22 April 2024
EMA/OD/0000102465
EMADOC-360526170-1928036
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Agilus (dantrolene sodium, hemiheptahydrate)
Treatment of malignant hyperthermia
EU/3/21/2443

Sponsor: Norgine B.V.

Note

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

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1. Product and administrative information

Product	
Designated active substances	Dantrolene sodium, hemiheptahydrate
Other name	-
International Non-Proprietary Name	Dantrolene sodium, hemiheptahydrate
Tradename	Agilus
Orphan condition	Treatment of malignant hyperthermia
Sponsor's details:	Norgine B.V. Antonio Vivaldistraat 150 1083 HP Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Norgine B.V.
COMP opinion	15 April 2021
EC decision	20 May 2021
EC registration number	EU/3/21/2443
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Kristina Dunder / Frantisek Drafi
Applicant	Norgine B.V.
Application submission	24 June 2022
Procedure start	14 July 2022
Procedure number	EMA/H/C/0006009
Invented name	Agilus
Proposed therapeutic indication	In combination with adequate support measures, Agilus is indicated for the treatment of malignant hyperthermia in adults and children of all ages. Further information on can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Agilus
CHMP opinion	21 March 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Eva Malikova / Michel Hoffmann
Sponsor's report submission	2 August 2022
COMP discussion and adoption of list of questions	13-15 February 2024
Oral explanation	17 April 2024
Sponsor's removal request	18 April 2024

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2021 was based on the following grounds:

"The sponsor Norgine B.V. submitted on 25 February 2021 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing dantrolene sodium, hemiheptahydrate for treatment of malignant hyperthermia (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products. Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing dantrolene sodium was considered justified based on literature data showing that the active substance can effectively prevent death in around 90% of treated patients;
- the condition is life-threatening due to tachycardia and other arrhythmias, acidosis, muscle rigidity, and hyperkalaemia. If untreated, the condition is fatal in more than 90% of cases;
- the condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing dantrolene sodium, hemiheptahydrate will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical data that demonstrate that the proposed product is easily dissolved in smaller infusion volume, which would enable a much shorter administration time of the proposed product compared the currently authorized formulation of dantrolene, offering the potential to reduce the morbidity and mortality associated with treatment delay. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled. The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled.

The COMP therefore recommends the designation of this medicinal product, containing dantrolene sodium, hemiheptahydrate as an orphan medicinal product for the orphan condition: treatment of malignant hyperthermia".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Malignant hyperthermia (MH) is an acute metabolic crisis resulting from a sudden increase in the concentration of sarcoplasmic calcium with consequent muscular contraction and other heat-generating metabolic processes.

MH is considered to be a pharmacogenetic disorder, after many susceptible subjects were discovered to have a mutation in the ryanodine receptor-1 (RYR1), which is a Ca2+ channel that resides on the sarcoplasmic reticulum (SR). RYR1 plays a pivotal role in excitation-contraction coupling and in determining sarcoplasmic Ca2+ concentrations. Disruption of its function increases these concentrations which drives the processes underlying the hypermetabolic crisis leading to malignant hyperthermia. In MH, the hypermetabolic crisis is triggered by the use of volatile anaesthetics and/or succinylcholine.

Early signs of malignant hyperthermia are sustained muscle contractions (usually first observed as rigidity of the masseter muscles), hyperventilation, severe metabolic acidosis, raised end-tidal CO_2 (despite hyperventilation), acidosis and unexpected tachycardia. Successive signs are cardiac arrhythmias and increased core body temperature, which is often a dramatic early sign and confirmatory (Rosenberg, 2015).

The approved therapeutic indication "In combination with adequate support measures, Agilus is indicated for the treatment of malignant hyperthermia in adults and children of all ages'' falls within the scope of the designated orphan condition "treatment of malignant hyperthermia".

Intention to diagnose, prevent or treat

The medical plausibility is confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any changes to the chronically debilitating or life-threatening nature of malignant hyperthermia since the orphan designation which was granted in 2021.

