ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 3 530 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 (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[b]	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. Thesame 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 (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1 000 to < 1/100)
Rare (≥ 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

[a]These adverse reactions were observed in nonclinical studies
[b]These 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 the national reporting system listed in Appendix V.

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 lymphangiomas 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:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

D. 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Agilus 120 mg powder for solution for injection
dantrolene sodium hemiheptahydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 120 mg dantrolene sodium hemiheptahydrate.
After reconstitution, each mL of solution contains 5.3 mg dantrolene sodium hemiheptahydrate.

3. LIST OF EXCIPIENTS

Contains: hydroxypropylbetadex, macrogol (E1521).

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

6 vials
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution.
For single use only.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Discard any residual reconstituted solution.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the unopened vial in the outer carton in order to protect from light.
Reconstituted solution must be protected from light. Do not store above 25°C and do not refrigerate.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL

1. NAME OF THE MEDICINAL PRODUCT

Agilus 120 mg powder for solution for injection
dantrolene sodium hemiheptahydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 120 mg dantrolene sodium hemiheptahydrate.
After reconstitution, each mL of solution contains 5.3 mg dantrolene sodium hemiheptahydrate.

3. LIST OF EXCIPIENTS

Contains: hydroxypropylbetadex, macrogol (E1521).

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution.
For single use only.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Discard any residual reconstituted solution.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the unopened vial in the outer carton in order to protect from light.
Reconstituted solution must be protected from light. Do not store above 25 °C and do not refrigerate.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Agilus 120 mg powder for solution for injection
dantrolene sodium hemiheptahydrate

Read all of this leaflet carefully because it contains important information for you.
This medicine is used in emergency situations and the doctor will have decided that you needed it.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Agilus is and what it is used for

Agilus contains dantrolene sodium. It is a type of medicine called a direct-acting muscle relaxant. It attaches to a target within muscle cells and helps the muscles of the body to relax when they have become over-stimulated.

Together with other supportive measures, this medicine is used for the treatment of malignant hyperthermia in adults and children of all ages. Malignant hyperthermia is a life-threatening emergency condition in which the skeletal muscles of the body are over-stimulated and are unable to relax. This can cause a very fast increase of your body temperature and/or a build-up of waste products in the body (metabolic acidosis), which can stop vital organs from working properly.

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

You should not be given Agilus

- if you are allergic to dantrolene sodium or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

You will probably have been given this medicine before you read this leaflet.

Talk to your doctor or nurse if:

- you are currently taking medicines for high blood pressure or angina called “calcium channel blockers”. Taking these medicines at the same time as Agilus may increase the amount of potassium in your blood, which could cause you to experience irregular heart rhythms or an inability to move some of your muscles.
- if you think any medicine has been spilt on your skin, it should be washed off with water.

Liver damage has been observed in patients exposed to long term, oral use of dantrolene sodium. Tell your doctor if you think you have symptoms of liver damage (e.g. if your skin and eyes appear yellowish or you have abdominal pain and swelling).

Other medicines and Agilus

Tell your doctor if you are taking, have recently taken, or might take, any other medicines.

The following medicines may affect the way Agilus works or Agilus may affect the way they work:

- medicines for high blood pressure and angina called "calcium channel blockers" such as verapamil or diltiazem may result in heart failure if given at the same time as Agilus. (see warnings and precautions).
- muscle relaxants, such as vecuronium may enhance the muscle relaxing effect of Agilus if given at the same time.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, tell your doctor or nurse, if possible, before receiving this medicine.

Pregnancy

Agilus will not be used if you are pregnant, unless considered necessary. After you have been given Agilus, the muscles of your uterus (womb) may be weak. If you receive Agilus during a caesarean section, your new-born baby may experience muscle weakness.

Breast-feeding

You should not breast-feed whilst you are receiving Agilus, or for 60 hours after your last dose. Tell your doctor if you are breastfeeding.

Driving and using machines

After you have been given Agilus, your hand and leg muscles may be weak, and you may also have a feeling of dizziness or light-headedness. These effects may last for up to 48 hours after you have been given Agilus. Do not drive or operate machinery during this time.

Agilus contains cyclodextrin and sodium

This medicine contains 3 530 mg hydroxypropylbetadex (a cyclodextrin) in each vial, which is equivalent to 156.2 mg/mL in the reconstituted solution.

