacology).

The toxicokinetics include blood sampling on Day 1 and Day 14. The dose levels corresponded to the initial clinical dose of 2.5 mg/kg/day where pharmacokinetics of NPJ5008 and DANTRIUM IV was compared. Due to the low solubility of DANTRIUM IV, the volume required to achieve a higher dose level would exceed the volume limit allowed for IV administration in animals and could thus not be investigated. However, NPJ5008 was administered at 10 mg/kg/day.

Methods of analysis

Dantrolene and the metabolite 5-Hydroxydantrolene were quantified in rat plasma containing K2EDTA as an anticoagulant, using solid-phase extraction with LC-MS/MS detection. The validation of the LC-MS/MS method was not performed according to GLP compliance, however, conducted in accordance with policies and SOPs. The results of the assay validation were considered acceptable according to the

analytical report. This is agreed and issue regarding non-GLP validation of the HPLC MS/MS method is not pursued.

Plasma exposure NPJ5008 vs. DANTRIUM IV

The calculated relative percentage of dantrolene bioavailable after NPJ5008 infusion compared to DANTRIUM IV was 65.3 and 89.8% on Day 1, and 85.5 and 68.3% on Day 14, for males and females respectively.

The plasma exposure was lower in rats administrated with NPJ5008 compared to DANTRIUM IV at 2.5 mg/kg/day, both on Day 1 and Day 14. Day 1, Cmax of NPJ5008 was 75% of Cmax for DANTRIUM IV for both sexes. No obvious difference in AUC was found between the different formulations in females. For males however, AUC of NPJ5008 was only 65% compared to AUC of DANTRIUM IV. At Cmax on Day 14, Cmax of NPJ5008 was ~95% and ~81% of Cmax for DANTRIUM IV for males and females respectively, and the corresponding figures for AUC of NPJ5008 compared to DANTRIUM IV were ~86% and ~68%, for males and females respectively.

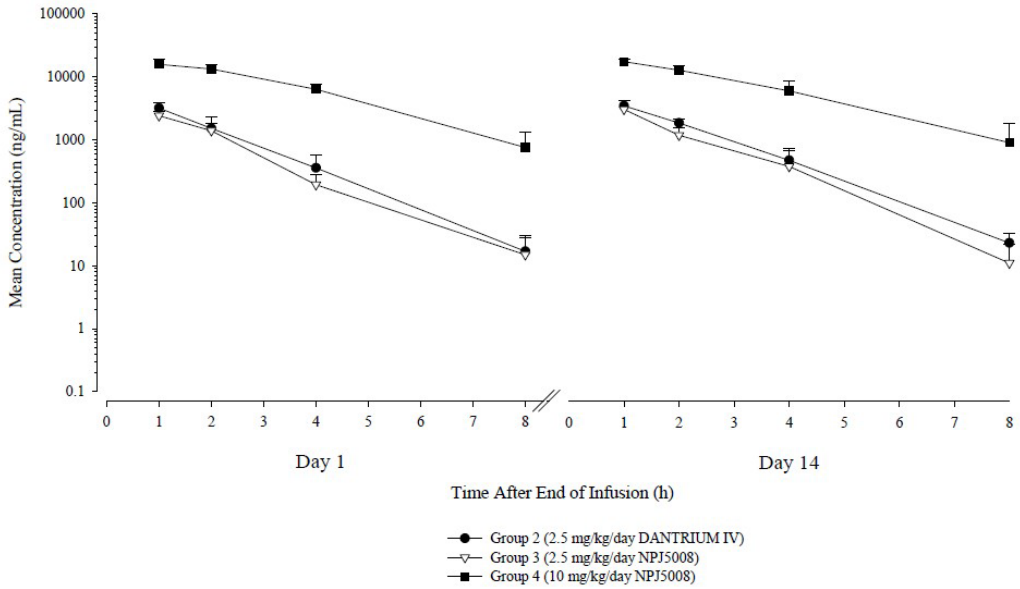
Analysis of the formulation concentrations showed that NPJ5008 had a slightly lower concentration than anticipated, and with normalisation for this, a small increase in bioavailability can be assumed. It is also likely that differences in kinetics could be influenced by the physical chemistry properties of the formulation which may add to the higher variance seen in the bioanalysis of NPJ5008.

Since bioavailability is unlikely to differ for the same dose of dantrolene in different formulations after IV administration, it must imply that the change in formulation affects the pharmacokinetics in some respect. Dantrolene's administration recommendation, i.e. 2.5 mg/kg x 4 with ten minutes intervals until MH resolves, is adapted to Dantrium IV's kinetics, which may also be considered in the treatment of MH since the dose will be titrated to clinical effect.

Dose proportionality

By increasing the dose of NPJ5008 4 times, from 2.5 mg/kg to 10 mg/kg, (Day 1) Cmax and AUC increased more than dose proportionally, i.e. Cmax increased x6.4 and x7.1, and AUC x14 and x9.0 for males and females respectively. Possible explanations for this may partly be underprediction of Cmax, since the first blood sampling occurs at 1 hour after end of infusion.

Mean (+SD) Concentrations (ng/mL) of Dantrolene in Combined Male and Females Rat Plasma on Days 1 and 14



Note: Samples were collected until 24.0 hours but were measured as below LLOQ (10.0 ng/ml) after 8.00 hours.

In addition, a higher degree of variance, particularly at the later time points has been presented. Importantly, there is no evidence of accumulation of either analyte (dantrolene or 5-hydroxydantrolene) in plasma following repeat dosing or impact on clearance of dantrolene via metabolism or renal elimination.

Sex difference in plasma exposure

NPJ5008´s exposure profile monitoring revealed minor sex-differences, which were less than 2-fold. Exposure parameters in males were slightly lower than females on Day 1 after NPJ5008 at 2.5 mg/kg/day. However, this reversed on Day 14, when higher Cmax and AUC values of NPJ5008 were generally observed in males. The kinetic data suggest that male exposure increases later than that of females for NPJ5008, and, in addition, supra-proportionality is higher in males after 14 days of exposure (60% higher than females at 10 mg/kg). No such tendencies can be discerned from Dantrium IV. These kinetic differences between the two formulations are unlikely to be an issue when administering for only a short period until the desired effect is achieved. Most importantly, no new toxicity could be detected between the two formulations at 2.5 mg/kg in either sex.

Plasma exposure of 5-hydroxydantrolene

The toxicokinetic profile of the metabolite, 5-hydroxydantrolene, followed that of dantrolene, independently of formulation, with regard to both exposure and a half-life of approximately 1 hour except for males on Day 14 where estimated half-life was 2 hours for dantrolene and 2.5 hours for 5-hydroxydantrolene.

Half-life

The estimated half-life is ~ 1 hour independently of sampling day, sex and formulation in the dose level of 2.5 mg/kg. At 10 mg/kg Day 14, the half-life increased to 2 hours for males. This may, at least partly, explain the increase in Cmax and AUC over females Day 14.

Clearance and volume of distribution at steady state

NPJ5008: On Day 1, CL value for males was 580 mL/h/kg and for females, from 185 to 417 mL/h/kg. Vss value for males was 1050 mL/kg and ranged from 465 to 794 mL/kg for females.

On Day 14, CL values ranged from 137 to 353 mL/h/kg for males and from 219 to 478 mL/h/kg for females. Vss values ranged from 513 to 720 mL/kg for males and from 492 to 867 mL/kg for females.

Dantrium IV: On Day 1, CL values were 379 and 375 mL/h/kg for males and females. Vss values were 752 and 709 mL/kg for males and females.

On Day 14, CL values were 302 and 326 mL/h/kg for males and females. Vss values were 640 and 625 mL/kg for males and females.

In conclusion, the CL and Vss values of the dantrolene in DANTRIUM IV were comparable with those of the dantrolene in NPJ5008.

Distribution

In a study, unlabelled and 14C-dantrolene were intravenously administered to the marmoset monkey; elimination half-life was 0.82 hours, blood clearance was 0.77 L/h/kg and volume of distribution was 0.91 L/kg. At the conclusion of the 5-hour infusion, steady state dantrolene concentrations were reached. There was no uptake of radioactivity into the brain. The intestine, liver, gall bladder, kidneys, and urinary bladder were the most often associated with 14C-radioactivity. The distribution in the muscle tissue was moderate. Bright spots in the lungs were identified as the result of undissolved drug. After 5 hours, the urine contained 7% radioactivity, most of which was 5-hydroxydantrolene, with only traces of dantrolene being identified. A study in rats confirmed no blood-brain barrier transport via transporter involvement of Mdr1a (P-glycoprotein). Additionally, dantrolene interacts with human organic anion transporters 1 and 3 (OAT1 and OAT3) transfected into human embryonic kidney (HEK) 293 cells.

Report CLS4_0069_0001 shows that dantrolene in DANTRIUM IV binds to human plasma proteins with a 95.1, 94.6, and 91.9% affinity for concentrations of 6 (matching with the clinical Cmax following an IV dose of 2.5 mg/kg of dantrolene), 40, or 100 g/mL, respectively. In comparison, dantrolene in NPJ5008 was bound to plasma proteins at the same concentrations with a 94.9, 93.1, and 91.8% affinity. Therefore, NPJ5008 was equivalent to DANTRIUM IV and the formulation change is not likely to have an impact on the binding to human plasma proteins. The RED platform and LC-MS/MS methods were used, and warfarin and verapamil were utilized as control substances (See also: Clinical Pharmacology).

Dantrolene is easily released from its weak complex with cyclodextrin and preferably binds to plasma proteins. In general, IV-administered cyclodextrins disappear rapidly from systemic circulation and are renally excreted intact. The t½ varies from 20 to 100 minutes. As a result, it is not likely that HP-β-CD will have any binding effects.

Metabolism

Dantrolene is metabolised by liver microsomes by two alternative pathways; the oxidative pathway, where dantrolene is hydroxylated to 5-hydroxydantrolene and by the reductive pathway, where dantrolene is reduced to amino-dantrolene which is subsequently acetylated to acetylamino-dantrolene. The 5-hydroxy metabolite has nearly the same potency as the parent molecule and may have a longer half-life than the parent compound. The acetylated compound is much less potent and is probably inactive at the concentrations achieved in clinical samples.

The role of CYP enzymes in dantrolene metabolism has been investigated. It was demonstrated that dantrolene is metabolized into two hydroxylated products by three distinct isozymes of rat liver P-450, namely CYP 1A1, 1A2, and 3A. CYP3A4 was the major enzyme involved. No data regarding inhibition or induction of P450 have been submitted.

In conclusion, differences in pharmacokinetics between NPJ5008 and DANTRIUM IV were observed in i) exposure at Cmax and AUC of dantrolene in rat ii) sexual differences in exposure of dantrolene in NPJ5008, which was not observed for DANTRIUM IV iii) a large difference in dose proportionality for NPJ5008 which was not investigated for DANTRIUM IV.

2.4.4. Toxicology

The non-clinical toxicology program the adverse effects attributed to the change in formulation of dantrolene, from mannitol and sodium hydroxide (DANTRIUM IV) to PEG3350 and HP-β-CD (NPJ5008) was investigated. The development of NPJ5008 relies mainly on data from the initial approvement of dantrolene as well as literature studies. Studies regarding genotoxicity, cancer, reproductive/developmental or juvenile studies have not been conducted for NPJ5008. A single repeated dose toxicity study for 14 days has been conducted, and an *in vitro* human whole blood haemolysis assay.

2.4.4.1. Repeat dose toxicity

NPJ5008 and DANTRIUM IV were compared in a single GLP compliant repeated dose toxicity study. Animals were subjected to daily infusion for 5 minutes for 14 days at dose levels of 2.5 mg/kg/day, and NPJ5008 was additionally administered at 10 mg/kg/day. Toxicokinetics were conducted on Day 1 and Day 14 (see section 3, Pharmacokinetics).

Post-dose clinical observations were noted up to 1-2 hours and included ataxia, low carriage, piloerection, elevated tail, mildly splayed gait, and mildly to moderately decreased activity as well as reduced food intake and body weight gain was observed in males at 10 mg/kg.

No new safety findings were reported with NPJ5008 compared to DANTRIUM IV, with the exception of the known class effects associated with the use of HP-β-CD in formulations (reversible kidney changes). Vacuolated renal tubular epithelial cells were found in all animals administrated either with NPJ5008 10 mg/kg/day or vehicle control formulation (HP-β-CD 176.5 mg/mL and PEG 3350 20 mg/mL). Vacuolated renal tubular epithelial cells were only found in one animal at the lower dose of NPJ5008, 2.5 mg/kg/day. No such kidney changes were observed with DANTRIUM IV. An increased incidence of vacuolated alveolar macrophages was also observed in males and one incidence of vacuolated Kupffer cells was noted in a female rat administered NPJ5008 at 2.5 mg/kg/day.

In addition, animals receiving 10 mg/kg/day of NPJ5008 had an increased urine volume of 59.7 and 28.9% for males and females respectively, compared to controls.

Creatine phosphokinase (CPK) values were increased in male rats receiving dantrolene independently of formulation, while females receiving NPJ5008 had decreased CPK values compared to controls. A decrease in alkaline phosphatase (ALP) was also found in all females treated with dantrolene, independently of formulation.

In the 14-day toxicity study, clinical observations of the site of injection were performed daily. According to the toxicological report, 4/10 females receiving NPJ5008 10 mg/kg dose level, an abnormal blue colour of the tail was recorded on a few occasions. Contributing reasons may be attributed to the higher infusion rate for the high dose level and smaller size of females compared to males along with repeated administrations. No such effects were observed in the clinical trial, despite a higher administration rate.

2.4.4.2. Genotoxicity

Dantrolene has been reported to be mutagenic in a bacterial reverse mutation (Ames) test with Salmonella typhimurium in the absence and presence of an exogenous liver metabolising system. No other genotoxicity studies have been conducted with dantrolene, or with NPJ5008. It is agreed that the collective benefit/risk for all ages will not be altered based on the fact that dantrolene is the only active

substance available for treatment of this serious condition (MH) and additionally, the intended short duration of use.

2.4.4.3. Carcinogenicity

Female Sprague Dawley rats fed a dantrolene formulation up to 60 mg/kg for 18 months showed an increased incidence of benign and malign mammary tumours. At 60 mg/kg/day there was an increase in the incidence of benign hepatic lymphatic neoplasms. In a 30-month SD rat study, at an unspecified high dose of dantrolene, female rats showed an increased incidence of hepatic lymphangiomas and hepatic angiosarcomas. Fischer-344 rats exhibited a dose related reduction in onset of mammary and testicular tumours. No carcinogenicity studies have been conducted for NPJ5008, and no carcinogenicity studies have been conducted with dantrolene since the referenced approval and no data has been found in the published literature. No differences are expected between the proposed formulation and the existing DANTRIUM IV formulation related to potential for carcinogenicity. Regarding their potential to cause cancer, NPJ5008 and DANTRIUM IV shouldn't differ from one another. A minor clarification has been added to existing information in section 5.3 of the SmPC.

2.4.4.4. Reproductive and developmental toxicity

No DART studies have been conducted with NPJ5008, nor with intravenous dantrolene.

Oral formulations of dantrolene given to adult rats and pregnant rabbits did not exhibit any adverse effects on fertility and reproductive capability up to 45 mg/kg/day. However, in rabbit pups, an increased formation of unilateral or bilateral supernumerary ribs were detected on gestational day 6 to 18.

No reproductive and developmental toxicity studies have been conducted with dantrolene since its approval. It is agreed that extrapolation from historical data from the use of IV dantrolene in all ages which is presented in the clinical overview is sufficient regarding reproductive and juvenile toxicity of the active substance dantrolene.

2.4.4.5. Toxicokinetic data

The doses in the GLP-compliant non-clinical study and subsequent toxicokinetic study were equal to lowest loading dose (2.5 mg/kg) and maximum recommended total daily dose (10 mg/kg/day) in human. Exposure of HP-β-CD was not evaluated in the non-clinical study. (See Pharmacokinetics).