Patients experience long-term debilitating symptoms. Werneid and Brandom carried out a survey of 66 eligible patients who had suffered an episode of MH to gain an insight into possible long term sequalae of the condition (Werneid et al, 2016). Of those patients with current muscle pain, 90% attributed it to their MH event and 100% with muscle weakness believed that MH was the cause. Notably, only 36% of respondents attributed current back or joint pain to the MH episode suggesting that this is likely to be related to generalised ageing, whereas muscle pain and weakness were more likely to be related to MH. This finding is consistent with the fact that skeletal muscle is involved in MH. In addition, 42% of patients also attributed current anxiety and/or depression to their MH event. Most (83%) of patients stayed in the intensive care unit between 1 - 4 days and 39% experienced the event over 25 years ago.

Malignant hyperthermia can be fatal if not treated quickly. The condition is characterised by an acute catabolic crisis caused by a sudden and sustained increase in the concentration of sarcoplasmic calcium that induces sustained muscular contractions and excessive stimulation of aerobic and anaerobic metabolism. This hypermetabolism can result in increased oxygen consumption, metabolic acidosis and an increase in core body temperature (as high as 43°C) due to rapid consumption of energy stores and ATP. If untreated, the symptoms can be followed by rhabdomyolysis, hyperkalaemia, cardiac arrest, haematuria, raised blood creatine kinase levels, (which can lead to fatal renal failure), disseminated intravascular coagulation (DIC), brain oedema and death (Riazi et al, 2018; Endo, 2009; Hopkins,

2000; Nelson, 2018). The life-threatening nature of this metabolic crisis when triggered by volatile anaesthetics and succinylcholine is well characterised; mortality before the introduction of dantrolene was reported in 70-80% of cases, falling to <5% in subsequent years after the introduction of dantrolene (Rosenberg, 2007; Litman, 2005). When dantrolene was not available between 1985 and 2010 the mortality rate was 56% (33/59), and was still notably high, at 36% (9/25), between 2011 and 2020. There were just 8 cases (8.7%) where dantrolene was used and in all of these cases patients survived the MH crisis (Gong, 2021).

The COMP has previously acknowledged that MH is chronically debilitating due to tachycardia and other arrhythmias, acidosis, muscle rigidity, and hyperkalaemia. If untreated, the condition is fatal in more than 90% of cases. The condition therefore remains chronically debilitating and life-threatening in nature.

Number of people affected or at risk

At time of the initial marketing authorisation in 2021, the COMP concluded that the condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union.

To estimate the yearly incidence of malignant hyperthermia of anaesthesia in the European Union population in the worst-case scenario, the sponsor used 1:5,000 (0.02%) as incidence of malignant hyperthermia of anaesthesia (upper end of the range 1:5,000-1:250,000) and 5.3% of the European Union population being administered volatile gases every year (upper end of the reported range 2.5%-5.3%). The figures are based on an abstract by Islander presented at the 33rd Annual Meeting of the European Malignant Hyperthermia Group (EMHG) (Islander, 2014). Supported by data from the Canisius Wilhelmina Ziekenhuis (MH expert centre in the Netherlands) which reports that MH is estimated to occur in 1 in 50,000 anaesthetics in adults and 1 in 15,000 in children. The same range is also found in literature and on Orphanet where the incidence reported for MH is between 1:5,000 to 1:100,000 anaesthesias (Walter, 2015; Yang, 2020) and in few cases even lower, as low as 1:250,000 (Rosenberg, 2015. It is noted that that none of the papers cited correspond to actual studies trying to measure prevalence/incidence but had other aims, however, due to the scarcity of publications on the epidemiology of MH, these sources can be accepted.

Using the most reliable estimates from the sources discussed in the application, the estimated incidence of MH at the date of submission is 0.1 in 10,000 persons in the Union. This equates to an estimated 4,797 persons affected in the EU27, Norway, Iceland and Liechtenstein.

The COMP agreed with the calculation of the prevalence.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Dantrolene intravenous (iv) formulation is approved for the treatment of MH in adults and children through national procedures in 10 countries of the EU: Austria, Belgium, Czech Republic, France, Denmark, Germany, Hungary, Ireland, Italy and the Netherlands (Dantrium iv/Dantrolen iv). Dantrolene is also approved for the treatment of malignant hyperthermia in Switzerland and the UK.

