



1. NAME OF THE MEDICINAL PRODUCT

Agilus 120 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 120 mg dantrolene sodium hemiheptahydrate.

After reconstitution with 20 mL water for injections, each millilitre of solution contains 5.3 mg dantrolene sodium hemiheptahydrate.

Excipients with known effect

Each vial contains 3530 mg hydroxypropylbetadex and 6.9 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

Yellow-orange lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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 (pCO₂) 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 ^b	300 mg ^b	56.5 mL

^aTotal volume of one reconstituted vial is 22.6 mL

^bFor 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.

Method of administration

For intravenous use.

Each vial should be prepared by adding 20 mL of water for injections and the vial shaken until the solution is dissolved. Reconstituted Agilus is a yellow-orange solution with a final volume of 22.6 mL.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.



4.4 Special warnings and precautions for use

The use of Agilus in the management of malignant hyperthermic crisis is not a substitute for other supportive measures. These must be individually continued in their various forms.

Caution should be exercised if hyperkalaemia symptoms occur (muscular paralysis, electrocardiogram changes, bradycardic arrhythmias) or in cases of pre-existing hyperkalaemia (renal insufficiency, digitalis intoxication etc.), as an increase in serum potassium has been demonstrated in animal studies as a result of the co-administration of dantrolene with verapamil. Concomitant use of Agilus and calcium channel blockers is not recommended (see section 4.5).

Agilus is only for intravenous use. Due to the high pH value of the solution (pH 9.5), extravascular injection must be avoided as it can lead to tissue necrosis. Due to the risk of vascular occlusion, intraarterial injections must be avoided.

Spill of solution on skin should be avoided. If solution gets on the skin, it must be removed with sufficient water (see section 6.6).

Liver damage may occur during dantrolene therapy. This has been observed during longer term, oral administration and may run a lethal course.

Excipients

Hydroxypropylbetadex

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

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

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

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

Sodium

This medicinal product contains 6.9 mg sodium per vial, equivalent to 0.345% of the World Health Organisation recommended maximum daily intake of 2 g sodium for an adult.



4.5 Interaction with other medicinal products and other forms of interaction

Isolated case reports and animal studies indicate an interaction between dantrolene and calcium channel blockers, such as verapamil and diltiazem, in the form of heart failure. Concomitant use of Agilus and calcium channel blockers is not recommended (see section 4.4).

Concomitant administration of Agilus with non-depolarising muscle relaxants, such as vecuronium, can enhance their effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data for the use of dantrolene in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Postpartum uterine atony has been reported after intravenous dantrolene therapy. The risk of floppy child syndrome in neonates has also been described when intravenous dantrolene was administered to the mother during caesarean section. Dantrolene crosses the placenta and should only be used during pregnancy when the potential benefit outweighs the possible risk to mother and child.

Breast-feeding

No information is available on the use of dantrolene during breastfeeding. According to its safety profile, a risk to a breastfed infant cannot be excluded as dantrolene is excreted in breastmilk. Therefore, breastfeeding should be discontinued during administration of Agilus. Based on elimination half-life of dantrolene, breastfeeding can be restarted 60 hours after the last dose.

Fertility

Data on the effects of dantrolene on fertility in humans are not available. In animal studies, no adverse effects on fertility were observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Agilus has a major influence on the ability to drive and use machines, as it can lead to skeletal muscle weakness, dizziness and light-headedness. Since some of these symptoms may persist for up to 48 hours, patients must not drive or use machines.

4.8 Undesirable effects

Agilus is a skeletal muscle relaxant. The most commonly reported adverse event of intravenous dantrolene administration, skeletal muscle weakness, is related to this mode of action.

The adverse reactions observed are linked to dantrolene and its formulations for acute, intravenous use and for chronic, oral use. Some of the adverse reactions listed may also be observed as a result of the underlying malignant hyperthermia crisis. Adverse reactions are presented below according to system organ class and frequency.



Frequencies are defined according to:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1\,000$ to $< 1/100$)

Rare ($\geq 1/10\,000$ to $< 1/1\,000$)

Very rare ($< 1/10\,000$)

Not known: frequency could not be estimated from the available data.