2.4.4.6. Other toxicity studies

Haemolytic potential

The haemolytic potential of NPJ5008 was investigated in comparison to the product DANTRIUM IV in two identical assays. No haemolysis was observed after treatment with either formulation, as shown in the spectra at 540 nm. The new dantrolene sodium hemiheptahydrate containing product NPJ5008 is a direct replacement or substitute for the DANTRIUM® IV which has reported incidences of possible haemolysis and discolouration of derived plasma samples occurring in trials. No explanation for the discolouration of plasma was achieved in the haemolytic assays performed by Applicant. However, according to chemicalbook.com, regarding properties of the impurity Dantrolene Related Compound B, the colour of this compound is yellow to dark yellow which may explain the discolouration of plasma samples occurring in trials.

A follow-up method was also developed to investigate the possibility if any interaction between the different formulations (NPJ5008 and DANTRIUM® IV) and the released haem molecules derived from lysed cells may occur. Haemolysis of the samples containing the different formulations was confirmed visually and as a double peak in the absorbance spectrum at 540 nm and no difference between NPJ5008 and DANTRIUM® IV could be observed.

In the assay using ICP-MS for investigation of iron release from lysed RBC, no interferences were observed using the mass of 56Fe for monitoring any interference.

In conclusion, there were no evidence that the discolouration of plasma would be due to haemolysis as the RBC appears to be intact.

Impurities

According to Applicant, the degradation and impurity profile of NPJ5008 follows and does not significantly differ from the marketed reference product DANTRIUM IV. The main impurity, Related Compound B (Degradant) [5-(4-nitrophenyl)-2- furaldehyde-2-carboxymethylsemicarbazone] was present in the batches used in the 14 days toxicity study. However, regarding the NMT% value according to the USP monograph for Dantrolene Sodium for Injection, see Quality section.

2.4.5. Ecotoxicity/environmental risk assessment

The Applicant has provided an ERA in accordance with the guideline for Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2). The log Kow of 1.77 at pH 7 was experimentally derived using OECD 107. The $PEC_{surface\ ater}$ of 0.0035 µg/L was calculated based on the maximum daily dose of 10 mg/kg/day and a refined Fpen, based on the orphan designation prevalence. Further studies were not conducted. Dantrolene is not a PBT substance, and a Phase I assessment is sufficient. The proposed use of dantrolene is not expected to pose a risk to the environment.

Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.77 (pH 7)	Potential PBT **N**
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	Refined, prevalence	0.0035 µg/L	> 0.01 threshold **N**
Other concerns (e.g. chemical class)			**N**

2.4.6. Discussion on non-clinical aspects

2.4.6.1. Pharmacokinetics

The method of analysis for quantification of dantrolene and the metabolite 5-Hydroxydantrolene in the toxicokinetic evaluation was not evaluated according to GLP regulations. The results of the assay validation were considered acceptable according to the analytical report. This is agreed and issue regarding non-GLP validation of the HPLC MS/MS method is not pursued.

Differences in pharmacokinetics between NPJ5008 and DANTRIUM IV were observed in the 14-day GLP compliant toxicity study. Since bioavailability is unlikely to differ for the same dose of dantrolene in different formulations after IV administration, it must imply that the change in formulation affects the

pharmacokinetics in some respect by differences in physical chemistry properties. Dantrolene's administration recommendation, i.e. 2.5 mg/kg x 4 with ten minutes intervals until MH resolves, is adapted to Dantrium IV's kinetics, which may also be contemplated in the treatment of MH using Agilus.

2.4.6.2. Toxicity studies

The non-clinical program in the development of NPJ5008 has focused mainly on adverse effects attributed to the change in formulation of dantrolene, from mannitol and sodium hydroxide (DANTRIUM IV) to PEG3500 and HP-β-CD (NPJ5008). The development of NPJ5008 relies mainly on data from the initial approval of dantrolene as well as literature studies. Studies regarding genotoxicity, cancer, reproductive/developmental or juvenile studies have not been conducted for NPJ5008. A single repeated dose toxicity study (GLP) for 14 days was conducted, and an *in vitro* human whole blood haemolysis assay as well as interaction between the different formulations and released heme-molecules. Toxicokinetics were conducted on Day 1 and Day 14. This approach is acceptable.

No new safety findings were reported with NPJ5008 compared to DANTRIUM IV, with the exception of the known class effects associated with the use of HP-β-CD in formulations (reversible kidney changes and increased incidence of vacuolated alveolar macrophages observed in male rats, see below).

The haemolytic potential of NPJ5008 was investigated in comparison to the product DANTRIUM IV in two identical assays. No haemolysis or interaction with heme-molecules were observed after treatment with either formulation.

2.4.6.3. Impurities

According to Applicant, the degradation and impurity profile of NPJ5008 follows and does not significantly differ from the marketed reference product DANTRIUM IV. The main impurity, Related Compound B (Degradant) [5-(4-nitrophenyl)-2- furaldehyde-2-carboxymethylsemicarbazone] was present in the batches used in the 14-days toxicity study and is considered toxicologically qualified.

2.4.6.4. Excipients

HP-β-CD

The quantity of the new excipient HP-β-CD in an initial 2.5 mg/kg dose of NPJ5008 is more than the threshold described in the annex to the European Commission guideline on excipients. However, the applicant did not address in its initial submission the potential risk associated with this level and in particular the potential for HP-β-CD-induced ototoxicity described in recent publications covering investigations in both humans and non-clinical test species. Therefore, a question was raised whether new non-clinical toxicity studies would provide further information to enable a proper risk assessment. The Applicant has responded by providing a comprehensive literature review on non-clinical and clinical data on HP-β-CD-induced ototoxicity. Despite some lack in information, the provided non-clinical discussion is considered sufficient from a non-clinical point of view.

Briefly, rat appears to be not only the most investigated species with regards to ototoxicity of HP-β-CD but also the most sensitive species to this effect. Further evaluation of ototoxicity risk in other species would therefore not be considered of value. In addition, since the development of ototoxicity after high and frequent doses of HP-β-CD is well known, non-clinical studies over a long time treatment period would not provide any useful data for Agilus which is intended for acute use only. Reports on patients with Neumann-Picks disease type C (NPC) treated with HP-β-CD both intrathecally and intravenously have been published. However, the data is scarce and includes only a small number of patients of various ages. Although evidence in NPC patients suggests a possibility of recovery in a couple of weeks

after intravenous administration of HP-β-CD, non-clinical studies in rats have shown a second phase of ototoxicity 6-8 weeks after treatment. The value of a new non-clinical study is thus questionable.

In the discussion by Applicant's response, published non-clinical data on HP-β-CD-induced ototoxicity from studies in mice, rats, and cats was presented. In all these studies HP-β-CD was administered subcutaneously. Rat was considered to be the most sensitive species where a single dose of 500 to 1000 mg/kg SC was considered to be the NOEL for development of ototoxicity. However, no exposure was measured in any of the studies where ototoxicity was investigated. At a dose of 2000 mg/kg, significant hearing loss has been observed in rat, particularly at high frequencies. Despite unknown bioavailability of HP-ß-CD for the SC administration route, it is considered that these data provide a sufficient characterisation of ototoxic effects in relation to total systemic exposure (AUC) in terms of scaling per mg/kg dose. However, given the subcutaneous route in these studies it cannot be assured that these studies would also cover potential ototoxic effects associate by the maximum plasma concentrations (C_{max}), achieved after IV administration in the treatment of MH. It should be kept in mind that the NOAEL value for ototoxicity in rat after IV administration may be lower compared to SC administration.

No margins to human exposure can be achieved for either C_{max} or AUC as the public literature presents either ototoxicity after SC administration connected to dose level or plasma exposure only after IV administration. Consequently, no threshold of plasma exposure for the development of ototoxicity has been identified. The literature suggests that the development of ototoxicity may be both C_{max}-related ("all or nothing" response) and AUC-related (build-up/accumulative effect), and additionally, include unpredictable individual variations in the sensitivity for developing ototoxicity.

An initial dose of 2.5 mg/kg dantrolene contains approximately 73.5 mg/kg HP-β-CD. In some rare cases doses up to 40 mg/kg dantrolene have been administered according to the applicant. This correspond to a dose level of 1177 mg/kg HP-β-CD and is slightly above the NOAEL limit for development of ototoxicity in rat after the SC administration route. This has, however, been a single case with administration over more than 24 hours. Most clinical cases reported have required less than 10 mg/kg dantrolene.

Of interest, an IV dose of 2500 mg HP-β-CD /kg in NPC over a time period of 8 hours equals 300 mg HP-β-CD/kg over a time period of 1 hour and seem to lack relevant ototoxic effects in human NPC subjects. In terms of HP-β-CD content in Agilus, a dose of 2.5 mg/kg Agilus repeated every ten minutes until a total dose of 10 mg/kg dantrolene is achieved, corresponds to a similar HP-β-CD dose level as administrated for 1 hour in NPC subjects. With Agilus, a HP-B-CD dose of 300 mg/kg will be administered rapidly and over a time period of 30 minutes, and in NPC patients within 1 hour but the infusion will on the other hand go on for a total period of 8 hours. Thus, a dose of Agilus at 10 mg/kg within 30 minutes appears safe, though, in case of severe MH this dose may be exceeded. In addition, the HP-B-CD plasma concentration in children under the age of 2 years may be higher due to lower renal capacity and a safe dose for the youngest may therefore also be lower.

HP-β-CD in children/juveniles

Studies performed in juvenile mice showed that in 7-day-old and 49-day-old npc+/+ or npc-/- mice, only about 40% of the HP-β-CD had been cleared from the body in the 7-day-old mice 6 hours after the SC injection, while more than 90% had been removed in the 49-day-old mice at a dose of 4000 mg/kg of HP-β-CD. Thus, the exposure time of HP-β-CD in plasma was six times greater in the 7-day-old mice than in the mature animals, suggesting a lower glomerular filtration rate also known for human infants. In another study in juvenile rats administered 4000 mg/kg HP-ß-CD, most of the auditory functions were abolished but the hearing damage became more extensive the older the animals were. However, the increased severity with age may be dependent on the later development of the ear structures in rat in comparison to human, where the auditory system is almost fully developed at birth.

According to the European Commission guideline on Cyclodextrins (EMA/CHMP/333892/2013, last updated 09/10/2017), a juvenile rat study at IV doses up to 400 mg/kg/day HP-β-CD from PND 16 on to PND 44, showed that the toxicological findings were very similar to those observed in adult rat

studies at similar dose levels and duration. No novel toxicity was seen. However, the publications on the HP-β-CD-related ototoxicity in non-clinical species and in human have escalated only recently, no recommendations or warnings have been included in the last update of the guideline.

PEG 3350

There were no effects found in relation to the excipient, PEG 3350. This medicinal product contains 17.7 mg/mL of PEG 3350 and is used to prevent bubbling in reconstituted solutions, so it brings the benefit of easier dispersion preparation.

2.4.6.5. Ecotoxicity/environmental risk assessment

Dantrolene PEC surface water value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

Dantrolene is already used in existing marketed products and no significant increase in environmental exposure is anticipated. Therefore, Dantrolene is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, the CHMP considers that the submitted data is sufficient to determine that a risk of substantial and possible irreversible effects on the auditory function cannot be excluded in patients with severe MH requiring repetitive rapid administrations of Agilus, particularly if required in children under the age of 2 years.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Pharmacokinetic properties of dantrolene as a pharmacologically active substance are described previously for the already approved IV products containing dantrolene. Therefore, the current overview of Clinical Pharmacology is primarily focused on newly generated data concerning the new dantrolene product under assessment.

The present application is submitted as a Hybrid Application under Article 10(3) to cross reference the new dantrolene sodium product (NPJ5008) to the reference product DANTROLEN IV / DANTRIUM IV 20 mg powder for solution for injection (hereafter referred to as DANTRIUM IV). In order to bridge to the reference product, the current submission was supported with one clinical study specifically conducted on NPJ5008 product and with literature references.

The present application concerns a reformulation of dantrolene sodium, where the mannitol and sodium hydroxide in the reference product have been substituted with β-cyclodextrin and Macrogol 3350 in NPJ5008, with the purpose of increasing the solubility of the drug substance (please see Quality section for more details on drug formulation).

Overall, there are only three new studies (2 *in vitro* and 1 *in vivo*) which have been conducted to support and inform the Clinical Pharmacology of the new product NPJ5008:

• Blood haemolysis study – Study CLS4_0069_0003

• Plasma protein binding study - Study CLS4_0069_0001

• Comparative pharmacokinetic study in humans - NPJ5008-01/2020 (QSC204721)

Summary of plasma protein binding study (CLS4_0069_0001) and comparative PK study in humans (QSC204721) are provided below. For the blood haemolysis study (CLS4_0069_0003) please refer to the non-clinical section for more details.

Plasma protein binding study (CLS4_0069_0001)

The Applicant has conducted a dedicated *in vitro* study denoted as CLS4_0069_0001 in order to investigate the plasma protein binding of dantrolene in two formulations (i.e., NPJ5008 and DANTRIUM IV) at 6, 40 and 100 µg/mL in human plasma (mixed gender, anticoagulated with K_3EDTA). Protein binding was evaluated using Rapid Equilibrium Dialysis (RED) platform and LC-MS/MS methods. Warfarin and verapamil were used as control compounds.

The main study experiments demonstrated that the percentage fraction unbound of dantrolene in DANTRIUM IV and NPJ5008 was comparable in human plasma K_3EDTA at 6 µg/mL, 40 µg/mL and 100 µg/mL. Experiment at concentration of 6 µg/mL was conducted in order to match the clinical C_{max} which was observed following intravenous administration of 2.5 mg/kg (as reported in the literature data, Flewellen, 1985). At this specific concentration of 6 µg/mL in human plasma, protein binding for dantrolene was 94.9% (or 5.1% fu; fraction unbound).

Clinical study NPJ5008-01/2020 (QSC204721), Part 1

Part 1 of the clinical study NPJ5008-01/2020 (QSC204721) was a bioequivalence (BE) assessment of NPJ5008 vs. the reference product DANTRIUM IV. It was a randomised, open-label, single-dose, 2-period crossover study conducted in 16 healthy males and females of non-childbearing potential, aged 18 to 55 years, with a weight of minimum 55 kg and a body mass index between 19.0 and 32.0 kg/m^2. In the first dosing period sentinel dosing was performed; two subjects were dosed 24 hrs ahead of the remaining subjects, and the randomisation schedule was constructed such that one of the sentinel subjects was randomised to regimen AB and the other was randomised to regimen BA (see dosing regimens in the table below). All 16 subjects completed both study periods.

Table 2. Dosing regimens in study NPJ5008-01/2020 (QSC204721), Part 1.

Regimen	Investigational Medicinal Product[1]	Dose	Route
A	NPJ5008 120 mg powder for solution for injection (Test). Each vial was reconstituted with 20 mL water for injection.	60 mg as 11.3 mL of a 5.3 mg/mL solution	IV solution infused over at least 1 min
B	DANTRIUM IV 20 mg powder for solution for injection (Reference). Each vial was reconstituted with 60 mL water for injection.	60 mg as 186 mL of a 0.32 mg/mL solution	IV solution infused over at least 5 min

[1] NPJ5008 and DANTRIUM IV were supplied as the sodium salt form of dantrolene (dantrolene sodium)

Blood samples for PK assessments were collected pre-dose, immediately after the end of IV infusion (±2 min) and at 0.08, 0.16, 0.25, 0.50, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 60, 36, 48 and 72 hours after end of infusion.