Guidelines for the management of acute MH crises have been published by both the European Malignant Hyperthermia Group (EMHG) (Glahn et al, 2020) and the Malignant Hyperthermia Association of the United States (MHAUS) (MHAUS, 2012); both recognising dantrolene as the cornerstone of successful MH treatment. According to these guidelines, the essential points for treating an acute MH crisis are immediate discontinuation of trigger agents, hyperventilation and administration of dantrolene. This should be followed by symptomatic treatment as needed, including management of hyperthermia, hyperkalaemia, acidosis and arrhythmias.

Non-invasive treatments of hyperthermia include strategic ice packing, forced air cooling, circulating cool water blankets, cold iv fluids and ice-water immersion. Patients experiencing MH should be monitored closely for 48-72 hours, since (even despite dantrolene treatment) 20% to 25% of patients will experience a recrudescence of the syndrome (Burkman et al, 2007; Rosenberg et al, 2015). MHAUS guidance also states that a maintenance dose of dantrolene should be continued after the initial treatment phase is successful at either 1mg/kg IV every 4-6h or 0.25 mg/kg/hr by infusion for at least 24 hours or longer if clinically indicated (MHAUS, 2012).

Significant benefit

The sponsor did not seek protocol assistance for this application. The sponsor claimed that it would not be feasible or ethical to attempt a controlled clinical trial to demonstrate improved efficacy in this rare, life-threatening condition.

Agilus (NPJ5008) has been developed as a formulation improvement over DANTRIUM IV, with the aim of improving the solubility of dantrolene and thereby increasing the vial strength and reducing the number of vials required to administer the product. NPJ5008 contains different excipients from the existing dantrolene i.v. formulation; mannitol and sodium hydroxide have been replaced with hydroxypropyl beta cyclodextrin (HP-β-CD) and Macrogol 3350. Each vial of NPJ5008 contains 120 mg dantrolene sodium, hemiheptahydrate, whereas DANTRIUM IV contains 20 mg.

The concentration in NPJ5008 is 120 mg dantrolene/ vial and the new excipients are HP-β-CD and Macrogol (PEG) 3350 (see table 1 below for comparison of preparation/administration time between the two products).

Table 1. 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
[2]For a single operator to prepare and administer vials sequentially

The only clinical data the sponsor submitted was a comparative pharmacokinetic study in humans - NPJ5008-01/2020. Part 1 of the clinical study was a bioequivalence 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. Part 2 of clinical study 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.

The sponsor claimed significant benefit based on the improved efficacy. The main arguments are presented below:

- Natural history of the condition

The sponsor highlighted the importance of the clinical need for treatment with dantrolene as early as possible in an MH episode. The progressive ischaemia caused by MH within skeletal muscle and the impact of this reduced tissue perfusion on the ability of dantrolene to reach its site of action, also within the muscle, are well understood. Current EU treatment guidelines (Glahn, 2020) themselves refer to an explanation of the physiological requirement to stop uncontrolled calcium release on suspicion of MH by discontinuing triggering agents and administering dantrolene; dantrolene being a skeletal muscle relaxant that slows the release of calcium from the sarcoplasmic reticulum, permitting the cell time to re-establish homeostasis, and not acting at the neuromuscular junction (Tautz, 2010).

The sponsor argued that the progression towards ischaemia in skeletal muscle during an MH episode and the direct mode of action of dantrolene on the muscle itself make it inevitable that dantrolene must be administered early enough in the course of MH for muscle perfusion to be adequately assured and therefore that more than 16 minutes faster administration of a (more than) 16 times more concentrated dose of dantrolene (based on a 2.5 mg/kg dose for a 48 kg individual; delivered by 1 vial of NPJ5008 vs 6 vials of Dantrium IV) constitutes a significant advantage. Therefore, this introduces the possibility of a first vial effect, using a single vial of 120 mg NPJ5008, to break the MH hypermetabolic crisis.

- Registry data showing a correlation between time to treatment and outcomes

The sponsor presented three independent analyses of data taken from established malignant hyperthermia registries and spanning several years (Larach 2010, Riazi 2014 and Brandom 2015), provide real world evidence, where controlled clinical trials are not possible because of the rarity and fulminant nature of MH. The methods and results of these studies are presented below.

