UK Prescribing Information: Agilus® (dantrolene sodium hemiheptahydrate) 120 mg powder for solution for injection

Prescribers should refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each vial contains 120 mg dantrolene sodium hemiheptahydrate powder for solution for injection.

Indication: For the treatment of malignant hyperthermia (MH) in adults and children of all ages in combination with adequate support measures.

Dosage and administration: Treatment with Agilus should be started as soon as a malignant hyperthermia crisis is suspected. An initial dose of Agilus of 2.5 mg/kg body weight should be administered rapidly by intravenous (IV) injection. As long as the main clinical symptoms persist, a 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. Hypermetabolic features of MH 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. For all bodyweights, the initial dose and any repeat doses should not exceed 300 mg. No dose adjustment is required for the paediatric population. Agilus is for intravenous use only. 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.

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions: The use of Agilus in the management of malignant hyperthermia is not a substitute for other supportive measures and these must be individually continued. Caution should be exercised if hyperkalaemia symptoms occur or in cases of pre-existing hyperkalaemia as an increase in serum potassium has been demonstrated in animal studies as a result of co-administration of dantrolene with verapamil. Concomitant use of Agilus and calcium channel blockers is not recommended. Due to the high pH of the solution, extravascular injection must be avoided as it can lead to tissue necrosis. Intra-arterial injections must be avoided due to the risk of vascular occlusion. If solution gets on the skin, it must be removed with sufficient water. Liver damage may occur during dantrolene therapy. Each vial of Agilus contains 3530 mg hydroxypropylbetadex (a cyclodextrin) which has been associated with ototoxicity in animal studies; 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. The potential risk for hearing impairment may be of particular concern in patients with increased risk of hearing loss. Exposure to hydroxypropylbetadex from Agilus is expected to be higher in patients with renal impairment. Agilus contains 6.9 mg sodium per vial, equivalent to 0.345% of the World Health Organisation recommended maximum daily intake for an adult.

Interactions: Concomitant use of Agilus and calcium channel blockers such as verapamil and diltiazem is not recommended since isolated case reports and animal studies indicate an interaction in the form of heart failure. Concomitant administration of Agilus with non-depolarising muscle relaxants such as vecuronium can enhance their effect.

Fertility, pregnancy and lactation: Data on the effects of dantrolene on fertility in humans are not available. There are no or limited data for the use of dantrolene in pregnant women. Dantrolene crosses the placenta and should only be used during pregnancy when the potential benefit outweighs the possible risk to mother and child. No information is available on the use of dantrolene during breastfeeding. A risk to a breastfed infant cannot be excluded as dantrolene is excreted in breastmilk. Breastfeeding should be discontinued during administration of Agilus and can be restarted 60 hours after the last dose.

Undesirable effects: Skeletal muscle weakness is the most commonly reported adverse event of intravenous dantrolene administration and is related to its mode of action. Frequency of undesirable events could not be estimated from available data.

Undesirable effects of dantrolene (acute intravenous use and chronic oral use) include: hypersensitivity, anaphylactic reaction, hyperkalaemia, dizziness, somnolence, seizure, dysarthria, headache, visual impairment, cardiac failure, bradycardia, tachycardia, thrombophlebitis, respiratory failure, respiratory depression, abdominal pain, nausea, vomiting, gastrointestinal haemorrhage, diarrhoea, dysphagia, jaundice, hepatitis, hepatic function abnormal, hepatic failure including fatal outcome, idiosyncratic or hypersensitive liver diseases, urticaria, erythema, hyperhidrosis, muscle weakness, muscle fatigue, crystalluria, uterine hypotonus, fatigue, administration site reaction and asthenia.

Prescribers should consult the SmPC in relation to other adverse reactions.

Legal category: Prescription Only Medicine (POM)

Pack size: 6 vials

NHS Price: £2,184.85 per pack

Marketing authorisation holders: Norgine Pharmaceuticals Limited, Norgine House, Widewater Place, Moorhall Road, Harefield, Uxbridge, UB9 6NS, UK (GB); Norgine B.V., Antonio Vivaldistraat 150, 1083 HP Amsterdam, Netherlands (NI)
Marketing authorisation numbers: PLGB 20011/0075 (GB); EU/1/24/1805/001, EU/1/24/1805/002 (NI)

Date of preparation: August 2024

Ref: UK-EC-AGI-2400008

Adverse events should be reported. Reporting forms and information can be found at http://www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Norgine Pharmaceuticals Ltd on: Tel: +44 (0)1895 826 606 Email: medinfo@norgine.com

NORGINE

UK Prescribing Information: Dantrium (dantrolene sodium) IV 20mg

Please refer to full Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Each vial contains 20mg dantrolene sodium powder for solution for injection.