The results of the PK parameters chosen for bioequivalence assessment are presented in the table below. On average, the overall exposure of dantrolene for 60 mg NPJ5008 - as measured by AUC(0-

last) and AUC(0-inf) - was 90.24% and 90.44% of that for 60 mg DANTRIUM IV, respectively, and the 90% CI for both parameters fell within the conventional bioequivalence limits of 80.00% to 125.00%.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) for dantrolene, N=16.

Treatment	$AUC_{0\text{-last}}$ ng*h/ml	$AUC_{0\text{-}\infty}$ ng*h/ml
Test (60 mg NPJ5008)	12100 ± 2300	12500 ± 2410
Reference (60 mg Dantrium IV)	13500 ± 2950	13900 ± 3060
***Ratio (90% CI)**	**90.24 (85.94 – 94.76)**	**90.44 (85.97 – 95.14)**
$AUC_{0\text{-last}}$ area under the plasma concentration-time curve from time zero to time of last measurable concentration $AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity		

The results of the PK parameters chosen for bioavailability assessment are presented in the table below. The AUC(0-6) and AUC(0-72) for 60 mg NPJ5008 was on average 88.35% and 90.27%, respectively, that for 60 mg DANTRIUM IV, and the 90% CI for both parameters fell within the conventional bioequivalence limits of 80.00% to 125.00%.

However, the peak exposure of dantrolene, as measured by Cmax, for 60 mg NPJ5008 infusion was 92.76% of that of 60 mg DANTRIUM IV, and the 90% confidence interval fell slightly below the lower acceptance limit of 80.00%.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for dantrolene, N=16.

Treatment	$AUC_{0\text{-}6}$ ng*h/ml	$AUC_{0\text{-}72}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test (NPJ5008)	4270 ± 636	12400 ± 2370	1140 ± 350	0.100 (0.01 – 4.01)
Reference (Dantrium IV)	4860 ± 889	13800 ± 3020	1240 ± 450	0.155 (0.14 – 4.16)
***Ratio (90% CI)**	**88.35 (84.95 – 91.89)**	**90.27 (85.89 – 94.88)**	**92.76 (78.27 – 109.93)**	**-**
C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration				

Following single dose infusion doses of 60 mg NPJ5008 and DANTRIUM IV, maximum plasma concentrations of dantrolene occurred between 0.01 and 4.01 hrs post-start of infusion and between 0.14 and 4.16 hrs post-start of infusion, respectively. Secondary peaks and transient plateaus were observed in the initial phase of the concentration-time profiles (up to ~10 hrs) for both formulations; thereafter the dantrolene concentrations declined in a monophasic manner.

The mean plasma dantrolene concentration vs time profiles for both regimens (60 mg NPJ5008 and 60 mg DANTRIUM IV) are presented in figures below.

Figure 2. Plasma concentrations of dantrolene (arithmetic mean ± SD) after the administration of 60 mg NPJ5008 IV and 60 mg DANTRIUM IV, respectively; 0 to 72 hours post dose (linear scale).

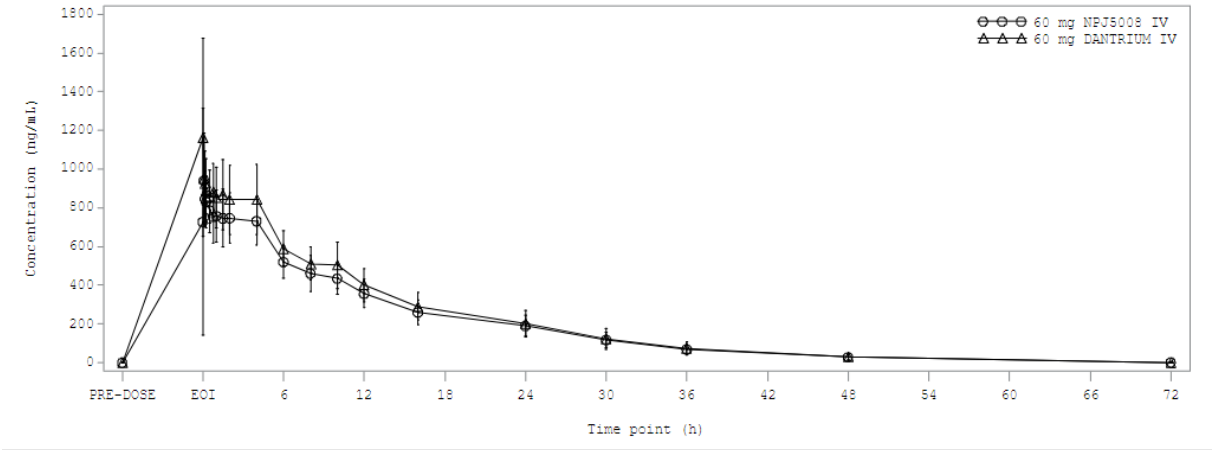
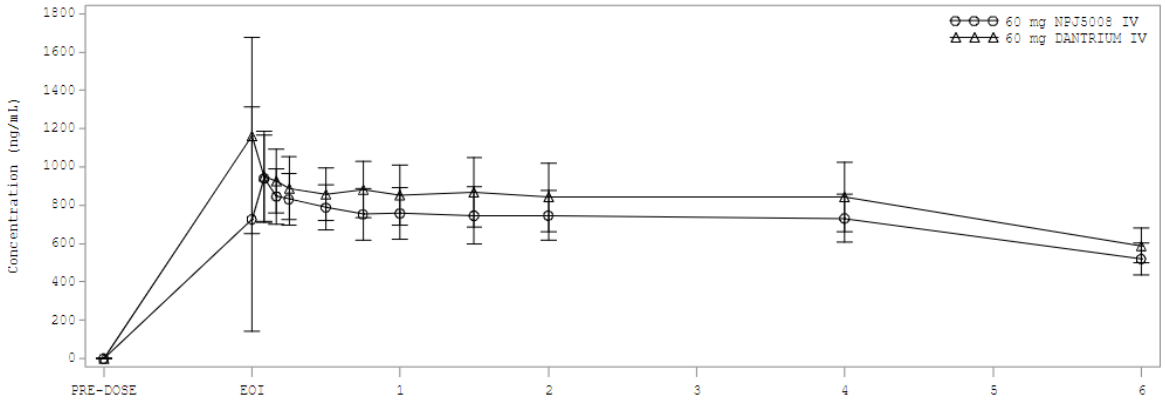


Figure 3. Plasma concentrations of dantrolene (arithmetic mean ± SD) after the administration of 60 mg NPJ5008 IV and 60 mg DANTRIUM IV, respectively; 0 to 6 hours post dose (log-linear scale).



The geometric means (geometric CV%) of PK parameters obtained in 16 subjects dosed with 60 mg dantrolene product NPJ5008 and the reference product in Part 1 of this clinical study are provided below.

Table 5. Plasma PK parameters for dantrolene and metabolite following 60 mg NPJ5008 and 60 mg DANTRIUM IV - Part 1 of clinical study NPJ5008-01/2020 (QSC204721).

Analyte	Dantrolene (Free Acid)		5-Hydroxy-Dantrolene	
Treatment	60 mg NPJ5008	60 mg DANTRIUM IV	60 mg NPJ5008	60 mg DANTRIUM IV
Parameter (unit)	N = 16	N = 16	N = 16	N = 16
Tmax[1] (h)	0.100 (0.01-4.01)	0.155 (0.14-4.16)	6.02 (4.00-10.0)	10.1 (1.64-16.1)
Cmax (ng/mL)	1090 (29.7)	1170 (34.8)	114 (25.3)	138 (34.1)
Cmax/D (ng/mL/mg)	23.1 (29.7)	24.9 (34.8)	2.40 (25.3)	2.93 (34.1)
AUC(0-6) (ng.h/mL)	4230 (15.4)	4790 (18.8)	497 (27.4)	581 (40.0)
AUC(0-72) (ng.h/mL)	12200 (20.8)	13500 (23.9)	2890 (19.9)	3380 (21.2)
AUC(0-last) (ng.h/mL)	11900 (20.6)	13200 (23.9)	2880 (19.6)	3370 (21.1)
AUC(0-last)/D (ng.h/mL/mg)	252 (20.6)	279 (23.9)	60.9 (19.6)	71.4 (21.1)
AUC(0-inf) (ng.h/mL)	12300 (21.1)	13600 (24.2)	2920 (19.9)	3420 (20.8)
AUC(0-inf)/D (ng.h/mL/mg)	260 (21.1)	287 (24.2)	61.9 (19.9)	72.4 (20.8)
T1/2 (h)	9.041 (27.9)	8.476 (21.8)	10.171 (20.3)	9.488 (24.0)
CL (mL/min)	63.5 (21.1)	58.2 (24.2)	NC	NC
Vz (L)	49.7 (22.7)	42.7 (21.1)	NC	NC
Vss (L)	53.3 (14.9)	46.3 (16.6)	NC	NC
MPR Cmax (N/A)	NC	NC	0.099 (32.8)	0.112 (37.4)
MPR AUC(0-last) (N/A)	NC	NC	0.230 (23.3)	0.243 (30.3)
MPR AUC(0-inf) (N/A)	NC	NC	0.227 (22.9)	0.240 (29.9)
Frel AUC(0-last) (%)	90.2 (13.1)	NC	NC	NC
Frel AUC(0-last)/D (%)	91.3 (13.1)	NC	NC	NC
Frel AUC(0-inf) (%)	90.4 (13.0)	NC	NC	NC
Frel AUC(0-inf)/D (%)	91.5 (13.0)	NC	NC	NC

[1]: Median (range); N: number of subjects in the dataset; NC: Not Calculated; NA: not applicable

Clinical study NPJ5008-01/2020 (QSC204721), Part 2

Part 2 of clinical study NPJ5008-01/2020 (QSC204721) also involved collection of PK data generated with NPJ5008 product at the higher dose of 120 mg whereas Part 1 (i.e. BE part of this study) included administration of NPJ5008 at the dose of 60 mg.

According to the Applicant, Part 2 of this study was planned to enrol 10 healthy volunteers, and even to test the high dose of 240 mg. However, review of the ongoing safety data for the first four subjects dosed in Part 2 of the study showed that, while no study stopping criteria had been met, there appeared to be an increased number and severity of AEs as the dose of NPJ5008 increased from 60 mg to 120 mg. The adverse events were expected based on the mode of action and dose of intravenous dantrolene to a healthy conscious volunteer. The sponsor and Principal Investigator assessed that the aims of the study could be sufficiently met after the 120 mg dose. A prudent approach to safety was adopted and the study was stopped early after 5 subjects had received the 120 mg NPJ5008 dose. Therefore, no subjects were enrolled into the planned 240 mg NPJ5008 group.

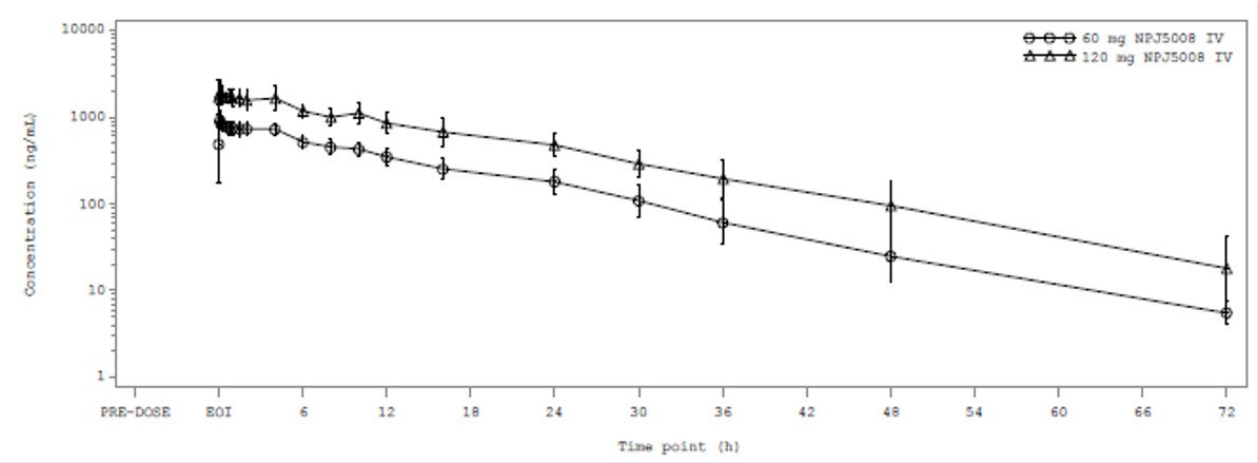
The geometric means (geometric CV%) of PK parameters obtained in five subjects dosed with 120 mg dantrolene product NPJ5008 in Part 2 of this clinical study are provided below.

Table 6. Plasma PK parameters for dantrolene and metabolite following NPJ5008 120 mg – Part 2 of clinical study NPJ5008-01/2020 (QSC204721).

Treatment	**120 mg NPJ5008**	
Analyte	**Dantrolene (Free Acid)**	**5-Hydroxy-Dantrolene**
Parameter (unit)	**N = 5**	**N = 5**
Tmax[1] (h)	0.149 (0.07-0.8)	10.064 (10.05-16.17)
Cmax (ng/mL)	2090 (24.2)	208 (22.5)
Cmax/D (ng/mL/mg)	22.1 (24.2)	2.20 (22.5)
AUC(0-6) (ng.h/mL)	9400 (25.7)	765 (17.4)
AUC(0-72) (ng.h/mL)	30500 (31.1)	6150 (23.6)
AUC(0-last) (ng.h/mL)	30400 (31.7)	6150 (23.6)
AUC(0-last)/D (ng.h/mL/mg)	322 (31.7)	65.2 (23.6)
AUC(0-inf) (ng.h/mL)	30900 (31.5)	6270 (23.9)
AUC(0-inf)/D (ng.h/mL/mg)	327 (31.5)	66.4 (23.9)
T1/2 (h)	10.993 (18.5)	11.212 (19.4)
CL (mL/min)	50.5 (31.5)	NC
Vz (L)	48.0 (29.2)	NC
Vss (L)	49.2 (24.5)	NC
MPR Cmax (N/A)	NC	0.095 (35.6)
MPR AUC(0-last) (N/A)	NC	0.193 (24.0)
MPR AUC(0-inf) (N/A)	NC	0.193 (23.7)

[1]: Median (range); N: number of subjects in the dataset; NC: Not Calculated; N/A: not applicable

Figure 4. Geometric mean (± geometric SD) plasma dantrolene concentrations (ng/mL on logarithmic10/linear scale) following intravenous administration of 60 mg or 120 mg NPJ5008 to healthy volunteers during Part 1 and Part 2 (Clinical Study NPJ5008-01/2020).



Dose proportionality

According to the Applicant, the exploratory objective of assessing the dose linearity of the NPJ5008 doses used in Parts 1 and 2 of the clinical study NPJ5008-01/2020 (QSC204721) could not be performed as three dose levels were not administered in the study. As an alternative, assessment was performed on PK parameters corrected for nominal dose received between the 60 mg and 120 mg NPJ5008 dose levels. In summary, the results of this analysis indicated that the peak exposure per mg (following salt correction) was not significantly different when comparing the two dose levels, whereas the overall exposure per mg was significantly lower for the 60 mg dose level when compared to the

120 mg dose level. This implies an approximately dose-proportional increase in maximum exposure (Cmax) and a supra-proportional (33%) increase in the overall exposure (AUC).

In conclusion, based on the limited clinical data (i.e. only two dose levels available at 60 and 120 mg) with the limited number of study subjects, AUC implied a slight tendency towards more than dose-proportional increase with increasing IV doses of NPJ5008 product. Of further note, the choice of subtherapeutic doses with NPJ5008 drug product (i.e. 60 mg and 120 mg which are both lower than the actual initial therapeutic minimum dose of 2.5 mg/kg) in the conducted clinical study by the Applicant, appears acceptable considering the healthy-volunteer population of this study and the safety considerations. Therefore, potential administration of higher dantrolene doses (in the therapeutic range) to healthy volunteers would not be plausible.