1. Larach et al, 2010. Clinical presentation, treatment, and complications of malignant hyperthermia in north America from 1987 to 2006

Cases of MH reported to the North American MH Registry between 1st January 1987 and 31st December 2006 were analysed for clinical characteristics, treatment, and complications. Complications were defined as a change in consciousness level and/or coma; disseminated intravascular coagulation; pulmonary oedema; cardiac, renal, or hepatic dysfunction; or "other" complication as specified by the reporting clinician. Cardiac arrest or death cases were included if additional complications were reported as part of their event. Complication data covered 181 patients. Of these, 34.8% (n = 63) reported 1 or more complications other than recrudescence, cardiac arrest, or death. The median complication number observed in 63 cases was 1 (first quartile, 1; third quartile, 2; range 1–5). According to the multivariable model, the likelihood of a complication increased 1.61 times (95% CI, 1.16 –2.25) for every 30-minute increase in time between the first sign and the first dantrolene dose and 2.85 times (95% CI, 1.60 –5.08) for every 2°C increase in maximum temperature. The Hosmer-Lemeshow goodness of fit test for this model is P = 0.140. When 6 patients who had experienced cardiac arrest were eliminated from the multivariable dataset, the multivariable model still identified these 2 variables as increasing the likelihood of an MH complication with a Hosmer-Lemeshow goodness of fit test (P = 0.135).

2. Riazi et al, 2014. Malignant hyperthermia in Canada: Characteristics of index anaesthetics in 129 malignant hyperthermia susceptible probands

Between 1992 and 2011, 373 Canadian individuals with adverse anaesthetic reaction were referred to the Malignant Hyperthermia Unit (MHIU) in Toronto, Ontario, Canada for MH diagnostic testing. Of these, 129 individuals, whose MH susceptible status was confirmed by caffeine-halothane contracture testing were selected. All episodes were characterized with regard to dantrolene administration time, defined as minutes between first clinical sign and first dantrolene dose.

The following complications due to MH were included: disseminated intravascular coagulation, renal and cardiac dysfunction, coma, compartment syndrome (requiring fasciotomy), and pulmonary oedema. This study excluded death. All the complications, as a group, were analysed for association with the interval between onset of clinical signs and dantrolene administration.

Of the 129 MHS probands with adverse anaesthesia reactions that were included in this study, a total of 26 patients (20.1%) suffered complications. The most common complications were renal dysfunction and cardiac dysfunction. Fifty-seven (44.2%) patients received dantrolene treatment after an adverse anaesthetic reaction. The median time between onset of the first clinical sign and dantrolene administration was 20 minutes (IQR, 15–20), with a range of 12 to 70 minutes (IQR, 15–25).

When the time between onset of the first clinical sign and dantrolene administration was longer, the proportion of patients experiencing a complication was larger (23.5 vs 15.0 minutes, $P = 0.005$). For each 10-minute delay in administration of dantrolene, complications increased substantially (the exact Cochran-Armitage trend test shows that complication rate increased with increasing minutes to dantrolene use, $P < 0.001$).

When dantrolene was given, a higher complication rate was observed when the time between the first clinical sign and dantrolene use was longer.

3. Brandom et al, 2015. Update on dantrolene in the treatment of anaesthetic induced malignant hyperthermia

Adverse metabolic/muscular reaction to anaesthesia reports (AMRAs) received after January 1, 2007 and before December 31, 2013 in the north American malignant hyperthermia registry (NAMHR) were examined with the goal of describing any changes in the administration of dantrolene, complications associated with dantrolene or with the MH episode itself that might contribute to increased morbidity. 152 AMRAs reported signs of MH in events that occurred with at least one anaesthetic drug and dantrolene given at some point during the event.

Documented complications included: cardiac dysfunction, change in consciousness level and/or coma, disseminated intravascular coagulation, hepatic dysfunction, pulmonary oedema, and renal dysfunction. Patient survival was documented separately. For this study, serious complications associated with the MH episode were defined as any of the complications listed above, or described in free text, or the need for defibrillation or CPR. Death during the MH episode or later in the same hospitalization as the MH episode was also considered to be a serious complication of MH.