Indication: In combination with adequate support measures, Dantrium IV is indicated in adults and children in the treatment of malignant hyperthermia (MH).

Dosage and administration: Rapid intravenous (IV) injection at least 2.5mg/kg body weight. As long as the main clinical symptoms of MH persist, bolus injection should be repeated. In most cases, a total dose of 10mg/kg body weight per 24hr is sufficient, but may need to be exceeded in individual cases. No dose adjustment required for a paediatric population.

Each vial should be prepared by adding 60ml of sterile water for injection and the vial shaken until the solution is dissolved. After reconstitution, the solution should be filtered using the single use filter provided when drawing up the solution into the syringe. The reconstituted solution must be used within 6 hours but filtered immediately before use. Remove the filtration device from the syringe prior to attachment to an intravenous cannula or giving set.

Contraindications: Hypersensitivity to dantrolene or any of the excipients.

Warnings and precautions: The use of Dantrium IV in the management of malignant hyperthermic crisis is not a substitute for other supportive measures.

Dantrium IV may only be infused intravenously. Extravascular injection/infusion must be avoided as it can lead to tissue necrosis. Intraarterial injections must be avoided due to the risk of vascular occlusion. If solution gets on the skin, it must be removed with sufficient water.

Due to the potential for undissolved crystals/particles to appear in the re-constituted product, use of the filtration device when drawing up the solution is required at all times.

Each vial of Dantrium IV contains 3g mannitol. This amount should be considered if mannitol is used to prevent and treat renal complications related to malignant hyperthermia.

Caution should be exercised in cases of pre-existing hyperkalaemia or if hyperkalaemia symptoms occur as an increase in serum potassium has been demonstrated in animal trials as a result of dantrolene.

Liver damage may occur during dantrolene therapy, dependent on the dosage and duration of therapy, and may run a lethal course.

This medicine contains less than 1mmol sodium (23mg) per vial that is to say essentially “sodium free.”

Interactions: It is recommended that Dantrium IV and calcium channel blockers should not be used at the same time due to isolated case reports of an interaction in the form of heart failure. Administration of dantrolene may potentiate the effects of non-depolarising muscle relaxants.

Fertility, pregnancy and lactation: There are no or limited data from the use of dantrolene in pregnant women. Dantrolene crosses the placenta, and should be given only when the potential benefits have been weighed against the possible risk to mother and child. No information is available on the use of dantrolene sodium during breastfeeding. Breastfeeding should be discontinued during administration of Dantrium IV and can be restarted 60 hours after the last dose. Data on the effects of dantrolene on fertility in humans are not available.

Effects on ability to drive and use machines: Dantrium IV has major influence on the ability to drive and use machinery, as it can lead to weakness, dizziness and light-headedness.

Undesirable effects: Frequency of undesirable effects is unknown (could not be estimated due to present data): allergic reactions, anaphylaxis, hyperkalaemia, drowsiness, dizziness, general weakness, somnolence, convulsion, speech disorder, headache, cardiac failure, bradycardia, tachycardia, thrombophlebitis, pulmonary oedema, pleural effusion, respiratory failure, respiratory depression, abdominal pain/cramps, nausea, vomiting, gastrointestinal bleeding, diarrhoea, jaundice, hepatitis, hepatic dysfunction including fatal hepatic failure, idiosyncratic or hypersensitive liver diseases, urticaria, erythema, hyperhidrosis, muscle weakness, muscle fatigue, crystalluria, uterine hypotonia, fatigue, and administration site reactions.

Prescribers should consult the SmPC in relation to all adverse reactions.

Legal category: POM

Cost: £612 per 12 vial pack

Marketing Authorisation holder: Norgine Pharmaceuticals Limited, Norgine House, Widewater Place, Moorhall Road, Harefield, Uxbridge, UB9 6NS, UK.

Marketing Authorisation number: PL 20011/0034

For further information contact:
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Adverse events should be reported. Reporting forms and information can be found at http://www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Norgine Pharmaceuticals Ltd on: Tel: +44 (0)1895 826 606 Email: medinfo@norgine.com

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