Clinical PK Prediction for Hydroxypropyl-beta-cyclodextrin (HP-β-CD)

The literature was reviewed for HP-β-CD PK data following IV administration. The selection of references was focused on IV administration of HP-β-CD either as the test material, or as an excipient in other drug products where dosing regimens in the literature were aligned with the dose regimens reported. Data were available following single or repeat doses of HP-β-CD across all age groups except neonates. Few data were available for individual subjects, but where mean data were available, standard deviations were used to assess variability.

A number of PK data gaps were identified for PK parameters matching HP-β-CD dosing regimens in the clinical literature. PK data for these gaps were simulated by modelling the dosing regimen in the literature using HP-β-CD PK simulation models. Three simulation models were developed: a linear weight model (LWM), an allometric model Allometric (ALM) based on body weight ratios, and another Allometric + GFR (ALGFRM) with the addition of glomerular filtration rate (GFR) to account for plasma clearance. ALGFRM was used to take account of the known clearance route of HP-β-CD and thereby potentially provide a more physiologically based approach for parameter estimation. The structural model was a 2-compartment distribution model with first order elimination (Abdel-Rahman, 2007). The PK model(s) were validated across a number of datasets in the literature, comparing predicted and observed AUC and C_{max}. Subsequently, the ALGFRM model was used to simulate HP-β-CD exposure given under the Agilus IV dosing regimen. The results are further discussed in the Safety section.

2.5.2.2. Pharmacodynamics

Mechanism of action

Experimental evidence suggests that dantrolene inhibits the release of calcium in skeletal muscle cells by increasing the affinity of the RYR for Mg^{2+} and that it requires elevated cytoplasmic Mg^{2+} to adequately close RYR (18, 19). This results in a marked reduction in muscle contraction in response to electrical stimulation or stimulation by pharmacological agents without affecting action potential patterns (20).

Primary and Secondary pharmacology

In vivo studies in MH-susceptible pigs show that dantrolene inhibits abnormal excitation-contraction coupling and reverses and prevents development of MH. However, in vitro studies using isolated skeletal muscle from susceptible animals produced variable results, with inhibition, no effect or potentiation of halothane- and caffeine-induced muscle contraction. Dantrolene appears to have some effects on smooth muscle and cardiac tissue in vitro, but these are inconsistent and negligible. Dantrolene may affect calcium release from nerve terminals and nerve terminal responses, and appears to have a marked GABAergic effect, but is devoid of anticonvulsant and anaesthetic properties.

2.5.3. Discussion on clinical pharmacology

The present application is submitted as a Hybrid Application under Article 10(3) to cross reference the new dantrolene sodium product, NPJ5008, to the reference product DANTRIUM IV.

The Applicant has conducted only one clinical study which generated new Clinical Pharmacology data as detailed above.

In the clinical study NPJ5008-01/2020, part 1, bioequivalence was shown between NPJ5008 and the DANTRIUM IV in terms of overall dantrolene exposure (AUC), whereas the ratio of peak exposures (Cmax) fell slightly below the bioequivalence acceptance limits of 80.00% - 125%. However, this minor Cmax discrepancy is not considered of concern, as individual dose titration is applied in clinical practice.
The dantrolene doses used in this clinical study (part 1 and 2) conducted in healthy volunteers were lower than the actual initial therapeutic minimum dose of 2.5 mg/kg, as proposed in the SmPC. Therefore, there are no clinical PK data available for the new drug formulation NPJ5008 within the therapeutic range. Administration of higher dantrolene doses to healthy volunteers ould not be feasible due to the safety concerns.

Importantly, the currently intended dosing (as stated in SmPC section 4.2) is proposing the initial minimum dose of 2.5 mg/kg (i.e., which is relatively close to the dose of 120 mg or 1.38 mg/kg, as investigated by the Applicant in the clinical study), which will be afterwards titrated based on the achieved effect (i.e., it will not be a PK-guided dosing). Therefore, the overall safety and efficacy data for dantrolene are considered as the main factors for assessing the appropriateness of the current dantrolene product and its proposed posology (see also Clinical efficacy and safety aspects). Finally, when considering the IV route of administration of dantrolene, it is less probable that the potential formulation differences would result in large/relevant differences in terms of the systemic exposure (unlike for other extravascular routes where such scenario would be more likely).

In addition to this clinical study data, the Applicant has submitted published literature references to support the present application. All submitted references appear adequate and acceptable in terms of Clinical Pharmacology aspects.

To investigate the HP-β-CD exposure developed three PK models to simulate HP-β-CD concentration-time profiles. The models were validated by simulating the dosing scenarios found in literature and simulated exposure was compared with reported exposure. Overall, the LWD model under predicted the reported data, whereas ALM and ALGFRM (in particular) tended to over predict the reported data. An overprediction of the data can be viewed as a worst-case scenario, thus the ALGFRM results are used in the assessment of benefit-risk. However, there are some uncertainties in the simulations:

i) The Cmax after short infusions seems to be under-predicted (Szathmary ref), thus Cmax could be higher after an IV bolus. It should be noted, however, that short infusion data is only available in adults which tend to be less well predicted overall.

ii) No variability was included in the simulations, which means that AUC and Cmax for upper percentiles of the distributions are not reported. Given a literature search the Applicant reports a mean variance mean variance of 23% for Cmax and 29% for AUC which can be considered fairly low variability.

iii) Only a few different body weights and ages have been included in the simulations. In the age group ≤2 years the following ages have been included: neonate, 4 months, and 2 years.

The above-mentioned uncertainties have been considered when assessing the simulation results. Regarding the possibility of an under predicted Cmax (i), the fact that the ALGFRM model over predict the exposure gives some reassurance that an extremely higher Cmax would not be expected. Furthermore, the simulated Cmax for the 2.5 mg and 5 mg Agilus dosing is well below the exposure previously reported (see predicted plasma exposure section below) allowing for some errors in the prediction. The simulation of mean values can also be accepted given the low variance in exposure(ii). Lastly, it is accepted to interpolate between 4 months and 2 years as it expected that the highest

exposure will be predicted in the neonate and 4-month age groups. It is acknowledged that the Applicant has explored both allometric scaling and kidney maturation (GFR) to describe HP-β-CD in all age groups. For the purpose of this Application, the focus is mainly on the prediction of the paediatric exposure. In addition, the Applicant has made a serious attempt to validate the PK model against available literature data. In conclusion, the modelling and simulation methodology is accepted to provide exposure predictions for HP-β-CD following Agilus IV administration.

2.5.4. Conclusions on clinical pharmacology

The Applicant has conducted only one clinical study which generated new Clinical Pharmacology data. In addition, the Applicant has referred to published literature to support the present Hybrid application submission. Overall, the available Clinical Pharmacology data are considered sufficient for the purpose of the present Hybrid application.

2.5.5. Clinical efficacy

The NPJ5008 development programme has focused on the change introduced as compared to the reference product DANTRIUM IV in the formulation, where hydroxypropyl beta cyclodextrin (HP-β-CD) and Macrogol 3350 are substituted for mannitol and sodium hydroxide. The reference product was first approved in Austria in 1984. It is currently approved nationally in 10 EU countries, the UK and Switzerland.

MH is a rare and fulminant unexpected reaction to anaesthesia and controlled clinical trials in MH patients are unfeasible. No clinical study in MH has been provided or is considered required. The assessment of clinical efficacy in this application therefore rests on a PK bridge to the reference product and additional support from literature data and international consensus treatment guidelines.

2.5.5.1. Main study(ies)

N/A.

2.5.5.2. Supportive studies- Literature

The Applicant has identified 21 publications in patients with MH, from the time period of 01 JAN 1979 until 30 JUN 2019. This literature search also covered other MH-like conditions. Since the indication applied for is restricted to MH, these publications are not considered of relevance for assessment of the efficacy. Editorials (2) and narrative reviews (20, 22-25) without original data are also not considered further in this context.

The remaining 16 publications are briefly summarised in the table below:

Table 1: Brief summary of publications 01 JAN 1979 to 30 JUN 2019 reporting efficacy data in MH.

Ref	Methodology/design	Number of patients treated with IV dantrolene[a] Mean age or range	IV dantrolene dose	Comment
Kolb-1982 (26)	Multicentre, unblinded, single-arm study of iv dantrolene in MH.	**11** patients treated as per protocol: 7 months to 26 years **4** patients treated late (>24 hours after diagnosis): 15-34 years	Mean dose in 11 patients: 2.5 mg/kg	
Jacquot-1985 (27)	A survey was conducted of all anaesthesia departments, in February 1984, to assess the incidence of peri-anaesthetic MH occurring in France.	**6** patients (oral/iv not specified)		Report in French.
Mauritz-1986 (28)	An analysis of suspected MH cases reported between 1975 and 31 MAR 1986.	**10** patients (oral/iv not specified)		Report in German.
Carr-1995 (29)	Medical records of patients who underwent an elective muscle biopsy were reviewed.	MH reaction treated with dantrolene: **4** patients (iv only) 3-26 years		Chart review of MS-susceptible patients.
Allen-1998 (30)	A review of the database of the NAMHR for cases of presumed MH triggered by desflurane.	**11** patients 5-70 years		Relevant database to identify cases related to a specific trigger.
Kawamoto-2001 (31)	Data from 146 subjects with anaesthesia-related MH susceptibility history who had received a muscle biopsy for the determination of CICR rate were analysed for 23 different clinical variables.	**146** subjects (no information on how many subjects received dantrolene; oral/iv not specified) age ranged from 0-66 years	No information available.	Prediction model for Ca-induced Ca release (CICR) rate. Limited relevance for the current application and assessment of dantrolene efficacy.
Pollock-2002 (32)	Data from a single centre MH database were collected. Method of treatment was one of the data	MHS: 13 cases (oral/iv not specified) MHN: **4** cases (oral/iv not specified)	Initial dose: 1.5-2 mg/kg Max. dose: 17	Relevant review of dose in a single-center case series.

Ref	Methodology/design	Number of patients treated with IV dantrolene[a] Mean age or range	IV dantrolene dose	Comment
	points analysed.		mg/kg over 36 hours	
Burkman-2007 (33)	Data from the NAMHR 1987 to Jan 1, 2005 were collected on patients who underwent general anaesthesia and had a likely MH reaction.	**244** patients (oral/iv not specified) Age range of the 308 MH cases: 0-75 years	Patients with no recrudescence: mean 6.8 mg/kg Patients with recrudescence: mean 9.4 mg/kg	The authors analyzed clinical variables associated with recrudescence after a clinical MH episode, using NAMHR 1987 to Jan 1, 2005.
Migita-2007 (34)	383 MH cases from a Japanese database were divided into three groups based on time and clinical factors.	Total **207** patients received dantrolene (oral/iv not specified) 1961-1984: 36 patients 1985-1994: 119 patients 1995-2004: 52 patients	No relevant information on dose.	Large case series identified from 1961 to 2004 in Japan.
Larach-2010 (35)	Cases of MH from JAN 1987 to Dec 2006 were collected from the NAMHR and a model of the risk of complications from MH created.	**229** events	Median total dose: 5.9 mg/kg (range: 0.02–100 mg/kg)	Reports to NAMHR January 1, 1987 to December 31, 2006.
Migita-2012 (36)	Cases of MH associated with sevoflurane and isoflurane from 1990-2009 were collected from the Japanese MH database and clinical factors analysed.	Total **70** patients received dantrolene (oral/iv not specified) Dantrolene and sevoflurane 43 patients Dantrolene and isoflurane 27 patients	No relevant information on dose.	Relevant database to identify cases related to a specific trigger.
Larach-2014 (37)	MH cases from the NAMHR from Jan 2007 to Dec 2012 were collected and the characteristics associated with cardiac arrest and death summarised.	The exact number of dantrolene-treated patients was not specified.	No relevant information on dose.	Study focused on impact of temperature monitoring on outcome.
Nelson-2014 (38)	A retrospective review of the NAMHR identified paediatric subjects (up to and including 18 years) with a CGS	**264** patients (193 [73%] dantrolene-treated patients (oral/iv not specified): **35** in the youngest age group (0 to 24	Mean initial dose: 2.4 mg/kg Mean total dose: 5.9	NAMHR study focused on paediatric cases. Information on both initial

Ref	Methodology/design	Number of patients treated with IV dantrolene[a] Mean age or range	IV dantrolene dose	Comment
	of ≥35 indicating 'very likely' or 'almost certain' MH.	months), 163 in the middle age group (25 months to 12 years), and 66 in the oldest group (13 to 18 years))	mg/kg	and total dose also in <2 year olds.
Riazi-2014 (39)	Between 1992 and 2011, a retrospective analysis of 129 Canadian proband survivors of adverse anaesthetic reactions, whose MHS status was confirmed by caffeine-halothane contracture testing. Data regarding demographics, clinical signs, laboratory findings, treatment and complications were retrospectively compiled and analysed.	**57** patients (oral/iv not specified)	No relevant information on dose.	Large relevant case series from 1992 to 2011 in Canada. An increased time interval between the first adverse clinical sign and dantrolene treatment was associated with increased complication rates.
Brandom-2014 (40)	AMRAs between 01 Jan 2007 and 31 Dec 2013 in the NAMHR of the MH Association of the US to describe any changes in the administration of dantrolene, complications associated with dantrolene or with the MH episode itself that might contribute to increased morbidity.	Total **152** cases (oral/iv not specified) Median 41 years (6-84) in 39 cases with SAEs/deaths due to MH episode Median 24 years (0-90) in 109 cases without complications due to MH episode	First dose: overall 3-660 mg Median dose 190 mg in 34 cases with SAEs/deaths due to MH episode Median dose 160 mg in 107 cases without complications due to MH episode	NAMHR study. Greater age of the patient, longer time from the beginning of the anaesthetic to the first sign of MH and longer time from the first sign of MH to the administration of dantrolene were all found to be associated with increased risk of complications
Pinyavat-2015 (41)	A review of medical records for patients with a discharge diagnosis of MH at 6 medical centres in North America.	**12** patients (oral/iv not specified)	No relevant information on dose.	The aim of this study was to estimate the accuracy of coding for MH in hospital discharge records. Limited relevance for the current application and assessment of dantrolene efficacy.

A complementary literature search was reported for the period of 1st July 2019 to 30th March 2022 without addition of any key clinical study data that alters the characterisation of efficacy.

2.5.5.2.1. Paediatric data on dose

The Applicant also presented a structured analysis of published MH case reports, with an emphasis on the paediatric target population. The age of the dantrolene-treated patients with MH in the literature review ranged from 7 weeks to 90 years, 210 patients with MH were included in the review of the case studies, and of these, 91 patients (43.3%) were under 18 years old, with a range from 8 days to 82 years (2). 21 patients were <2 years. 64.8% were male in the total paediatric population and 75.9% in the adult population. Across all age groups, the majority of patients were male, with no difference between the various paediatric age groups compared to the adult population.

The median initial therapeutic dose administered was similar for all but one paediatric age groups, ranging from 2.05 – 3.00 mg/kg. A single patient in the "0 to 27 days" group received 20 mg/kg, as an outlier. The median initial dose is consistent across the paediatric age groups and similar to the "18 years and over" median dose of 2.40 mg/kg.

Median maintenance doses administered were more variable, ranging from 3.00 - 6.00 mg/kg across the paediatric age-groups, similar to 4.20mg/kg in the "18 years and over" reference group. There were no data for the single patient in the "0 to 27 days" group. Median total doses administered were similar for all age groups, ranging from 2.50 - 6.00 mg/kg in the paediatric groups, with exception of the single patient in the "0 to 27 days" group (20mg/kg). These exposures are comparable to the median total dose of 3.20 mg/kg in the "18 years and over" group.

There appears to be no appreciable difference in exposure to intravenous dantrolene for MH across paediatric groups compared to adults.