The time between the beginning of anaesthetic administration and the recognition of the first sign of the MH episode, and the time between recognition of the first sign of MH and administration of the first dose of dantrolene were calculated for each case. These intervals were compared between the groups in which serious complications including death were reported, to the group without these complications.

Serious complications or death associated with the MH episode occurred in 40 cases, constituting 26% (20-34%; 95%CI) of the total cases. Death occurred in 7% (3-12%). Frequent serious complications associated with the MH episode were cardiac dysfunction, change in level of consciousness, renal dysfunction and pulmonary oedema. The other serious complications specifically reported with the MH episode included: compartment syndrome in three cases, pleural effusion, severe cellulitis, refractory bronchospasm, myoglobinuria, severe bleeding from all IV sites, elevated lipase with abdominal pain, and central nervous system injury, each in one case.

There were 112 cases with no serious complications or death reported. Both time intervals, Ind2 MH sign and Min 2 dantrolene, were significantly longer in the group with serious complications, ($p = 0.003$ and 0.023, M-W, respectively).

Logistic regression described a significant relationship between the risk of serious complications or death and both the time interval from the beginning of administration of the anaesthetic to observation of the first sign of MH, and the time interval between the observation of the first sign of MH and the administration of dantrolene. Age of the subject was also a significant factor in this regression. For the purpose of this regression analysis, cases in which a zero time interval was reported were assigned a value of one minute. It is unlikely that dosing of dantrolene was really begun in less than one minute from the observation of the first sign of MH because dantrolene has to be reconstituted.

The model presented in the report specifies that the odds of a serious complication or death increase; by 49% when patient age increases by 10 years, by 53% when the time from induction of anaesthesia to the first sign of MH doubles, and by 61% when the time from the first sign of MH to administration of dantrolene doubles. The present model predicts that the risk of complications increases 2.27 times when the time from the first sign of MH to administration of dantrolene increases from 10 min to 40 min, using median age of 29.5 years and median time from induction of aesthesia to the first sign of MH of 87 min.

- Indirect comparison of preparation and administration times for NPJ5008 and DANTRIUM IV with literature data

Using graphs from the three publications, the sponsor made an indirect comparison with the preparation and administration times from the sponsor's study :preparation and administration times for DANTRIUM IV and NPJ5008 have been overlaid onto the graphical representations of Riazi and Brandom to predict the reduction in serious complications or death from the faster administration associated with NPJ5008. The analysis by Larach has also been used to model a comparison of the likelihood of complications between DANTRIUM IV and NPJ5008 with every 30-minute increase in time to treatment.

Riazi, 2014

The times to prepare and administer a 2.5 mg/kg dose (using one operator) across a range of body weights have been overlaid onto the Riazi data to illustrate the percentage of MH complications that may arise in relation to the interval between first clinical sign of MH and first dose of dantrolene. This exercise illustrates that with the increasing time taken to prepare/administer an initial dose of DANTRIUM IV with increasing body weight, from 4 minutes to 54 minutes, the percentage of MH complications rises from 12% or less for body weights at or below 48 kg, to 67% for 120 kg BW and to 100% for 144 kg BW. In contrast, with an initial dose of NPJ5008 requiring within the range of 1 to 3 vials across the 3 to 144 kg body weights and taking between 2 to 6 minutes to prepare/administer, even for the highest body weight the percentage of MH complications is at less than 12%.

This exercise highlights that the rate of MH complications arising from time to treat using NPJ5008 is expected to be very low and not increasing with body weight, in contrast to when DANTRIUM IV is used, when the rate of complications rises steeply with delay to treatment, such as would happen in the time it takes to prepare an initial effective 2.5 mg/kg dose for the heavier patients.

Brandom, 2015

In the indirect comparison exercise, the risk of serious complications or death that may arise in relation to the minutes from the first clinical sign of MH to the initial dose of dantrolene, was overlayed with the sponsor's timing data for patient BWs 72, 96, 120 and 144 kg. It can be seen that the longer time taken to prepare/administer an initial dose of 2.5 mg/kg DANTRIUM IV versus NPJ5008 has a significant impact on the risk of serious complications or death as BW increases, independent of when the first clinical sign of MH is noted. For example, risk for a 72 kg patient increases from less than 0.21 rising to 0.42 at 30 and 145 minutes respectively (27 minutes to prepare/administer DANTRIUM IV), and for a 144 kg patient increases from 0.30 rising to 0.53 at 30 and 145 minutes respectively (54 minutes to prepare/administer DANTRIUM IV). In contrast, an initial dose of NPJ5008 requiring 2-3 vials across the 72-144 kg BWs, takes between <4 to 6 minutes to prepare/administer, even for the highest BW, with odds of serious complications or death reaching no higher than 0.21, even for the longer delay of 145 minutes to first sign of MH.