Table 2: List of adverse drug reactions

System Organ Class	Frequency	Adverse Drug Reactions
Immune system disorders	Not known	Hypersensitivity, Anaphylactic reaction
Metabolism and nutrition disorders ^a	Not known	Hyperkalaemia
Nervous system disorders	Not known	Dizziness, Somnolence, Seizure, Dysarthria, Headache
Eye disorders	Not known	Visual impairment
Cardiac disorders ^a	Not known	Cardiac failure, Bradycardia, Tachycardia
Vascular disorders	Not known	Thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory failure, Respiratory depression
Gastrointestinal disorders	Not known	Abdominal pain, Nausea, Vomiting, Gastrointestinal haemorrhage, Diarrhoea, Dysphagia
Hepatobiliary disorders	Not known	Jaundice ^b , Hepatitis ^b , Hepatic function abnormal, Hepatic failure including fatal outcome ^b , Idiosyncratic or hypersensitive liver diseases
Skin and subcutaneous tissue disorders	Not known	Urticaria, Erythema, Hyperhidrosis
Musculoskeletal and connective tissue disorders	Not known	Muscle weakness, Muscle fatigue
Renal and urinary disorders ^a	Not known	Crystalluria
Reproductive system and breast disorders	Not known	Uterine hypotonus
General disorders and administration site conditions	Not known	Fatigue, Administration site reaction, Asthenia

^aThese adverse reactions were observed in nonclinical studies

^bThese adverse reactions have been observed with chronic, oral treatment

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.



4.9 Overdose

Malignant hyperthermia is an emergency situation where rapid injection of a high dose of Agilus may be necessary (see section 4.2).

Dantrolene acts as a muscle relaxant. Severe muscle weakness with resultant respiratory depression can occur. Therefore, in cases of accidental overdose, symptomatic and general supportive measures should be employed.

The value of dialysis in dantrolene overdose is not known. There is no specific antidote for dantrolene.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: muscle relaxants, directly acting agents, ATC code: M03CA01.

Mechanism of action and pharmacodynamic effects

Dantrolene is a skeletal muscle relaxant that binds to the ryanodine receptor-1 (RYR1) suppressing release of calcium from the sarcoplasmic reticulum (SR). Dantrolene has little or no effect on the contraction of the cardiac muscle, except possibly at higher doses. A transient inconsistent depressant effect on the gastrointestinal smooth muscles was observed in case of high intravenous doses.

RYR1 acts as a calcium ion (Ca^{2+}) channel that resides on the SR of skeletal muscle and when activated leads to muscle contraction. In malignant hyperthermia susceptible individuals RYR1 function is disrupted by triggers such as volatile anaesthetics and/or succinylcholine and does not repolarize, leading to unregulated Ca^{2+} release from the SR. The consequent rise in sarcoplasmic Ca^{2+} causes sustained muscle contraction and excessive stimulation of aerobic and anaerobic metabolism which results in increased oxygen and adenosine triphosphate consumption, metabolic acidosis, and generates heat, which, together establishes a hypermetabolic state and hyperthermia ensues. Dantrolene binds to the RYR1 and stabilises its resting state, thereby suppresses the release of Ca^{2+} from the SR and arrests the metabolic cascade. Dantrolene therapy can only work when Ca^{2+} has not yet entirely been emptied from the SR, i.e. dantrolene should be used as early as possible, provided that muscle perfusion is still adequately assured.

Clinical efficacy and safety

The efficacy of dantrolene is well established. The assessment of known and potential risks of intravenous dantrolene is also based on post-marketing exposure data. Published studies in healthy volunteers provide supportive safety data.

In conscious healthy subjects ($n = 12$), depression of muscle twitch tension was found to stabilise within 2-3 minutes following repeat intravenous bolus doses of 0.1 mg/kg dantrolene every 5 minutes. There was no recovery before the next dose. A dose of 2.5 mg/kg has been shown to produce a maximum dose response in muscle.

Clinical efficacy and safety studies of Agilus have not been performed. A 2-part, part-randomised, open-label, single dose, relative bioavailability study of Agilus versus 20 mg intravenous dantrolene was performed in healthy adult volunteers ($n = 21$). Adverse events reported in the study for both



products were consistent with the known mechanism of action of dantrolene as a skeletal muscle relaxant and with previous literature.

In published case series quicker administration of dantrolene is correlated with improved outcomes. In the relative bioavailability study, the mean time taken to reconstitute 1 vial of Agilus (120 mg) and 1 vial of 20 mg intravenous dantrolene was 50 seconds, and 90 seconds, respectively.