Due to the high proportion of patients who recovered from the condition requiring dantrolene, it was not possible to assess the individual effects of initial dantrolene dose, demographics, severity of condition (based on body temperature), medication use, other medical procedures, or muscle rigidity status on outcome when considering all other characteristics together. No meaningful differences between the adult and paediatric population with respect to key characteristics were identified.

2.5.5.2.2. Impact on mortality

There are no data that can provide a direct quantitative estimate of the independent impact of dantrolene on mortality. That dantrolene has contributed substantially to the improved outcome of MH over the years is, however, undisputable. In a pioneering and ambitious effort 89 North American MH cases prior to the availability of dantrolene were characterised (9). The mortality was found to be 64%.

In a more recent US series of 152 MH cases death occurred in 7% (40). This dramatic reduction in mortality over time is not solely attributable to dantrolene. The importance of early recognition (and therefore also milder presentations being diagnosed to a larger extent), improved overall understanding of the condition, increased vigilance, improved supportive intensive care, and active cooling, are factors that in all likelihood also have contributed to improved outcome.

Dantrolene is still not widely available in all countries. Among 92 cases of MH reported in China from 1985 to 2020 only 8 cases (8.7%) were treated with dantrolene and in total 42 cases (45.7%) died (42). From 1985 to 2010 the total mortality was 54.1%, whereas the total mortality was down to 29.0% from 2011 to 2020. It was concluded that in countries where dantrolene is not readily available, early recognition of the condition and prompt supportive therapy are crucial for MH patients to survive.

The proportion of patients requiring dantrolene who recovered from the condition was 95.7% (201/210 patients) overall, with no difference between the age groups. The proportions of patients

who died from any cause were low (14 out of 210 total, 6.7%) overall and for all age groups of MH requiring dantrolene. The majority (9 out of 14; 64.3%) of deaths were due to the condition requiring dantrolene.

Table 2: Proportion of patients recovered by age groups

	0 to 27 days N=1	1 to 23 months N=20	2 to 11 years N=44	12 up to 18 years N=26	18 years and over N=116	Missing N=3
Patients who recovered, n (%)	1 (100.0)	19 (95.0)	41 (93.2)	26 (100)	112 (96.6)	2 (66.7)
Patients who died, n (%)	0 (0.00)	1 (5.0)	3 (6.8)	0 (0.00)	9 (7.8)	1 (33.3)

2.5.5.2.3. Faster administration potentially associated with better outcome

Early administration of dantrolene has been associated with better outcomes in the treatment of MH (39, 40). It should, however, be recognised that a comparison between early and late treatment in a non-interventional study setting almost always introduces a selection bias, from more mild cases being included in the early treatment group. It is nevertheless acknowledged that early treatment of MH is important and clearly advocated in treatment guidelines.

In Agilus, mannitol and sodium hydroxide have been replaced with HP-β-CD and Macrogol 3350, which has led to a decrease in both time for preparation and volume of water needed to dissolve each vial of product (please see table 3 below). Increased ease and speed of preparation and administration is an important clinical advantage for the treatment of an acute and life-threatening condition. It is acknowledged that this may have a direct impact on the efficacy of the product in terms of morbidity and mortality. But no claim of improved efficacy in terms of clinical outcome over the currently available DANTRIUM IV product is accepted, in the absence of comparative clinical data.

Table 3. Model of vial-to-patient timing estimates for a 2.5 mg/kg BW dose of Agilus vs Dantrium IV[1,2,3,4,5]

Patient weight (kg)	Cannula (22G=paed, 16G=adult)	Dose (mg)	No. of Vials		Vial-to-patient time estimates (min:sec)					
					1 Operator		2 Operators		4 Operators	
			Agilus	Dantrium IV	Agilus	Dantrium IV	Agilus	Dantrium IV	Agilus	Dantrium IV
3	22G	7.5	1	1	1:43	3:32	1:43	3:32	1:43	3:32
12	22G	30	1	2	1:46	7:40	1:46	4:02	1:46	4:02
48	22G	120	1	6	1:57	24:12	1:57	12:06	1:57	8:04
	16G				1:53	18:00	1:53	9:00	1:53	6:00
72	22G	180	2	9	3:47	36:18	1:57	20:10	1:57	12:06
	16G				3:43	27:00	1:53	15:00	1:53	9:00
96	22G	240	2	12	3:54	48:24	1:57	24:12	1:57	12:06
	16G				3:46	36:00	1:53	18:00	1:53	9:00
120	22G	300	3	15	5:44	60:30	3:47	32:16	1:57	16:08
	16G				5:36	45:00	3:43	24:00	1:53	12:00
144	22G	360	3	18	5:51	72:36	3:54	36:18	1:57	20:10
	16G				5:39	54:00	3:46	27:00	1:53	15:00

[1] Timings from Study No. TR21/025, in which the vial preparation/administration process was simulated using the following steps:
1) Dantrolene vial and WFI syringe/needle preparation process; 2) Reconstitution process; 3) Reconstituted dantrolene solution draw-up process; 4) Administration via a cannula (22G cannula for paediatrics or 16G cannula for adults) process. Additional steps are required for Dantrium IV, as use of a filter needle is required.

[2] Preparation/Administration Time per vial = 'Average Total Time'. Where less than a complete vial was required to make up the required mg dose, for that vial: Preparation/Administration Time per vial = 'Average Total Time' less the proportion of non-relevant 'Average Recorded Time for Administration through 22G cannula for paediatrics or through 16G cannula for adults'.

[3] Assumes patient has two venous access points.

[4] In the case of multiple operators, vial preparation and administration overall 'start-to-finish' times are assumed, with no assumptions for overlap of vial preparation/administration times across operators.

[5] Modelled using a 360 mg dose for 144 kg patient, i.e., no EMHG guideline 300 mg cap on initial dose

It is clear that early recognition of MH, early discontinuation of triggering agents, effective supportive care (including temperature control and general intensive care measures), are in addition to early treatment with dantrolene, important factors for reduced mortality in MH. It is obvious that outcome has improved over time, with the currently available dantrolene formulation. Important contributing factors are likely the increased awareness of MH and widespread use of endtidal-CO_2 and continuous temperature monitoring that facilitates early detection, coupled with improved general supportive care.

Early administration of dantrolene has been associated with better outcomes in the treatment of MH and the Applicant refers to two studies: In a Canadian case series, the relation between increased dantrolene administration time and the risk for complications was presented (39).

Unfortunately, the support for the importance of dantrolene preparation time from this study is very weak for the following reasons:

- It is a selection of 16 patients from a case series 129 MH cases.
- The "administration time" is the time from first symptom to first dose. This is not equivalent to dantrolene preparation time. The measured times also include doctors delay and the time needed to fetch the dantrolene vial. The time variable therefore does not isolate preparation time.
- 16 patients have been divided into 5 categories. It is evident that the number of patients in each category is low. The absence of a presentation on number of patients in each category, or any acknowledgement of uncertainty, weakens this data as support for the importance of preparation time.
- The cases were collected over a 20 years' period. Calendar time has not been taken into account and may be an obvious confounder for this correlation.

In another US case series of 152 MH patients during the period 2007-2013, the time between first symptoms and dantrolene administration was extracted from 123 cases (40). 30 cases had serious complications (or death) in association with the MH episode. The authors report the following:

> *There were 14 cases in which administration of dantrolene occurred more than 100 minutes after recognition of the first sign of MH. Plotting time from the first MH sign to administration of dantrolene showed that these cases were separated from the rest by ten minutes or more. In eight of these cases sinus tachycardia, elevated temperature, or hypercarbia was the first sign of MH noted. In the other six cases the first signs of MH noted included masseter muscle rigidity, generalized rigidity, hyperkalemia and decreased level of consciousness Furthermore, in nine of these 14 cases the first sign of the MH episode was not noticed until more than 100 minutes after the induction of anesthesia. In two of these cases, the first symptoms of MH did not present or were not recognized until the patient was in the intensive care unit postoperatively. In these two cases, in which positive pressure ventilation was continued after leaving the OR, dantrolene was given 137 and 240 minutes after the first sign of MH.*

The benefit of the new formulation in terms of reduced preparation time and reduced fluid volume is agreed but difficult to quantify. The reduction of preparation time is especially modest in the youngest age group.

2.5.5.2.4. Recrudescence

Effects of IV dantrolene are not expected to last beyond half-life. The biological half-life in plasma is generally 5 and 9 hours, although half-lives as long as 12.1±1.9 hours have been reported after a single iv dose (43).

In a large case series recrudescence was described in 24% (58/244 cases) (33). The initial dose of dantrolene used was not associated with the development of recrudescence. In another large case series 14.4% of 264 paediatric patients (of which 193 were treated with dantrolene) had recrudescence (38), with no difference observed across the age cohorts.

The currently proposed dose for treatment of recrudescence is in line with the European treatment guideline (EMHG) (15). But it is also noted that the Guideline from the Association of Anaesthetists provides a different recommendation (12):

> "*If recrudescence does occur, further bolus doses of dantrolene should be administered. If they are required within 6 h of the initial reaction, 1 mg.kg^{-1} should be used in the first instance but if it is more than 6 h since the previous dose of dantrolene, 2-3 mg.kg^{-1} should be used.*"

The Applicant has, however, adequately justified the use of the EMHG guideline as basis for the dose recommendation. The recommended repeat bolus dose of 1 mg/kg every 5 minutes in the UK is essentially equivalent to the repeat bolus dose of 2.5 mg/kg every 10 minutes recommended by EMHG.

2.5.6. Discussion on clinical efficacy

The AGILUS development programme has focused on the change introduced as compared to the reference product DANTRIUM IV in the formulation, where HP-β-CD and Macrogol are substituted for mannitol and sodium hydroxide. MH is a rare and fulminant unexpected reaction to anaesthesia; controlled clinical trials in MH patients are unfeasible and unethical. No clinical study in MH has therefore been provided or is considered required. The assessment of clinical efficacy in this application therefore rests on a PK bridge to the reference product and additional support from literature data and international consensus treatment guidelines.

Efficacy of dantrolene to reduce mortality and morbidity from MH is accepted based on the bridge to the reference product, results from preclinical disease models, and the collected clinical experience expressed in case series and consensus guidelines. While it is difficult to provide a quantitative estimate of the impact on mortality, it is accepted as substantial based on available data, published clinical experience, and well-established treatment guidelines.

The Applicant proposal to define the target age group as "…in adults and children of all ages" is acceptable for treatment with dantrolene. It is considered implicit for the reference product. Literature references provide support for use of dantrolene also in <2 years of age and the proposed posology has been used in reported cases in this age group.

While the benefit of the active substance dantrolene is not questioned, the focus for the benefit-risk discussion in this application is on the balance between benefit from the new formulation that permits faster and easier reconstitution and preparation of the dose, and consequently more rapid administration and lower fluid volume, against potential safety concerns with the new excipient(s).

The reduction of preparation time is most notable for higher body weight and correspondingly higher doses. The reduction of preparation time is in small children modest but remains relevant from a clinical perspective.

2.5.7. Conclusions on the clinical efficacy

The Clinical efficacy of dantrolene is accepted as substantial in terms of reduced mortality, based on the PK bridge to the reference product and other supportive evidence. The benefit of the new formulation in terms of more rapid administration and lower fluid volume is accepted but difficult to quantify and is least apparent in small children. It is, however, accepted that the reduced preparation time may translate into a direct impact on mortality and morbidity in all age groups.

2.5.8. Clinical safety

The safety characterisation of the substance dantrolene mainly rests on the PK bridge to the established safety profile of the reference product. Experience and potential safety concerns with dantrolene have been reported in the form of case reports and case series, some of them from specific MH disease registers. The age of the dantrolene-treated patients with MH in the literature review

ranged from 7 weeks to 90 years, 210 patients with MH were included in the review of case studies, and of these, 91 patients (43.3%) were under 18 years old, with a range across all age groups of 8 days to 82 years.

The key potential safety concerns in this application are related to the change in the formulation, where HP-β-CD and Macrogol 3350 are substituted for mannitol and sodium hydroxide.

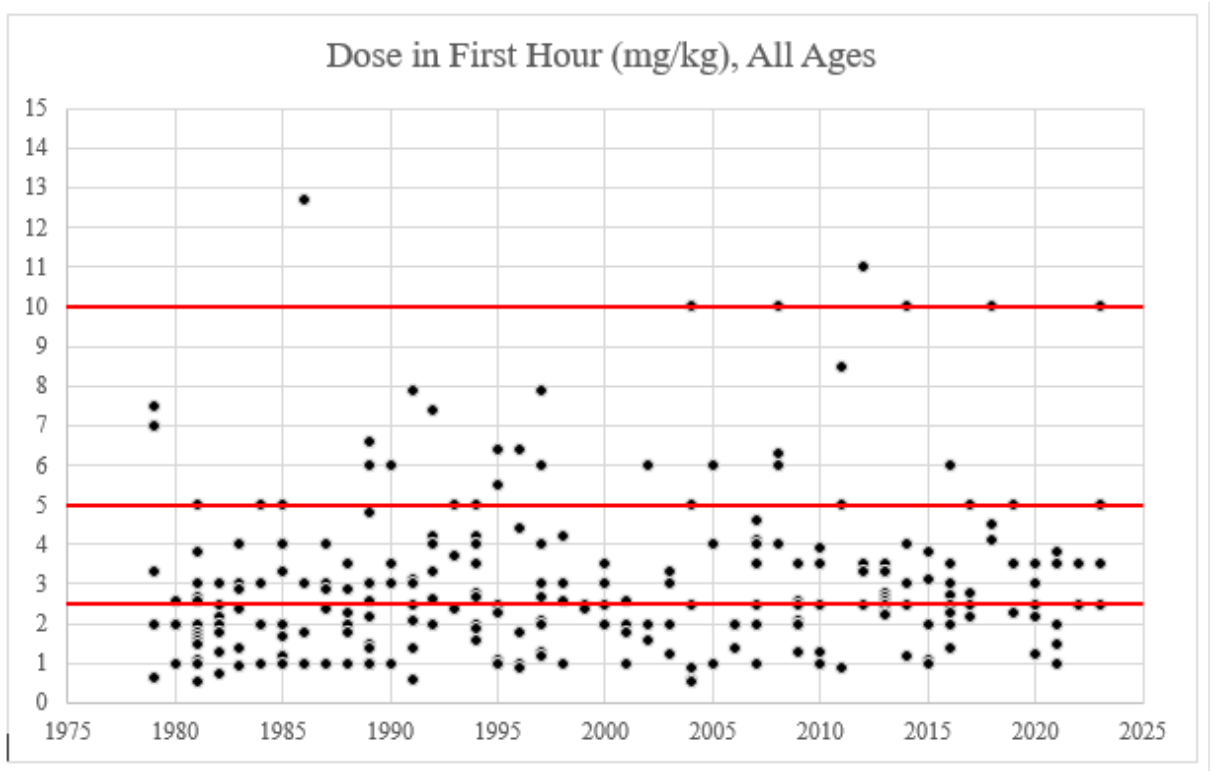
2.5.8.1.1. Excipient HP-β-CD

The posology of NPJ5008 recommends a starting dose of 2.5 mg/kg, and a cumulative dose of 10 mg/kg or more may be required.

From a review of case reports, a total dose of 10 mg/kg body weight per 24 h is sufficient in most cases but may in some rare cases need to be exceeded. This is largely in line with the EMHG guidance. The review of case reports indicates that in 9% of patients the dose over the first 24 hours exceeded 10 mg/kg, and in 2% this dose exceeded 15 mg/kg. When 18 more recent case reports from the period September 2020 to February 2023 were reviewed the doses administered did not exceed 8.5 mg/kg during the first 24 hours. For the discussion of potential clinical safety concerns related to HP-β-CD exposure it should be acknowledged that approximately 1/10 patients may be expected to receive dantrolene doses exceeding 10 mg/kg. A 10 mg/kg dose of Agilus results in an exposure to HP-β-CD of approximately 300 mg/kg.