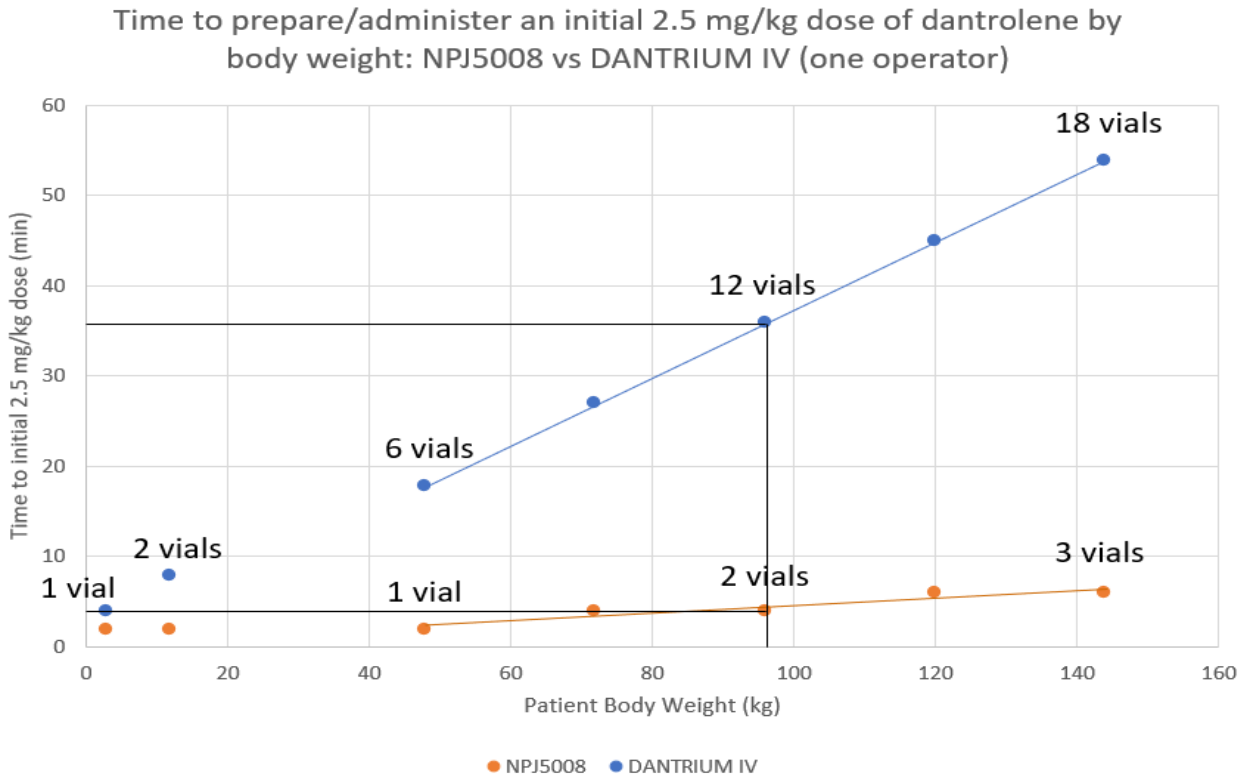
The effect is not so pronounced in paediatric patients where the total number of vials required is smaller. However, for completeness, the indirect comparison also used data for BWs from 3 kg to 48 kg. The risk for a 3 kg child increases from 0.02 rising to 0.04 at 30 and 145 minutes respectively (4 minutes to prepare/administer DANTRIUM IV), and for a 48 kg child increases from 0.04 rising to 0.11 at 30 and 145 minutes respectively (18 minutes to prepare/administer DANTRIUM IV). In contrast, with an initial dose of NPJ5008 requiring just 1 vial across the 3-48 kg BWs, takes <2 minutes to prepare/administer, even for the highest BW, with odds of serious complications or death reaching no higher than approximately 0.035, even for the longer delay of 145 minutes to first sign of MH.