In a laboratory simulation study of the overall vial preparation/administration process, the mean times taken to prepare and administer 1 vial of Agilus (120 mg) and 1 vial of 20 mg intravenous dantrolene were as follows:

- Adult cannula: 1 minute and 53 seconds, and 3 minutes, respectively
- Paediatric cannula: 1 minute and 57 seconds, and 4 minutes and 2 seconds, respectively

Recrudescence is estimated to occur in 10-15% of malignant hyperthermia patients and is more likely to occur in severe cases in which higher doses of dantrolene are required to control the initial reaction.

In a retrospective review and analysis of case studies containing adequate data between 1979 and 2020, 116 adult patients (18 years and older) received dantrolene as treatment for malignant hyperthermia. Among these patients, 112 (97%) were reported to have survived. The median therapeutic dose administered was 2.4 mg/kg and in the majority of patients (58%) a therapeutic dose of 2.5 mg/kg was sufficient to resolve an episode of malignant hyperthermia (MH). In 87% of patients, therapeutic doses did not exceed 5 mg/kg and in 95% of patients, doses did not exceed 10 mg/kg.

Paediatric population

In a retrospective review and analysis of case studies containing adequate data between 1979 and 2020, 91 paediatric patients (aged < 1 month up to 18 years old) received dantrolene as treatment for malignant hyperthermia. Among these patients, 87 (96%) were reported to have survived. The median therapeutic dose administered was similar for all paediatric age groups, ranging from 2 to 3 mg/kg, and in the majority of patients (59%) a therapeutic dose of 2.5 mg/kg was sufficient to resolve an episode of MH. In 89% of patients, therapeutic doses did not exceed 5 mg/kg and in 98% of patients, doses did not exceed 10 mg/kg.

5.2 Pharmacokinetic properties

In conscious healthy subjects (n = 12), a whole blood maximum concentration ($C_{\max}$) of 4.2 mcg/mL was reported after 2.4 mg/kg intravenous dantrolene, blocking up to 75% of skeletal muscle contraction. In patients with suspected or proven malignant hyperthermia (n = 6) who received prophylactic treatment with dantrolene 2.5 mg/kg intravenously, reported $C_{\max}$ values ranged between 4.3 and 6.5 mcg/mL.

Distribution

Dantrolene is reversibly bound to plasma albumin. In human plasma *in vitro* at the concentration of 6 mcg/mL of Agilus, dantrolene was 94.9% protein bound. Following a 120 mg single intravenous dose of Agilus to healthy volunteers the volume of distribution was 49.2 L.

Biotransformation

Metabolism in the liver takes place through microsomal enzymes both via 5-hydroxylation at the hydantoin ring and via reduction of the nitro group to amine with subsequent acetylation.



5-Hydroxydantrolene has similar activity to that of the parent substance, while the acetamino-dantrolene does not have any muscle relaxant effect.

Elimination

In a clinical study conducted in healthy volunteers with Agilus, the elimination half-life ($t_{1/2}$) for dantrolene was between 9-11 hours following 60 and 120 mg single intravenous doses.

Excretion is mainly renal and biliary, whereby renal excretion takes place, even in long-term use, at a ratio of 79% 5-hydroxydantrolene, 17% acetylamino-dantrolene and 1 to 4% unchanged dantrolene. Renal clearance (5-OH-dantrolene) is 1.8 to 7.8 L/h.

Paediatric population

The pharmacokinetic profile of dantrolene reported in one clinical study in children dosed at 2.4 mg/kg was similar to that observed in adults. The $t_{1/2}$ was about 10 hours in children ($n = 10$) between 2 and 7 years of age scheduled for minor elective surgery. No paediatric specific (any age group) safety issues have been identified compared to the adult population.

Hydroxypropylbetadex

Hydroxypropylbetadex, an ingredient of Agilus, is cleared unchanged by renal filtration, with a short half-life, of 1 to 2 hours, reported in patients with normal renal function.

5.3 Preclinical safety data

Subacute and chronic toxicity

A 14-day repeat dose intravenous study with Agilus was conducted in the rat at doses of 2.5 mg/kg/day (73.5 mg/kg/day hydroxypropylbetadex and 8.3 mg/kg/day PEG 3350) and 10 mg/kg/day (294.2 mg/kg/day hydroxypropylbetadex and 33 mg/kg/day PEG 3350). The no adverse effect level (NOAEL) dose was 2.5 mg/kg/day for Agilus (human equivalent dose for dantrolene 0.4 mg/kg/day). Kidney effects were observed on repeated administration in the 10 mg/kg/day treatment group (human equivalent dose for dantrolene 1.6 mg/kg/day) as well as in the control group receiving the same volume of excipients. Thus, the kidney effects were linked to hydroxypropylbetadex's known toxicity of vacuolated renal tubular epithelial cells in both male and female rats and increased incidence of vacuolated alveolar macrophages in male rats but were of low grade. These effects are consistent with a well-established reversible class effect associated with the use of the excipient hydroxypropylbetadex when given chronically to rodents. No auditory functions/ototoxicity were investigated in this study.