In a review of 261 cases there were 35 cases <2 years old and 40 cases 2-6 years old. Looking at the dose they required during the first hour, a dose >10 mg/kg was rare (see Fig. 2 below).

Figure 2: Dantrolene dose (mg/kg) administered in first 1-hour period of dosing in 261 published MH case reports in all ages, by year.



The amounts of HP-β-CD expected with the proposed posology are above the lowest observed event levels (LOELs) for cyclodextrins mentioned in the European Commission guidance on excipients. As administration of anaesthetics triggering MH should not be repeated, it can, however, be assumed that this will represent the patient's lifetime dose of NPJ5008.

The use of cyclodextrins as excipients in pharmaceutical products is discussed in the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1) together with its annex (EMA/CHMP/302620/2017 Rev. 1), questions and answers (EMA/CHMP/495747/2013) and supporting report (EMA/CHMP/333892/2013). In its review of literature, the CHMP supporting report finds that in animals, HP-β-CD and SBE-β-CD at high doses (>300 mg/kg) can cause vacuolation of the kidney tubular cells without loss of kidney function. In clinical studies where patients were exposed to HP-β-CD, either as the therapeutic agent (NPC1 studies) or as an excipient, there were no reports of adverse effects on renal function. Exposure to HP-β-CD from Agilus is, however, expected to be higher in patients with renal impairment, and the potential risks associated with HP-β-CD may be higher in these patients.

The CHMP supporting report also finds that amounts of approximately 250 mg/kg/day of HP-β-CD are reported to be safe in humans older than two years when given for 21 days. A possible risk to young infants is described, in relation to the lower glomerular filtration rate in this age group, although it is also noted that in a few case reports, the use of IV products with high doses of HP-β-CD and SBE-β-CD in neonates and young children did not result in signs of toxicity. The report points out that although there is considerable experience with cyclodextrin-containing parenteral products such as voriconazole and itraconazole in adults (SBE-β-CD and HP-β-CD, respectively) these products are not indicated in paediatric patients under 2 years of age and so there is little data available in this age group. The IV formulation of voriconazole contains SBE-β-CD, and IV formulation of itraconazole contains HP-β-CD. VFEND (voriconazole) contains 3200 mg cyclodextrin for 200 mg of voriconazole. It should be acknowledged that the dose of HP-β-CD provided with approved voriconazole products is lower and administered over longer time compared to the proposed posology of NPJ5008. The recommended voriconazole loading dose is 6 mg/kg every 12 hours during the first 24 hours. This means that a 6 mg/kg voriconazole dose is associated with approximately 100 mg/kg cyclodextrin. This is higher than the cyclodextrin dose resulting from a 2.5 mg/kg dose of NPJ5008 but lower than from a 10 mg/kg dose of NPJ5008. The safety and efficacy of VFEND in children below 2 years has not been established and hypoacusis is labelled as an uncommon adverse reaction.

In a study of itraconazole 33 children received a single dose of 100 mg/kg HP-β-CD administered as a constant-rate IV infusion over 1 hour. Concentrations of HP-β-CD fell below quantifiable limits by 12 hours. The age group 6 months–2 years appeared to have a higher AUC_{24} and $T_{1/2}$, and a lower C_{max} compared to other age groups. The apparent differences related to age which the Applicant suggests is caused by individual outliers. It is unclear if there are relevant age-dependent differences in expected HP-β-CD exposure levels.

There is also potentially relevant clinical data from treatment with HP-β-CD both intrathecally and IV in patients with Niemann-Pick Type C1 (NPC1) disease. In a Phase 1, randomized, double-blind, parallel group study 13 adult subjects with NPC1 received either 1500 mg/kg or 2500 mg/kg HP-β-CD IV over 8-9 hours every 2 weeks for a total of 7 doses (14 weeks). 10 subjects completed the study; 6 subjects at the 1500 mg/kg dose and four subjects at the 2500 mg/kg dose. Two subjects withdrew after meeting a stopping rule related to hearing loss. The most common TEAE 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 group.

While the total dose in this study with NPC1 patients (44) was notably higher than the 450 mg/kg provided with NPJ5008 in a 15 mg/kg dantrolene dose, the HP-β-CD plasma concentration-time profile is expected to be substantially different due to a substantially faster administration rate of HP-β-CD in the treatment of MH (i.e., IV injection) compared to the study in NPC1 patients (i.e., IV infusion over 8-9 hours). While the total dose delivered with the proposed posology of NPJ5008 in MH are 3- to 4-fold lower compared to those used in NPC1 and is expected to result in a substantially lower exposure over 24 hours (i.e., lower AUC parameter), the substantially different concentration-time profiles create uncertainty regarding consequences for the magnitude of risk for both nephrotoxicity and ototoxicity. If the latter is related to transition of HP-β-CD to the intrathecal compartment, then the high infusion rate (in spite of a notably lower total 24-hour dose) could be a concern.

To address this concern the Applicant has combined data from the literature and PK/PD-modelling with the aim to establish a threshold for HP-β-CD plasma exposure associated with hearing impairment and then compare this to the predicted HP-β-CD plasma exposures following Agilus IV administration in

clinically relevant doses for the treatment of MH. No such clear binary threshold value for C_{max} or AUC from HP-β-CD exposure related to hearing impairment incidence could be demonstrated. The data indicate a high degree of cross-over in HP-β-CD exposure in relation to hearing impairment.

The results from trials with treatment of NPC1 are the only relevant clinical data available to assess the risk for hearing impairment. Interpretation for the MH context is, however, clearly challenging:

(a) Hearing impairment is also a feature of the disease in NPC1. This means that development/worsening of hearing impairment may be a consequence of the disease, but also that treatment with HP-β-CD may improve hearing impairment caused by the disease.

(b) Cognitive impairment may be a feature of NPC1, further hampering evaluation of hearing impairment.

(c) The HP-β-CD clinical dose range used in the treatment of NPC1 is narrow, mainly 1000-3000 mg/kg.

(d) The number of patients with HP-β-CD exposure monitored in a clinical setting is low and the number of cases that developed hearing impairment is very low.

Of 178 NPC1 subjects monitored in clinical trials for hearing impairment after treatment with HP-β-CD, in 9 subjects (5%) hearing impairment was reported. In 8 out of these 9 subjects the hearing impairment resolved a few weeks after cessation of treatment, was of slight to mild severity, not considered a SAE and/or not clinically noticeable by the subject or their guardian. In these 9 subjects HP-β-CD doses ranged from 1500 to 2500 mg/kg. That hearing impairment was observed in few of the exposed patients and was in most cases temporary and not severe. This is to some extent reassuring but must be contextualised against the exposure levels from the HP-β-CD exposure expected during treatment with the MH posology.

To elaborate on this, the Applicant has reviewed the literature available on PK for HP-β-CD following IV administration, and as a complement, developed two simulation models. The predicted HP-β-CD C_{max} are approximately 300 µg/mL after a single 2.5 mg/kg Agilus dose, 800-1000 µg/mL after a single 10 mg/kg Agilus dose, and 1100-1500 µg/mL after a single 15 mg/kg Agilus dose. These C_{max} levels are comparable to but not higher than those identified in the literature review of treatment of NPC1 with HP-β-CD.

Figure 3. Box-plot based on C_{max} data from the allometric and glomerular filtration rate model, where the distributions of C_{max} have been plotted in relation to hearing impairment. All subjects provided in the raw data have been included (note that duplicate records may exist). Red dots indicate individual observations. There is a clear overlap of C_{max} distributions and no dose-response related to C_{max} can be claimed with any certainty.

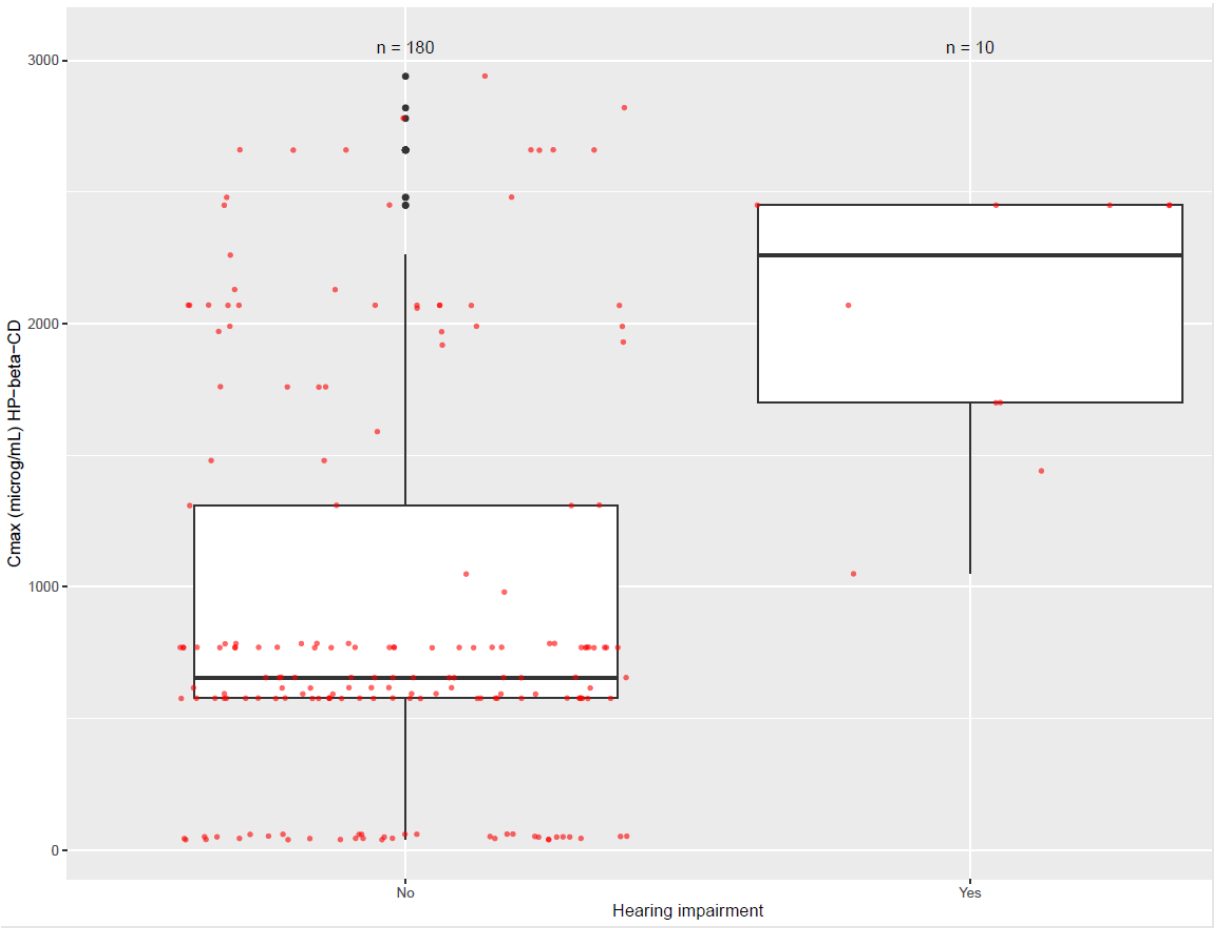
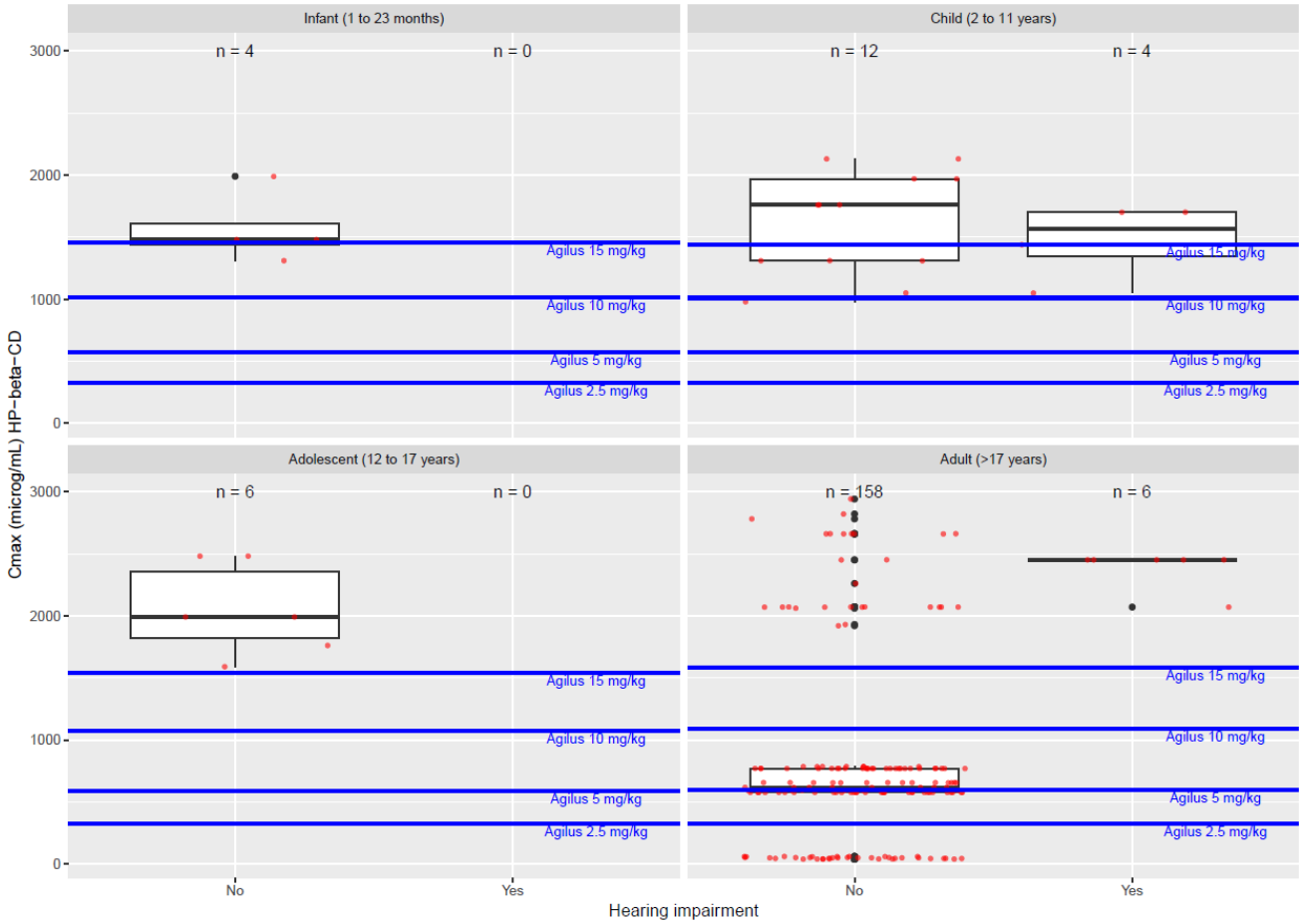

n = 180
n = 10
3000
2000
1000
0
Cmax (microg/mL) HP−beta−CD
No
Yes
Hearing impairment

Figure 4. Box-plot based on C_{max} data from the allometric and glomerular filtration rate model. The distributions of C_{max} have been plotted in relation to hearing impairment, with age groups in separate panels. All subjects provided in the raw data have been included (note that duplicate records may exist). Red dots indicate individual observations. Simulated expected C_{max} levels of HP-β-CD from proposed Agilus doses are indicated with blue lines.



With the available data, it is not possible to determine a threshold HP-β-CD level for the risk of hearing impairment. The predicted exposure levels in terms of C_{max} is comparable to those observed when HP-β-CD is used for the treatment NPC1, but importantly not higher. The HP-β-CD exposure resulting from the higher end of proposed Agilus posology may be compatible with a risk for hearing impairment, but it is not possible to further quantify this risk with the available data or any data possible to attain pre-marketing. The C_{max} levels associated with the few cases of observed hearing impairment are above those expected from a 10 mg/kg dose of Agilus, which is to some extent reassuring.