Larach, 2010

Larach et al have modelled that the likelihood of a complication increases 1.61 times for every 30-minute increase in time between the first sign and the first dantrolene dose. Figure 7 below illustrates the time to prepare/administer an initial 2.5 mg/kg dose of dantrolene in relation to patient body weight, NPJ5008 vs DANTRIUM IV (assuming a single operator). No more than 3 NPJ5008 vials are required to treat even the largest body weight patient, and that all three vials can be prepared and administered in less than 6 minutes. In comparison, this is markedly longer when increasing numbers of vials (from 1 up to 15 vials or more) of DANTRIUM IV are required with increasing body weight; for example, it takes 45 minutes or more to prepare/administer an initial effective 2.5 mg/kg dose for patients of ≥120 kg BW.

As illustrated in Figure 7 (refer to the black lines), using DANTRIUM IV a single operator takes 36 minutes to prepare/administer a 2.5 mg/kg initial effective dose to a 96 kg patient. In contrast the same dose of NPJ5008 will take no more than 4 minutes to prepare/administer to a 96 kg patient, approximately 30 minutes shorter time than with DANTRIUM IV. Following Larach's finding this patient will be at a 1.61 times greater likelihood of a complication when treated with DANTRIUM IV compared with when treated with NPJ5008. Thus, using NPJ5008 removes the intrinsic likelihood of more complications in heavier patients due to the time it takes to prepare/administer the current dantrolene i.v. formulation in accordance with their body weight.

Figure 1. Relationship of patient body weight to time to initial 2.5 mg/kg dantrolene dose (based on sponsor's study)1



[1]Lines of best fit for 48-144 kg patients estimated for Times to initial 2.5 mg/kg dose using the 16G adult cannula (22G paediatric cannula points not included).

COMP conclusion

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. According to the sponsor, the benefit of the new formulation (Agilus) permits faster and easier reconstitution and preparation of the dose, and consequently more rapid administration.

The sponsor claimed that there is evidence of a relationship between the time from first signs of MH to administration of the first dose of dantrolene (in the formulation of DANTRIUM IV) and risk of complications and severe complications (including death). According to the sponsor, this evidence is based on 3 articles published in peer-review journals (Riazi, 2014, Brandom, 2015 and Larach, 2010) and it is reflected in existing regulatory guidance requiring for rapid administration of dantrolene to treat MH. It takes longer to prepare, reconstitute and administer the dose needed to treat an MH patient with DANTRIUM IV than with NPJ5008, with differences in time being more pronounced in heavy subjects. This is because the time to prepare the number of vials needed to treat subjects with MH increases with body weight, and because of the lower content of dantrolene in DANTRIUM IV compared to NPJ5008 (20mg vs 120mg) and lower volume needed to dissolve (120mL vs 20mL). The sponsor includes results from a bioequivalence study of the two formulations in healthy volunteers stating that bioequivalence between the two formulations was demonstrated for a tolerable dose of 60mg of NPJ5008 in this healthy volunteer setting. In the calculation of preparation times however, a dose of 120mg is considered. The sponsor concludes the risk of complications and severe complications

of MH are lowered if treated with NPJ5008 compared with DANTRIUM IV, and provides quantifications of the expected risk reduction, with some of those quantifications based on the indirect comparison.

However, in the Figure 1 from Riazi et al, 2014 publication the bar plot shows percentage of subjects with complications for each administration time interval, but the number of subjects used to calculate those plots is not reported. Therefore, it is not possible to understand the uncertainty behind these estimated percentages, which is likely to be large considering the total number of subjects is 16. The number of patients and the number and type of complications should be clarified.

In Table 2 from Brandom et al, 2015 the confidence intervals (CI) values are missing. In addition, the sponsor should clarify whether the logistic regression analysis is multivariate analysis and whether it is adjusted or not.

