Health Technology Briefing
December 2022

NPJ5008 for treating malignant hyperthermia

Company/Developer	Norgine Pharmaceuticals Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 35366	NICE ID: Not Available	UKPS ID: 666917

Licensing and Market Availability Plans

Currently in clinical trials

Summary

Dantrolene sodium is a muscle relaxant drug that is used for the treatment of malignant hyperthermia (MH). An improved formulation of dantrolene sodium (NPJ5008) is currently in development. MH is a rare life-threatening condition triggered by general anaesthetic drugs used in surgery. MH is more common in males, or those who have had a close relative experience the condition, but can occur in anyone, with nearly half of reported MH cases being in children. MH symptoms include high body temperature, elevated carbon dioxide levels, sustained muscle contractions, and can result in death if not treated quickly. There are currently no NICE recommended treatments for MH. Faster delivery of medication to patients with MH have been shown to reduce mortality.

During an MH episode, the triggering anaesthetic causes abnormal receptors (proteins) in the patient's skeletal muscle to become stuck in the open position, resulting in sustained muscle contraction, leading to the symptoms of the disease. Dantrolene sodium stabilises these abnormal receptors allowing them to close and break the deadly metabolic cascade. Dantrolene sodium is administered intravenously. If licenced, NPJ5008 will offer a new treatment option for patients with MH.

Proposed Indication

The treatment of malignant hyperthermia (MH).[a]

Technology

Description

NPJ5008 is in development as a new formulation of dantrolene sodium (Dantrium).[a] Dantrolene sodium a postsynaptic skeletal muscle relaxant that acts as an antagonist to defective ryanodine receptors (calcium channels in the sarcoplasmic reticulum of the skeletal muscle), therefore halting and preventing the further progression of the symptoms of MH. Dantrolene sodium acts intracellularly in skeletal muscle to lessen the excitation-contraction coupling interaction between actin and myosin within the individual sarcomere. This function occurs by stabilising ryanodine receptors 1 (RYR1) within the sarcoplasmic reticulum, which inhibits the release of calcium ions vital to the contraction process.[1,2]

Key Innovation

Faster administration with dantrolene has been directly correlated with improved outcomes in the treatment of MH, and so speed of preparation and administration relate directly to the efficacy of the product.[3] If licensed, NPJ5008 will offer a new treatment option for patients with MH, who currently have no NICE recommended technologies.

Regulatory & Development Status

Dantrolene sodium (IV) currently has Marketing Authorisation in the EU/UK for the treatment of MH.[2]

Dantrolene sodium is currently in phase III/II development for:[4]

- Heat stroke
- Drug toxicity

Dantrolene sodium was awarded orphan drug status in the EU in 2014 for the treatment of MH.[5]

NPJ5008 is not currently in phase III/ II development for any other indications.[6]

Patient Group

Disease Area and Clinical Need

MH is a rare anaesthetic emergency. Symptoms of MH result from homeostatic mechanisms within the skeletal muscle cells that compensate for increased cytoplasmic calcium released by the triggering volatile anaesthetic drugs and/or succinylcholine. The compensation by cellular processes results in increased metabolism, increased oxygen consumption and carbon dioxide production, increased heart rate and body temperature, sustained skeletal muscle contraction and often cardiac arrythmias. Compartment syndrome often also occurs due to mass swelling, as well as blood clots, and renal injury. MH can occur on highly variable time scales from 10 minutes after anaesthetic administration up to hours later. MH is more common in paediatric patients and males, and in patients who have received suxamethoniumsuccinylcholine.[7]

[a] Information provided by Norgine Pharmaceuticals

In the UK, there are approximately 20 confirmed new cases of MH each year.[7] Data from the Royal College of Anaesthetists' National Audit Projects (NAP5 and NAP6), estimate the incidence of MH in the UK to be approximately 1:100,000 general anaesthetics administered. Approximately 3.13 million general anaesthetics are administered every year in the UK.[8,9] MH has a mortality rate of approximately 4% in the UK.[7] In England (2021-22), there were 8 finished consultant episodes (FCE) (ICD-10 code: T88.3, malignant hyperthermia due to anaesthesia), that resulted in 5 admissions, 10 FCE bed days, and 1 day case.[10]

Recommended Treatment Options

Once MH is suspected anaesthetists will stop the administration of the anaesthetic drugs causing the reaction and try and cool the patient. Dantrolene sodium is licensed for use in MH and widely used but does not have a NICE recommendation.[11,12]

Clinical Trial Information

Clinical trial information was confidential at the time of producing this briefing.

Estimated Cost

The cost of NPJ5008 was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- European Malignant Hyperthermia Group. Consensus guidelines on perioperative management of malignant hyperthermia suspected or susceptible patients. 2021.[13]
- Association of Anaesthetists. Guidelines: Malignant hyperthermia. 2020.[7]

Additional Information

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