It has not been possible to determine the relation between specific PK parameters and the risk for hearing impairment in non-clinical studies. This adds to the uncertainty of the assessment. The major theoretical concern is, however, for $C_{max.}$ The dose of HP-β-CD used in the NPC1 studies is clearly higher than in the treatment of MH but administered over a substantially longer period (8-12 hours). The AUC and the cumulative exposure predicted with the MH posology are therefore also substantially lower compared to treatment of NPC1.

It is also reasonably reassuring that the cases of hearing impairment observed in the NPC1 studies have mostly been transient and mild and have mainly occurred in conjunction with HP-β-CD C_{max} levels at or above those predicted from a 10 mg/kg Agilus dose.

2.5.8.1.2. Excipient Macrogol 3350

A 2.5 mg/kg dose of AGILUS contains 8.3 mg/kg of Macrogol; therefore 10 mg/kg of AGILUS will contain 33.3 mg/kg. As mentioned above, any treatment with NPJ5008 is likely to represent a lifetime dose in a period of approximately 48 h or less. Macrogol is predominantly marketed as an oral osmotic agent for the treatment of constipation and is not included in the Commission guideline on excipients referenced above.

There have been reports relating Macrogol 3350 to hypersensitivity reactions. No hypersensitivity reactions were observed in the relative bioavailability study (Study NPJ5008-01/2020) that were conducted with AGILUS.

2.5.8.2. Patient exposure

The only exposure to the product is in the relative bioavailability study (Study NPJ5008-01/2020), please see section 3.3.7.3.1 below.

2.5.8.3. Adverse events

The adverse effect most frequently reported in the literature following treatment with dantrolene is muscle weakness, which is directly related to its mode of action as a skeletal muscle relaxant.

2.5.8.3.1. Safety reported in bioavailability study (NPJ5008-01/2020)

This was a phase I single centre, 2-part, part-randomised, open-label, IV, single dose study in healthy male and female subjects. Part 1 of the study was a bioequivalence assessment of AGILUS vs the DANTRIUM IV reference product in subjects weighing at least 55 kg at a dose of 60 mg dantrolene. On a mg/kg basis, the subjects received a range of doses of AGILUS of 0.56 to 0.97 mg/kg.

All subjects in Study NPJ5008-01/2020 reported AEs during the study after dosing with AGILUS and DANTRIUM IV. A similar profile of AEs was reported following dosing with AGILUS and the reference product DANTRIUM IV. Nervous system disorders, musculoskeletal disorders and eye disorders were the most commonly reported AEs in both parts of the study. No serious AEs were reported.

Table 4. Incidence of Adverse Events: Safety Analysis Set (Part 1 of the study)

	60 mg NPJ5008 IV (N=16)			60 mg DANTRIUM IV (N=16)		
	n	(%)	Total Number of Events	n	(%)	Total Number of Events
Subjects reporting TEAEs	16	(100)	61	15	(93.8)	49
Nervous system disorders	15	(93.8)	27	15	(93.8)	23
Dizziness	14	(87.5)	14	14	(87.5)	14
Dysarthria	6	(37.5)	6	6	(37.5)	6
Headache	2	(12.5)	3	0		0
Somnolence	1	(6.3)	1	2	(12.5)	2
Balance disorder	2	(12.5)	2	0		0
Dysgeusia	0		0	1	(6.3)	1
Hypoaesthesia	1	(6.3)	1	0		0
Musculoskeletal and connective tissue disorders	9	(56.3)	9	11	(68.8)	11
Muscular weakness	8	(50.0)	8	9	(56.3)	9
Arthralgia	1	(6.3)	1	0		0
Limb discomfort	0		0	1	(6.3)	1
Pain in extremity	0		0	1	(6.3)	1
Eye disorders	9	(56.3)	10	7	(43.8)	8
Vision blurred	9	(56.3)	10	6	(37.5)	7
Visual impairment	0		0	1	(6.3)	1
General disorders and administration site conditions	4	(25.0)	5	2	(12.5)	4
Catheter site related reaction	1	(6.3)	1	1	(6.3)	1
Feeling cold	1	(6.3)	1	1	(6.3)	1
Infusion site discomfort	1	(6.3)	1	1	(6.3)	1
Fatigue	1	(6.3)	1	0		0
Feeling hot	1	(6.3)	1	0		0
Infusion site pain	0		0	1	(6.3)	1
Respiratory, thoracic and mediastinal disorders	3	(18.8)	3	2	(12.5)	2
Dyspnoea	3	(18.8)	3	2	(12.5)	2
Gastrointestinal disorders	3	(18.8)	3	1	(6.3)	1
Abdominal discomfort	0		0	1	(6.3)	1
Flatulence	1	(6.3)	1	0		0

	60 mg NPJ5008 IV (N=16)			60 mg DANTRIUM IV (N=16)		
	n	(%)	Total Number of Events	n	(%)	Total Number of Events
Nausea	1	(6.3)	1	0		0
Vomiting	1	(6.3)	1	0		0
Vascular disorders	3	(18.8)	3	0		0
Flushing	2	(12.5)	2	0		0
Hot flush	1	(6.3)	1	0		0
Skin and subcutaneous tissue disorders	1	(6.3)	1	0		0
Cold sweat	1	(6.3)	1	0		0

Subjects received 60 mg NPJ5008 and 60 mg DANTRIUM IV in a randomised manner at a separate dosing n is the number of subjects reporting at least 1 event

Part 2 of the study was a safety arm in a separate group of subjects that planned to assess higher doses of 120 mg (i.e. up to approximately 2.2 mg/kg) of NPJ5008. Part 2 planned to enrol 10 subjects but stopped after 5. While no study stopping criteria had been met, there appeared to be an increased number of AEs per subject and increased severity of AEs as the dose of AGILUS increased from 60 mg to 120 mg. The study was therefore stopped early after 5 subjects had received the 120 mg NPJ5008 dose. Consequently, no subjects received the planned 240 mg AGILUS. The subjects received a range of doses in Part 2 of 1.29 to 1.43 mg/kg.

Overall, the majority of AEs reported in the study were mild. However, in Part 1, 3 moderate AEs were reported after dosing with 60 mg AGILUS (two AEs of muscular weakness assessed as being related to IMP and one of headache assessed as being unrelated to IMP), and one moderate AE of muscular weakness reported after dosing with 60 mg DANTRIUM IV, which was assessed as related to the IMP. In Part 2, 5 moderate AEs, all of which were related to the IMP, were reported after dosing with 120 mg NPJ5008 (3 of dizziness and 2 of muscular weakness) and one severe AE of muscular weakness was reported which was related to the IMP and expected.

Muscle weakness related AEs, together with their speed and frequency of occurrence and dose dependency, indicate the desired pharmacological action and do not represent a safety concern for the use of AGILUS in the intended indication, in which patients will be under intensive care.

2.5.8.4. Serious adverse event/deaths/other significant events

Hepatitis has been described as a side effect of the medication after prolonged use and at doses of more than 100 mg/d mainly in adults. This is not expected to be a major concern in the MH indication but has also been described after shorter treatment durations. In a case report of a patient in which the drug was used for sympathetic overactivity in the PICU the child developed asymptomatic hepatitis on day 3 after starting the medication at a dose much lower than previously described [14].

2.5.8.5. Safety in special populations

2.5.8.5.1. Paediatric patients

In the Applicants analysis of case reports, valid such reports were identified in all paediatric groups, totalling 91/210 (43.3%) of all case reports. Paediatric patients who received IV dantrolene ranged in age from 8 days

to 82 years, with a median age of 32 years in the adult group. The majority were male in both the adults and paediatric populations. The median initial dose of 2.40 mg/kg in 18 years and over and the median range of 2.05 – 3.00 mg/kg in paediatric groups are similar to the 2.5 mg/kg dose recommended for all adults and children of all ages. Death from MH was 4.4% and 3.4% for the paediatric and adult populations respectively, in total. Death due to any cause (where data available) was reported as 5% for the 1-23 months old.

Excipient HP-β-CD

The CHMP supporting report on cyclodextrins used as excipients (9 October 2017, EMA/CHMP/333892/2013) finds that amounts of approximately 250 mg/kg/day of HP-β-CD are reported to be safe in humans older than two years when given for 21 days. A possible risk to young infants is described, in relation to the lower glomerular filtration rate in this age group, although it is also noted that in a few case reports, the use of IV products with high doses of HP-β-CD and SBE-β-CD in neonates and young children did not result in signs of toxicity. The report points out that although there is considerable experience with cyclodextrin-containing parenteral products such as voriconazole and itraconazole in adults (SBE-β-CD and HP-β-CD, respectively) these products are not indicated in paediatric patients under 2 years of age and so there is little data available in this age group.

The IV formulation of voriconazole contains SBE-β-CD, and IV formulation of itraconazole contains HP-β-CD. VFEND (voriconazole) contains 3200 mg cyclodextrin for 200 mg of voriconazole. It should be acknowledged that this dose of HP-β-CD provided with approved voriconazole products is lower and administered over longer time compared to HP-β-CD exposure from NPJ5008. The recommended voriconazole loading dose is 6 mg/kg every 12 hours during the first 24 hours. This means that a 6 mg/kg voriconazole dose is associated with approximately 100 mg/kg cyclodextrin. This is lower than the cyclodextrin dose resulting from a 10 mg/kg dantrolene dose of NPJ5008 (300 mg/kg HP-β-CD). The safety and efficacy of VFEND in children below 2 years has not been established. Hypoacusis is labelled as an uncommon adverse reaction.

The paediatric clinical data from treatment of NPC1 with HP-β-CD is very limited. Among 16 children in the age group, 2-11 years some degree of hearing abnormality was observed in 4 children. C_{max} levels were above those expected from a 10 mg/kg Agilus dose. Only few exposed children <2 years of age could be identified in the literature.

There remains a concern that safety of the proposed HP-β-CD exposure in children, in particular but not limited to those <2 years of age, is not well characterised. The review of available data has, however, not strengthened a particular safety concern for the youngest age group.

2.5.8.5.2. Reduced renal function

The excipient HP-β-CD is almost entirely excreted renally intact. A warning is therefore provided in section 4.4 in the SmPC.

2.5.8.6. Post marketing experience

No post-marketing data is available as NPJ5008 has not yet been marketed in any country.

2.5.9. Discussion on clinical safety

The safety characterisation of the active substance dantrolene mainly rests on the PK bridge to the established safety profile of the reference product. The key question for the assessment of safety in this application concerns potential safety concerns related to the change in the formulation, where hydroxypropyl beta cyclodextrin (HP-β-CD) and Macrogol 3350 are substituted for mannitol and sodium hydroxide. The relative bioavailability study (NPJ5008-01/2020) does not add relevant safety data. It reflects a clinically irrelevant dose of both the active substance dantrolene and the new excipients and is not sufficiently sensitive to detect any differences in safety profile between the two products, especially since the majority of patients as expected experience adverse reactions at the lowest dose.

The quantity of the new excipient HP-β-CD in an initial 2.5 mg/kg dose of NPJ5008 is more than the threshold described in the annex to the European Commission guideline on excipients. The proposed posology for NPJ5008, in line with the European clinical MH guideline, states that in most patients 10 mg/kg dantrolene is usually sufficient, but some patient may need a higher dose. Looking at the dose they required during the first hour, a dose >10 mg/kg was rare. The safety evaluation concerning HP-β-CD is therefore mainly focused on a HP-β-CD dose of up to 300 mg/kg (corresponding to 10 mg/kg dantrolene), administered in less than one hour.

HP-β-CD and hearing impairment

From a non-clinical point of view, the submitted data is sufficient to determine that a risk of substantial and possible irreversible effects on the auditory function from HP-β-CD exposure cannot be excluded. It has not been possible to determine the relation between specific PK parameters and the risk for hearing impairment in non-clinical studies.

The available clinical data on HP-β-CD exposure from use in other medicinal products and from treatment of Niemann-Pick Disease Type C1 (NPC1) are of interest. The exposure from IV formulations of itraconazole and voriconazole is higher than the cyclodextrin dose resulting from a 2.5 mg/kg dose of NPJ5008 but lower than from a 10 mg/kg dose of NPJ5008. Hypoacusis is labelled as an uncommon adverse reaction to the voriconazole formulation with HP-β-CD. The safety and efficacy of voriconazole products in children below 2 years has not been established.

In studies where HP-β-CD has been used for treatment of NPC1 intrathecal administration of HP-β-CD has been associated with hearing loss. The risk for hearing loss appears greater with intrathecal administration compared to IV administration. Only few cases have been reported after intravenous administration. The hearing impairment was then in most instances temporary and not severe. This is to some extent reassuring but must be contextualised against the exposure levels from the HP-β-CD exposure expected during treatment with the MH posology.

While the 24 hour HP-β-CD dose has been 3- to 4-fold higher in the treatment of NPC1 than the expected exposure with NPJ5008, the dose has in NPC1 patients been delivered over 8-9 hours resulting in substantially different concentration-time profiles. The concentration-time profiles will therefore be substantially different and a high C_{max} was therefore a potential concern in the MH setting.

When combining data from the literature and PK-modelling it was not possible to determine a HP-β-CD exposure threshold for the risk of hearing impairment. The predicted exposure levels in terms of C_{max} are comparable to those observed when HP-β-CD is used for the treatment NPC1, but not higher. The HP-β-CD exposure resulting from the higher end of proposed NPJ5008 posology may be compatible with a relevant risk for hearing impairment, but it is not possible to further quantify this risk with the available data or any data possible to attain pre-marketing. The C_{max} levels associated with hearing impairment are above those expected from a 10 mg/kg dose of NPJ5008. It is, however, reasonably reassuring that the cases of hearing impairment observed in the NPC1 studies have mainly occurred in conjunction with HP-β-CD C_{max} levels at or above those predicted from a 10 mg/kg Agilus dose. These cases of hearing impairment have also mainly been temporary and mild. A warning related to potential hearing impairment is provided in the product information.

HP-β-CD and potential effects on the kidney

Non-clinical studies have also indicated vacuolisation in renal tubule cells following HP-β-CD exposure. In clinical studies where patients were exposed to HP-β-CD, either as the therapeutic agent (NPC1 studies) or as an excipient, there were no reports of adverse effects on renal function. Exposure to HP-β-CD from Agilus is, however, expected to be higher in patients with renal impairment, and the potential risks associated with HP-β-CD may be higher in these patients. A warning is therefore provided in the product information.

2.5.10. Conclusions on the clinical safety

The safety characterisation of the substance dantrolene mainly rests on the PK bridge to the established safety profile of the reference product. It is not a concern. The new excipient HP-β-CD is, however, a potential new safety concern. The dose of the excipient HP-β-CD in this new formulation exceeds the threshold described in EMA guidance documents, is associated with ototoxicity in non-clinical data, and cases of hearing impairment has been observed when HP-β-CD is used for treatment of NPC1 in clinical studies. It is, however, reasonably reassuring that the cases of hearing impairment observed in the NPC1 studies have mainly occurred in conjunction with HP-β-CD Cmax levels at or above those predicted from a 10 mg/kg Agilus dose. These cases of hearing impairment have also mainly been temporary and mild. No other new relevant safety concerns have been identified.

2.6. Risk management plan

The applicant updated RMP version 0.4 with data lock point and date of final sign off on the 13th of February 2024.

2.6.1. Safety concerns

Summary of safety concerns

The applicant identified the following safety concerns in the RMP version 0.4:

Table SVIII.1: Summary of safety concerns

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

2.6.2. Pharmacovigilance plan

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product. A follow-up questionnaire for the characterisation of the important potential risk 'Hearing loss' is agreed. The follow-up questionnaire is accepted considering the need for detailed information to evaluate the safety concern hearing loss. The questionnaire is included in Annex 4 and has appropriate sections on (1) patient details, (2) information regarding the drug including dosage and duration, (3) Information regarding the hearing loss, (4) concomitant drugs and (5) reporter details.

