## VI.2 Elements for a Public Summary

### VI.2.1 Overview of disease epidemiology

Malignant hyperthermia (MH) is a rare inherited disorder in which patients develop life-threatening reactions when exposed to inhaled anaesthetics for general anaesthesia (anaesthetic that affects the whole body and usually causes a loss of consciousness).

Although accurate estimates of the number of patients affected by MH are difficult to make, MH is likely to occur in about 1 per 10,000 to 250,000 anaesthetic procedures in a normal hospital population including both adults and children. Both sexes can be affected although it is seen more frequently in males, particularly between the ages of 10 to 30 years old. It is also important to note that a history of previous anaesthesia without complications does not exclude the possibility of MH. The classic signs of MH include a rapid rise in body temperature, abnormally rapid heart rate, abnormally rapid breathing, increased carbon dioxide production, increased oxygen consumption, increased levels of potassium within the blood and muscle stiffness. If untreated syndrome is likely to be

fatal, however fatality occurs in less than 5% of MH cases following the availability of dantrolene treatment.

### VI.2.2 Summary of treatment benefits

Dantrolene is the only available drug for this life-threatening medical emergency and it is reported that death rate in MH affected patients has fallen from 70-80% to less than 5% following the availability of dantrolene for its treatment . This improvement is also due to the increased awareness of the condition, supportive care and the availability of genetic testing. Following diagnosis of MH, DNA analysis can be performed to screen for a Ryanodine receptor 1 (RYR1) mutation in an individual and in their family members.

A study of 129 patients, which confirmed to be susceptible to MH, found that complications occurred in 20.1% of patients, the most common complication being kidney dysfunction. When 20 or more minutes between the first adverse sign and dantrolene treatment elapsed, complication rates increased to greater than or equal to 30% .

### VI.2.3 Unknowns relating to treatment benefits

Dantrolene appears to be equally effective in patients of different age, sex and race when it is used as recommended to treat malignant hyperthermia.

.

### VI.2.4 Summary of safety concerns

**Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Risk of side effects when used with other medicine (Drug interaction) | Dantrolene may interact with drugs known as calcium channel blockers. These drugs are taken to lower blood pressure. When taken with dantrolene this could lead to heart problems. Dantrolene may also have an effect on certain muscle relaxants, like vecuronium. | Patients should be monitored while receiving dantrolene. Caution is advised when using other medicines at the same time, such as calcium channel blockers of muscle relaxants. |
| Dantrolene-induced liver problem (hepatic dysfunction) | Dantrolene can potentially cause liver toxicity, which could be fatal. This chance is increased in certain patients: those receiving high dose treatment, prolonged treatment, female patients and elderly patients. | Always use the minimum dose required for the minimum duration. Patients should be monitored while receiving dantrolene. |

**Important potential risks**

| Risk | What is known (including reason why it is considered a potential risk) |
|---|---|
| Risk of causing local tissue damage (skin reaction) or in the vein due to particles forming following mixing (Visible | Risk of causing local tissue damage (skin reaction) or in the vein where the drug is being injected. As per the information leaflets, the number of patients affected is not known. Treatment depends on the |

| | |
|---|---|
| particle formation in reconstituted solution) | severity, extent, and symptoms. If left untreated local tissue damage can result in skin necrosis and possible death. |
| Medication errors (during administration or mixing) | Medication errors can occur due to the requirement to mix dantrolene solution with water (reconstitute) and also due to the specific administration requirements. |
| Treatment not working effectively (Lack of efficacy) | Lack of efficacy can occur due to the wide dosing range of dantrolene. |
| Serious skin reactions including the leaking into surrounding tissue (extravasation) | Due to the high pH (alkaline solution) of dantrolene, there is the potential for skin cell death (necrosis) if the solutions touches the surrounding tissue. |

**Missing information**

| **Risk** | **What is known (including reason why it is a missing information)** |
|---|---|
| Use in pregnancy and lactation (breastfeeding) | The safety of dantrolene in pregnant or breastfeeding women has not been established and should only be used when potential benefits outweigh the risks to the mother and child. |
| Use for other indications or at doses higher than recommended<br><br>(Off label use) | Dantrolene is only indicated for the treatment of malignant hyperthermia. As such, its safety and efficacy for the treatment of other conditions is not known. The safety of dantrolene at doses higher than those recommend is not known. |

### VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures).

These additional risk minimisation measures are for the following risks:

## Risk of causing skin damage (skin reaction) or in the vein due to visible particle formation

| **Risk minimisation measure** | Filtering device |
|---|---|
| Objective and rationale | The objective is to make sure that particles remain in the vial and are not drawn up to the syringe and they do not get administered to patients. This way risk of severe skin reactions leading to potential skin necrosis or thrombophlebitis is minimised |
| Description | The filtering device is part of the pack and distributed with every vial of DANTRIUM. Instructions on how to use it are included in the product information, including pictograms for a better understanding of the usage. |

| **Risk minimisation measure** | Dear Healthcare Professional Communication |
|---|---|
| Objective and rationale | The objective is for HCPs to understand how to apply the filtering device and also to inform them of the risk of not applying the filtering device<br><br>The letter also instructs on what to do with old product which was accompanied by a different filtering device. |
| Description | Letters to healthcare professional ensuring that communication about the need to always apply the filtering device when drawing up the product from the vial, before administering to patients. |

**Medication error**

| | |
|---|---|
| **Risk minimisation measure** | Physician's leaflet containing information for healthcare professionals on product re-constitution (in UK, IE, NL only)<br><br>Dear Healthcare Professional Co**mmunication** |
| Objective and rationale | The objective is for HCPs to understand how to apply the filtering device and also to inform them of the risk of not applying the filtering device<br><br>The letter also instructs on what to do with old product which was accompanied by a different filtering device. |
| Description | Guide to physicians, including letters to healthcare professional ensuring that communication about the need to always apply the filtering device when drawing up the product from the vial, before administering to patients. |

## VI.2.6 Planned post authorisation development plan

Not applicable

## VI.2.7 Summary of changes to the Risk Management Plan over time

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| 1.0 | 18 Jul 2014 | • New RMP, produced to specifically address risk management of the introduction of an in-line filter device to manage the risk of particle formulation in reconstituted solution from a special request from the MHRA.<br>• This has been adopted as an interim measure, pending definitive remediation activities to avoid an out of stock situation. | First RMP submitted to MHRA only |
| 1.1 | 29 Feb 2016 | • Template update to comply with the new EU-RMP | Template update only erroneously were considered administrative only on the basis that the DLP has not changed and no new data was evaluated |
| 2.0 | 07 April 2017 | • This version of the RMP was created to remove the additional risk minimisation measure of bi-monthly report to monitor ICSRs to check for increased incidence/ severity of thrombophlebitis & skin reactions for the important identified risk 'Particle formation | N/A |

| | | | |
|---|---|---|---|
| | | (of active substance) in reconstituted solution in some batches'. The bi-monthly monitoring revealed no safety concerns with the use of the filtration device. All newly released packs of Dantrolene sodium will now be supplied with a filtration device as a permanent fixture to prevent the particle formation.<br>• Proposed text added for posology and route of administration in the EEA.<br>• Summary of the non-clinical findings and their relevance to humans were updated in section Module SII – Non-clinical part of the safety specification.<br>• Non-study post authorisation patient exposure data updated.<br>• Fertility, pregnancy and lactation added as a missing information under summary of safety concerns and Pharmacovigilance Plan.<br>• Summary of risk minimisation updated for important identified risk and missing information.<br>• Annex 2 SmPC and Package Leaflet and Annex 3 Worldwide marketing authorisation by country (including EEA) updated. | |
| 3.0 | Nov-2017 | • Addressing the comments from MHRA and other Concerned Member States during the assessment of the WorkSharing variation to include the filtration device BBraun mini-spike as a permanent fixture to the quality issue of particle formation.<br>• Update on the List of Safety Concerns in line with CA request<br>• Update of the text referred to as Routine Risk Minimization measure in line with the updated SmPC and PILs<br>• Inclusion of the filtration device as RMM to address the risk of increased incidence/severity of skin reactions or thrombophlebitis due to particle formation<br>• Inclusion on DHCP and Physician leaflet as additional RMM to inform HCPs of the need to use the filtration device, to address the risk of medication error.<br>• Updates throughout the RMP to include the new list of safety concerns | |

| | | | |
|---|---|---|---|
| | | • Provided a short summary of the review of the bi-monthly reports prepared to evaluate the possible adverse drug reactions pre and post filtration device<br>• Updates of the Elements for the Public Summary section : lay language and consistency with the other RMP sections | |
| 3.1 | 03 May 218 | • Addressing the comments from MHRA and other Concerned Member States<br>• Rewording the particle formation risk and adding venous thromboembolism and embolism to other organs as description of severity and impact of the risk<br>• Inclusion of the quality tests that have been performed to characterize the particles<br>• Addition of information in V.2 Risk minimisation measure failure<br>• Rephrasing the text in section VI.2 Elements for Public Summary<br>• Modification of DHPC text in line with MHRA request | NA |
| 3.2 | 28 Nov 2018 | • Addressing the comments from Belgium and Ireland CA<br>• Adding the DHCP as RMM to the particle formation risk<br>• Adding indication background to DHPC<br>• Adding Annual Report as other routine PhV activity in part III | None |

# Part VII: Annexes