The sponsor also submitted indirect comparison of preparation and administration times for Agilus and DANTRIUM IV with the literature data from the registries mentioned above.

The graph from Riazi 2014 (Figure 1) is a barplot showing descriptive statistics on the percentage of MH complications for increasing time intervals between first clinical sign of MH and first dose of dantrolene. It is based on 16 subjects and the study period is 1992-2011. No modelling attempt of the relationship between time from first MH clinical sign to first dose of dantrolene was reported. The indirect comparison of the sponsor was limited to annotating this graph by including an eyeball estimated risk of MH complications with both NPJ5008 and DANTRIUM IV for different body weights, for which the time to first dose administration would correspond with the time intervals shown in the graph.

The bar plot shows percentage of subjects with complications for each administration time interval, but the number of subjects used to calculate those percentages are not reported. Therefore, it is not possible to understand the uncertainty behind these estimated percentages, which is likely to be large considering the total number of subjects is 16. Consequently, taking the eye-ball estimates of these percentages at face value as the sponsor has done in the indirect comparison exercise is highly questionable. It is not clear from the text if the list of complications is the same in NPJ5008 and DANTRIUM IV in this exercise. There are 13 patients with 1 complication and 13 patients with >1 complications. Figure 1 displays complications of 16 patients and it is not clear which ones were used. Unfortunately, only percentages are displayed, so it is also not clear whether multiple complications per patient are considered.

A further complication to the comparison is that a bioequivalent dose of NPJ5008 was not used. When describing the estimated times of administration of NPJ5008, it would appear the sponsor calculated those based on the 120mg dose, which is double the 60mg for which bioequivalence with DANTRIM IV was shown. In the indirect comparison there is limited/no consideration to the time gap between the end of the study period (2011) and now, and the potential improvements in clinical practice in this setting.

The graph from Brandom et al, 2015 consists of predictive curves of risk (odds) of complications for increasing dantrolene administration time. These predictive curves come from a logistic regression model fitted in Brandom et al, 2015. The model was fitted using data from 152 subjects and it included terms for age, time from induction to anaesthesia to first MH clinical sign, and time from the first MH clinical sign and first administration of dantrolene. Brandom et al, 2015 produced predictive curves for the combination of 2 ages (15 and 52 years old) and 2 times between induction to anaesthesia and first MH clinical sign (30 and 145 minutes). As in the previous case, the sponsor has annotated this graph with estimated risk (odds) of complications under NPJ5008 and DANTRIUM IV for various body weights based on the corresponding dose preparation time needed with each formulation. However,

uncertainty on the estimated model parameters is not accounted for in the predictive curves. Overlap in the list of complications between Brandom et al and the calculation of risk of MH complications for NPJ5008 is not discussed. It's not clear if the bioequivalent dose was used to compare preparation times for NPJ5008.

Finally, the study period of the study by Brandom et al was 2007-2013, which feels distant in time in terms of evolution of standard of care which could have changed in the last 10 years.

4. COMP list of issues

1. The sponsor should clarify the following regarding the literature data provided:

i) In the Figure 1 from Riazi et al, 2014 publication it is not clear whether one complication per subject is reflected in this plot or whether multiple complications per subject were used. The number of patients and the number and type of complications should be shared. Please provide the confidence intervals (CI) in addition to point estimates.

ii) In Table 2 from Brandom et al, 2015 the CI are missing. In addition, the sponsor should clarify whether the logistic regression analysis is a multivariate analysis and whether additional covariables were included in the model. The results seem to be presented on a log scale and the sponsor is invited to present the results as Odds ratios together with an interpretation. Uncertainty on the estimated model parameters is not accounted for in the predictive curves.

iii) The sponsor should clarify to what extent the endpoints reported in the publications are aligned (i.e. "Complications" vs. "Serious Complication or Death"). The sponsor is also invited to reflect on the comparability of the samples that are presented in Riazi et al (2014) and Brandom et al (2015), are the two populations overlapping or do they differ?

2. The indirect comparisons submitted by the sponsor have many methodological issues described above.

    i) In the indirect comparisons the time gap between the end of the study period (2011 and 2015) and now, and the potential improvements in clinical practice in this setting are not taken into account. The sponsor is invited to provide more recent data which could reflect the current clinical practice.