No additional PhV activities are required.

2.6.3. Risk minimisation measures

Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

No additional risk minimisation measures are required.

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

2.6.4. Conclusion

The CHMP considered that the risk management plan version 0.4 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports 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.

Based on the concerns regarding the excipient HP-β-CD, the PRAC Rapporteur is of the opinion that a separate entry in the EURD list for Agilus is needed. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the product information.

2.8. Product information

The attached product information is considered acceptable.

2.8.1. User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. Assessment of the User Testing is attached in Appendix I.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication for Agilus is:

> *In combination with adequate support measures, Agilus is indicated for the treatment of malignant hyperthermia in adults and children of all ages.*

MH is a rare and fulminant unexpected reaction to anaesthesia. The incidence of malignant hyperthermia (MH) events is difficult to estimate but is likely somewhere in the range 1/15 000 to 1/75 000 anaesthetic procedures. These estimates are not easily interpreted because of the difficulty to define the denominator appropriately.

The diagnosis of MH is in the acute phase purely clinical. MH reactions can range from fulminant life-threatening presentations to mild, non-specific symptoms that can go unrecognized. Due to incomplete penetrance of the genetic disorder, MH-susceptible individuals might undergo several anaesthetic procedures that are uneventful prior to developing a fulminant MH reaction. Different MH-causative genetic variants may also generate different sensitivities to different triggering anaesthetic agents, further contributing to the variability in MH clinical presentation.

3.1.2. Available therapies and unmet medical need

The key components in successful management of MH are early recognition, discontinuation of triggers, general supportive care, cooling, and treatment with dantrolene. The rarity of this condition and the acute life-threatening presentation mean that well-established consensus guidelines and institutional treatment protocols are essential.

Dantrolene sodium is a highly lipophilic hydantoin derivative poorly soluble in water. Experimental evidence suggests that dantrolene inhibits the release of calcium in skeletal muscle. It is an established key component in the treatment of MH since 1979. The key feature of this new product, Agilus, is a new formulation that facilitates the dissolution of dantrolene and allows faster preparation and reduced amount of fluid administration. This have been major issues with the currently available formulation.

3.1.3. Main clinical studies

The present application is submitted as a Hybrid Application under Article 10(3) with DANTRIUM IV as reference product. No clinical study in MH patients has been provided or is considered required, as MH is a rare and fulminant unexpected reaction to anaesthesia and controlled clinical trials in MH patients are unfeasible. The development programme of Agilus in this current hybrid application is focused on the change introduced as compared to the reference product DANTRIUM IV in the formulation, where hydroxypropyl beta cyclodextrin (HP-β-CD) and Macrogol 3350 are substituted for mannitol and sodium hydroxide. The applicant has performed one comparative bioavailability study in healthy volunteers, comparing the new drug formulation NPJ5008 (Agilus) and the reference product Dantrium IV. The assessment of clinical efficacy and safety of the dantrolene component in this application therefore rests on a PK bridge to the reference product and additional support from literature data and international consensus treatment guidelines. Non-clinical data is of importance for assessment of safety of the new excipients (HP-β-CD and Macrogol 3350) that are not included in the reference product. For safety evaluation of HP-β-CD, studies where HP-β-CD has been used for treatment of patients with NPC1 are of relevance.

3.2. Favourable effects

Efficacy of dantrolene to reduce mortality and morbidity from MH is accepted based on the bridge to the reference product, results from pre-clinical disease models, and the collected clinical experience expressed in case series and consensus guidelines. The development programme of AGILUS and the current hybrid application, are focused on the change (compared to the reference product DANTRIUM IV) in the formulation, where hydroxypropyl beta cyclodextrin (HP-β-CD) and Macrogol 3350 are substituted for mannitol and sodium hydroxide. The focus for the benefit-risk discussion is on the balance between benefit from the new formulation that permits faster and easier reconstitution and preparation of the dose, and consequently more rapid administration, against safety concerns with the new excipient(s).

The specific benefit with the new formulation is a shorter reconstitution time. The magnitude of this benefit is related to the total amount of dantrolene needed, and consequently dependent on patient weight. For a 3 kg child, a 2.5 mg/kg dose requires 7.5 mg of dantrolene. One vial of the reference product DANTRIUM IV is then sufficient, and the reduction of reconstitution time using Agilus is then 1 minute and 49 seconds, assuming a single operator handles the administration. For a 72 kg patient, approximately 23 minutes shorter reconstitution and administration time of the 9 vials needed is estimated, assuming a single operator. It is accepted that these time savings may have an impact on both morbidity and mortality. The reduction of preparation and administration time is in small children modest but remains from a clinical perspective relevant also in the youngest age group.

3.3. Uncertainties and limitations about favourable effects

There are no data that can provide a direct quantitative estimate of the independent impact of dantrolene on mortality. The fact that dantrolene has contributed substantially to the improved outcome of MH over the years is, however, undisputable. In a North American MH case series reported prior to the availability of dantrolene, mortality was 64%. In a more recent US series of 152 MH cases death occurred in 7%. This dramatic reduction in mortality over time is not solely attributable to dantrolene. The importance of early recognition (and therefore also milder presentations being diagnosed to a larger extent), improved overall understanding of the condition, increased vigilance, widespread use of endtidal-CO_2 and temperature monitoring that facilitates early detection, improved supportive intensive care, and active cooling, are factors that have also likely contributed to improved outcome.

Early administration of dantrolene has in case series been associated with better outcomes in the treatment of MH. It should, however, be recognised that a comparison between early and late treatment in a non-interventional study setting almost always introduces a selection bias from more mild cases being included in

the early treatment group. It is nevertheless acknowledged that early treatment of MH is important and clearly advocated in treatment guidelines.

Favourable effects of AGILUS have been demonstrated by relying for the active substance dantrolene on the bridging to the authorised product Dantrium IV in the bioavailability study NPJ5008-01/2020. Similarity based on usual bioequivalence criteria was shown in terms of overall exposure, whereas AGILUS showed slightly lower peak exposure (C_{max}) than Dantrium IV. There were study drawbacks such as different speed of administration (although possibly inevitable due to difference in administered volumes) and subtherapeutic dose levels, making the study results less informative. Still, the similar exposures as well as conformity of the plasma profiles of the products, support the bridging of efficacy from the reference product. Considering that the individual dose escalation (until improvement of physiological and metabolic abnormalities) should reduce any hypothetical impact of minor differences in peak exposures on efficacy and safety.

In AGILUS, mannitol and sodium hydroxide have been replaced with HP-β-CD and Macrogol 3350, which has led to a decrease in both time for preparation and volume of water needed to dissolve each vial of product. Increased ease and speed of preparation and administration is an important clinical advantage for the treatment of an acute and life-threatening condition. This improvement therefore has the potential to directly impact the efficacy of the product. However, no claim of improved efficacy in terms of clinical outcome over the currently available DANTRIUM IV product is accepted, in the absence of comparative clinical data.

In small children the reduction of reconstitution and administration time is modest. While this reduction is considered clinically relevant the magnitude of benefit in terms of reduced morbidity and mortality cannot be quantified with any acceptable precision. This remains as an uncertainty for the benefit of the new formulation in the youngest age group.

3.4. Unfavourable effects

The safety characterisation of the active substance dantrolene mainly rests on the PK bridge to the established safety profile of the reference product. The reference product was first approved in Austria in 1984. It is currently approved nationally in 10 EU countries, the UK and Switzerland. Experience and potential safety concerns with dantrolene have been reported in the form of case reports and case series, some of them from specific MH disease registers. The adverse effect most frequently reported in the literature following treatment with dantrolene is muscle weakness, which is directly related to its mode of action as a skeletal muscle relaxant. The bioavailability study supports bridging of dantrolene safety from the reference product to the test product. The safety characterisation of the active substance dantrolene is sufficient and is not a concern.

The key safety concern of AGILUS is the risks associated with the new excipient HP-β-CD. According to "*Questions and answers on cyclodextrins used as excipients in medicinal products for human use*" (EMA/CHMP/495747/2013 published October 2017), the threshold for parenterally administrated HP-β-CD is 200 mg/kg/day for >2 weeks of usage. An Agilus dose level of up to 10 mg/kg corresponds to up to 300 mg/kg HP-β-CD administered in 50 minutes. There may be additional doses given to treat recrudescence but continued treatment for several days beyond the acute stage is highly unlikely.

With respect to paediatric patients, the guideline states that the major concern in children under 2 years is that the lower glomerular filtration rate can lead to higher blood levels of cyclodextrins, leading to an increase in extra-renal adverse effects. The decreased renal tubular function might reduce the risk of renal toxicity due to lower intra-renal osmotic pressure. However, it is currently not known whether there is a risk of ontogeny-related direct tubular cell toxicity unrelated to osmotic pressure. In clinical studies where patients were exposed to HP-β-CD, either as the therapeutic agent (NPC1 studies) or as an excipient, there are no reports of adverse effects on renal function. Exposure to HP-β-CD from Agilus is, however, expected to be higher in patients with renal impairment, and the potential risks associated with HP-β-CD may be higher in these patients. A warning is therefore provided in the product information.

In the submitted toxicity study, the maximum dose level tested was 10 mg/kg of dantrolene. The current pre-clinical data on toxicology is limited to an exposure corresponding to a dantrolene dose of up to

10 mg/kg. No new safety findings were reported with AGILUS compared to DANTRIUM IV in this study, with the exception of the known class effects associated with the use of HP-β-CD in formulations (reversible kidney changes). The non-clinical program and the literature search is considered sufficient for the particular substance Dantrolene and the use of HP-β-CD regarding the well-known reversible kidney changes.

Based on the clinical experience reported in the literature, ≤10 mg/kg of dantrolene within the first hour is sufficient for most patients. This corresponds to a HP-β-CD exposure of 300 mg/kg. The dose of the excipient HP-β-CD in this new formulation exceeds the threshold described in EMA guidance documents, is associated with ototoxicity in non-clinical data, and cases of hearing impairment has been observed when HP-β-CD is used for treatment of NPC1 in clinical studies. It is, however, reasonably reassuring that the cases of hearing impairment observed in the NPC1 studies have mainly occurred in conjunction with HP-β-CD C_{max} levels at or above those predicted from a 10 mg/kg AGILUS dose. These cases of hearing impairment have also mainly been temporary and mild.

No other new relevant safety concerns have been identified.

3.5. Uncertainties and limitations about unfavourable effects

Hydroxypropyl beta cyclodextrin (HP-β-CD)

The key question for the assessment of safety is potential safety concerns related to the change in the formulation, where hydroxypropyl beta cyclodextrin (HP-β-CD) and Macrogol 3350 are substituted for mannitol and sodium hydroxide.

Several recent publications have investigated the development of HP-β-CD- induced ototoxicity in non-clinical species, but no data can connect plasma exposure of HP-β-CD to the development of ototoxicity. Rat was considered to be the most sensitive species where a single dose of 500 to 1000 mg/kg was considered to be the NOAEL for the development of ototoxicity. At a dose of 2000 mg/kg, significant hearing loss and cochlear damage were observed in rats. No margins to human exposure can be achieved for either C_{max} or AUC and the data suggests that the development of ototoxicity may be both C_{max} related ("all or nothing" response) or AUC related (build-up/accumulative effect), and additionally, with unpredictable individual variability.

Predicted HP-β-CD exposure values have been provided to investigate the level of HP-β-CD exposure associated with the proposed posology. Based on literature data HP-β-CD concentration-time profiles have been simulated (predicted) across all age groups. There is some uncertainty regarding the upper limit of predicted C_{max}. However, given the observed HP-β-CD exposure range and the context for this assessment, the C_{max} predictions are considered acceptable.

While the expected exposure to HP-β-CD in the MH indication is below that observed in cases of hearing impairment in the NPC1 studies, it remains uncertain to what extent there is a risk for hearing impairment following treatment of MH.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The beneficial effect of dantrolene on mortality from MH is considered well established since many decades. This Application, however, concerns a new formulation of dantrolene, providing better solubility and consequently more rapid preparation and lower fluid volume load.

Indeed, the issues related to the currently available formulation of dantrolene are well known: the preparation of the dose needed requires substantial efforts, is time consuming, and may result in delayed emergency treatment and a high fluid load for the patient. The new formulation of AGILUS is therefore potentially a relevant progress for the treatment of MH. Early treatment has been correlated with improved

outcome in case series. Such data should, however, be interpreted with caution. It is based on few case reports and does not isolate the impact of preparation time from other delays. It is still acknowledged that the new formulation could potentially have a beneficial impact on morbidity and mortality, but the magnitude of benefit is difficult to estimate.

The reduction of preparation time is most notable for higher body weight and correspondingly higher doses. The reduction of preparation time is in small children modest but remains relevant from a clinical perspective.

With regards to the safety of AGILUS, there remains some uncertainty regarding the potential safety concern from exposure to the new excipient HP-β-CD. The assessment is based on non-clinical data, EMA regulatory guidance, experience from approved IV products containing HP-β-CD, results from clinical studies where HP-β-CD has been used to treat patients with NPC1, and modelling of expected exposure of HP-β-CD with the recommended doses of Agilus in the treatment of MH. Taken together it is considered sufficiently reassuring that in the admittedly few available observed clinical cases of hearing impairment in patients with NPC1 it has mostly been mild and transient, and these cases have had higher HP-β-CD exposure levels than expected from use of Agilus in the treatment of MH. A warning is provided in section 4.4 of the SmPC. Hearing loss is an important potential risk in the RMP and there is a targeted follow-up questionnaire for spontaneous case reports to further characterise this potential risk in the post-marketing setting.

3.6.2. Balance of benefits and risks

The benefit-risk balance for the active substance dantrolene is clearly favourable in the treatment of malignant hyperthermia. The new formulation has an identical target population but shortens the preparation and administration time and limits fluid volume. This is accepted as a benefit with a potential to improve morbidity and mortality. There is, however, an important potential risk for ototoxicity associated with the new excipient HP-β-CD. The Applicant has committed to undertake additional development work for a new formulation of the medicinal product that does not contain the excipient HP-β-CD. The development will include a detailed feasibility analysis of available alternatives, which will involve formulation work and could require additional non-clinical and clinical studies. Based on the development experience with AGILUS, the Applicant estimates that it will likely take approximately five years to develop an alternative formulation of the medicinal product that does not contain the excipient HP-β-CD. The Applicant is required to submit annual progress reports to the EMA during the development program.

Therefore the CHMP recommends the following:

Description of post-authorisation measure(s)
The MAH should undertake additional development work for a new formulation of the medicinal product that does not contain the excipient HP-β-CD. The development will include a detailed feasibility analysis of available alternatives, which will involve formulation work and could require additional non-clinical and clinical studies. This attempt to develop an alternative formulation of the medicinal product that does not contain the excipient HP-β-CD should be finalised within five years. The Applicant is required to submit annual progress reports to the EMA during the development programme.

3.6.3. Additional considerations on the benefit-risk balance

For the assessment of the new formulation of dantrolene the clinical utility of the product must also be acknowledged. This antidote needs to be stored at every anaesthesia department for the very uncommon event of MH.

A further complication to the evaluation of the benefit-risk balance is that it is not possible to verify the MH diagnosis in the acute situation. Diagnosis is then purely clinical based on suspicion, and guidelines advocate early treatment. This means that many patients may be treated with dantrolene without having a true MH reaction.

3.7. Conclusions

The overall benefit/risk balance of AGILUS is positive, subject to the conditions stated in section 4 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of AGILUS is favourable in the following indication:

In combination with adequate support measures, Agilus is indicated for the treatment of malignant hyperthermia in adults and children of all ages.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation 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.

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