In chronic toxicity studies with rats, dogs and monkeys, oral administration of dantrolene at greater than 30 mg/kg/day (human equivalent dose 4.8, 16.7 and 9.7 mg/kg/day, respectively) for 12 months led to a reduction of growth or body weight gain. Hepatotoxic effects and possibly renal obstruction were observed, which were reversible. The relevance of these findings to the acute intravenous use of dantrolene in the treatment of malignant hyperthermia in humans has not been determined.



Mutagenicity

Dantrolene yielded positive results in the Ames *S. typhimurium* test both in the presence and absence of a liver metabolising system.

Carcinogenicity

Dietary doses of dantrolene sodium in rats at doses of 15, 30 and 60 mg/kg/day (human equivalent dose 2.4, 4.8, and 9.7 mg/kg/day, respectively) for up to 18 months resulted in increases in benign hepatic lymphatic neoplasms at the highest dose level, and in females only, an increase in mammary tumours.

In a 30-month study in Sprague-Dawley rats fed dantrolene, the highest dose level produced a decrease in the time of onset of mammary neoplasms. Female rats at the highest dose level showed an increased incidence of hepatic lymphangiomias and hepatic angiosarcomas.

In a 30-month study in Fischer-344 rats, a dose-related reduction in the time of onset of mammary and testicular tumours was observed.

The relevance of these data for short term use of intravenous dantrolene for the treatment of malignant hyperthermia in humans is not known.

Reproductive toxicology

In male and female adult rats and female pregnant rabbits, oral formulations of dantrolene up to an achieved oral dose of 45 mg/kg/day (human equivalent dose 7.3 and 14.5 mg/kg/day respectively) did not have any adverse effects on rat fertility or general reproductive capability but in pregnant rabbits 45 mg/kg/day on gestational days 6-18 led to increased formation of unilateral or bilateral supernumerary ribs in the pups.

Hydroxypropylbetadex

There is evidence of hydroxypropylbetadex-induced ototoxicity in several nonclinical species following single and repeat subcutaneous dosing. In rats (the most sensitive species to hydroxypropylbetadex ototoxicity), a dose of 2 000 mg/kg is close to the critical dose for inducing significant hearing loss and cochlear damage following subcutaneous administration. Doses greater than 2 000 mg/kg cause significant hair cell damage and completely abolish distortion product otoacoustic emissions, whereas lower doses have relatively little effect on functional and structural measures. In literature studies, no ototoxicity from 500 to 1 000 mg/kg has been reported in rats. The relevance of these findings for human exposure to hydroxypropylbetadex is not clear.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex
Macrogol (E1521)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.



6.3 Shelf life

Unopened vial

3 years.

After reconstitution

Reconstituted solution should be used within 24 hours.

Reconstituted solution must be protected from light. Do not store above 25 °C and do not refrigerate.

Chemical and physical in-use stability after reconstitution has been demonstrated for 24 hours at 25 °C.

From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should not exceed 24 hours at 25 °C.

6.4 Special precautions for storage

The unopened vial does not require any special temperature storage conditions.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with a rubber stopper and a seal.

Pack sizes of 6 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each vial should be reconstituted by adding 20 mL water for injections and shaking for approximately 1 minute, before inspecting for particulates. Further shaking may be necessary. The reconstituted solution should be a yellow-orange colour and free from particulates. The volume of solution in a reconstituted vial is 22.6 mL.

Reconstituted Agilus solution must not be mixed with other solutions or given via the same venous access (see section 6.2).

Spill of solution on skin should be avoided. If solution gets on the skin, it must be removed with sufficient water (see section 4.4).



This medicinal product is for single use only and any residual reconstituted solution should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Norgine B.V.
Antonio Vivaldistraat 150
1083 HP Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1805/001
EU/1/24/1805/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 May 2024

10. DATE OF REVISION OF THE TEXT

29 May 2024

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