Tell your doctor if you have had problems with your hearing in the past e.g. if you are prone to ear infections. Cases of hearing impairment have been observed in patients given hydroxypropylbetadex for other conditions, in higher doses than recommended for Agilus. This hearing impairment is generally short-lived and mild. For patients requiring high Agilus doses (above 10 mg/kg) the treatment will be re-evaluated due to this risk.

The potential risk associated with hydroxypropylbetadex may be increased if your kidneys are not working properly.

This medicine contains 6.9 mg of sodium (main component of cooking/table salt) in each vial. This is less than 0.5% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Agilus is given

This injection is given to you by a healthcare professional, into a vein. The dose of Agilus you are given depends on your body weight. The dose will be repeated every 10 minutes until your symptoms improve. If your symptoms do not improve after receiving the medicine, the doctor may re-examine your diagnosis and consider alternative treatments. If you experience a relapse, your healthcare professional will inject Agilus again.

If you have been given too much Agilus

If you have received more Agilus than you should have, side effects may occur. Severe muscle weakness can occur, which might affect your breathing. Your doctor will monitor you closely.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects have been observed with the active substance of Agilus;

The frequency of the below side effects is not known (frequency cannot be estimated from the available data)

Serious side effects – your doctor will stop giving you Agilus straight away

- sudden, severe allergic reaction with breathing difficulty, swelling, light-headedness, fast heartbeat, sweating and loss of consciousness (anaphylactic reaction)

Other side effects

The following side effects have been observed with the active substance of Agilus:
- allergic reactions (hypersensitivity)
- high blood potassium levels (hyperkalaemia), which can cause tiredness, muscle weakness, feeling sick and heart rhythm disturbances
- dizziness, drowsiness, seizure, difficulty speaking (dysarthria), headache
- altered vision
- heart failure, slow heart rate (bradycardia), rapid heartbeat (tachycardia)
- inflammation in a vein leading to a blood clot and blockage (thrombophlebitis)
- difficulty breathing (respiratory failure), breathing that is too slow and shallow (respiratory depression)
- pain in the belly (abdominal pain), nausea (feeling sick), vomiting, bleeding in the gut and stomach with symptoms of blood in stools or vomit (gastrointestinal haemorrhage), diarrhoea, difficulty swallowing (dysphagia)
- yellow eyes and skin (jaundice)[*], inflammation of the liver (hepatitis)[*], liver failure that may be fatal[*], changes in blood test of liver function, liver disease due to an unknown cause or allergic reaction
- itchy rash (urticaria), reddening of the skin (erythema), excessive sweating (hyperhidrosis)
- muscle weakness, tired muscles
- crystal particles in the urine (crystalluria)
- weak contractions when giving birth (uterine hypotonus)
- feeling tired (fatigue), general weakness (asthenia), reactions at the injection site

[*]These side effects were observed in situations where dantrolene treatment has been given by mouth for a long time.

Reporting of side effects

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

5. How to store Agilus

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

This medicine will be stored in the hospital, and these instructions are intended for health care staff only.

Unopened vial: does not require any special temperature storage conditions. Keep the vial in the original carton to protect from light.

Reconstituted solution: Use within 24 hours. Reconstituted solution must be protected from light. Do not store above 25 °C and do not refrigerate.

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

For single use only. Discard any residual reconstituted solution.

6. Contents of the pack and other information

What Agilus contains

The active substance is dantrolene sodium hemiheptahydrate.

One 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.

The other ingredients are hydroxypropylbetadex (a cyclodextrin) and macrogol (E1521). See section 2 "Agilus contains cyclodextrin and sodium".

What Agilus looks like and contents of the pack

Glass vials, with a rubber stopper and seal, containing 120 mg of yellow-orange powder for solution for injection.

Carton of 6 or 10 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

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 (pCO_2) monitoring required) and hyperthermia persist, bolus injection of 2.5 mg/kg should be repeated every 10 minutes until physiological and metabolic abnormalities improve. 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

[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.

Method of administration

For intravenous use.

Special precautions for storage, preparation and handling

Preparation

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.

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.

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.

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

Handling

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

Reconstituted Agilus solution must not be mixed with other solutions or given via the same venous access.

Spill of solution on skin should be avoided. If solution gets on the skin, it must be removed with sufficient water.

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.