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 – this 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 are 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 breast-feeding.

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 when reconstituted. Some cases of hearing impairment have been observed from hearing tests in other clinical settings, in patients taking cyclodextrin. Tell your doctor if you have had problems with your hearing in the past e.g. if you are prone to ear infections.

The potential risk associated with cyclodextrin 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 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 ingredient 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, lightheadedness, fast heartbeat, sweating and loss of consciousness (anaphylactic reaction).

Other side effects

The following side effects have been observed with the active ingredient 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: Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 6 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 3350 (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

Norgine Pharmaceuticals Limited

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UB9 6NS,

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Manufacturer
Norgine B.V.
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The Netherlands

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Other sources of information
If you need the information on this leaflet in an alternative format, such as large print, or Braille please ring 0800 198 5000.

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.

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. If a cumulative dose of 10 mg/kg or above is considered, the diagnosis of malignant hyperthermia should be re-examined.

The volume of Agilus to be administered (in mL) for a 2.5 mg/kg dose is calculated as follows:

$$\text{Volume (mL)} = \text{Patient's body weight (kg)} \times 2.5 \text{ mg/kg} \times \frac{22.6 \text{ mL}}{120 \text{ mg}}$$

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.

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 6 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 6 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.