IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Multimin Solution for Injection for Cattle

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number	IE/V/0322/001/DC
Name, strength and pharmaceutical form	Multimin Solution for Injection for Cattle
Active substances	Manganese (as manganese carbonate), copper (as copper carbonate), zinc (as zinc oxide) and selenium (as sodium selenite)
Marketing Authorisation Holder	Warburton Technology 36 Fitzwilliam Square Dublin 2 Ireland
Legal basis of application	Full application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of completion of procedure	25th March 2015
Target species	Cattle
Indication for use	Supply of trace minerals to correct concurrent clinical or subclinical deficiencies of selenium, copper, manganese and zinc which can arise during critical phases of the production or breeding life cycle.
ATCvet code	QA12CX99
Concerned Member States	FR, UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

It has been shown that the product can be safely used in the target species. While local reactions at the injection site are common, swelling resolves over time. The potential for local reactions associated with use of the product is adequately described in the SPC.

The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the product was demonstrated according to the claims made in the SPC.

The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains 10 mg of manganese (as manganese carbonate), 15 mg of copper (as copper carbonate), 60 mg of zinc (as zinc oxide) and 5 mg of selenium (as sodium selenite) and the excipients benzyl alcohol, edetic acid, sodium hydroxide and water for injections.
The container/closure system is 100 ml or 500 ml clear polyethylene terephthalate bottles with rubber stoppers and aluminium caps.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance manganese (as manganese carbonate), is an established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance copper (as copper carbonate), is an established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance zinc (as zinc oxide), is an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance selenium (as sodium selenite), is an established active substance described in the European
Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with the specifications has been provided.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D. Control on Intermediate Products

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods has been provided.
Batch analytical data from the proposed production sites has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substances has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances when stored under the approved conditions.

Stability data on the finished product has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. ***G. Other Information*** Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has reviewed the published literature and presented information on the pharmacodynamic properties of manganese, copper, zinc and selenium. It can be accepted that the active substances included in the candidate formulation are essential trace mineral elements that have a role in a wide variety of metabolic pathways involved in proper physiological functioning. Appropriate information on the role/function of each mineral in different metabolic pathways is included in section 5.1 of the SPC.

Information on the pharmacokinetics of the individual active substances has been presented. While limited information on pharmacokinetics following parenteral administration is included, it is accepted that the general information on distribution, metabolism and excretion is applicable regardless of the route of administration. Also, it appears from the residue depletion data presented in Part 3B of the dossier that the minerals do not persist at the site of injection. It is reasonable to conclude, therefore, that once injected subcutaneously the minerals move from the site of injection and become systemically available. Given the proposed indication ("Supply of trace minerals….") and the fact that the residue depletion data presented appear to indicate that the minerals move rapidly from the site of injection and become systemically available, it is accepted that the pharmacokinetic data presented is adequate.

Toxicological Studies

A large body of toxicity data on each of the minerals has been presented. Much of this information has already been scientifically assessed by the CVMP within the context of the MRL applications. As all four of the mineral compounds
(manganese carbonate, copper carbonate, zinc oxide and selenium selenite) included in the candidate formulation are included in table 1 of the Annex to Commission Regulation No. 37/2010 with "no MRL required" status, it is concluded that, from a consumer safety perspective, the candidate formulation will not present an unacceptable risk.
In general terms, the data presented are adequate for risk characterisation in the user safety assessment.

Other Studies

The applicant has provided the results of an *in-vitro* skin irritation test and an *in-vitro* cornea irritation test which indicates that the proposed formulation will be non-irritant to skin and eyes.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. In this assessment, the applicant has adequately considered the most important routes of exposure (accidental self-injection, accidental dermal contact and accidental oral ingestion following hand-to-mouth contact). Based on the risk assessment conducted, it is noted that there are concerns relating to selenium toxicity in the event of accidental self-injection. None of these scenarios is considered to pose an unacceptable risk.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

Phase I

The environmental risk assessment can stop in Phase I because when the product is used as intended it does not pose a risk to the environment.

Conclusion

Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues Documentation

Residue Studies

The results of a GLP-compliant residue depletion study and a method validation report were provided.
For each of the minerals included in the combination, the general approach to the determination of the meat withdrawal period is as follows:

- For each animal at each time-point, the sum of the residues in the standard food basket was determined, where the residue amount in muscle is replaced by the amount at the injection site.
- When tissue concentrations were below the LOD or below the LOQ, ½ LOD or ½ LOQ values were used.
- At each time-point, total residues (based on the standard food basket) were compared to the tolerable upper intake level for adults. Tolerable upper intake level, as reported in published literature, can be accepted in the absence of formal ADIs.

The general approach used for determining an appropriate withdrawal period for meat is considered acceptable.

MRLs

The minerals are all listed in Table I of the Annex to Commission Regulation (EU) No 37/2010, with "No MRL required" status.

Withdrawal Periods

As advised, for determination of an appropriate meat withdrawal period, total residues at each time-point, were compared to an accepted tolerable upper intake level for adults. Using this approach an 8 day meat withdrawal period was proposed. It is accepted that this is more than adequate to ensure consumer safety.

Given the MRL status of each of the substances ('no MRL required'), a zero day withdrawal period can be accepted for milk.

IV. CLINICAL ASSESSMENT

Pharmacology

See Part III.

Tolerance in the Target Species of Animals

In order to investigate tolerance to the final formulation, the applicant has presented the results of four GLP target animal safety studies, one of which was a local tolerance study conducted with the product proposed for marketing. Based on the information presented, it is accepted that systemic toxicity does not occur at the recommended treatment dose or at three times the recommended treatment dose. However, the possibility exists for systemic intolerance at 5 x RTD following repeated administration on three consecutive days (characterised by liver pathology).

Regarding local tolerance, it is clear that injection site reactions can occur following subcutaneous administration of the candidate formulation at the recommended treatment dose. Clinically, injection site reactions are characterised by:

 mild pain at the time of injection which can persist for the first hour after injection; moderate to severe swelling at the injection site resolving within 48 hours; and mild induration up to Day 14.

Based on the TAS studies conducted, it is accepted that tolerance to the product has been adequately characterised. While the results of the TAS studies suggest that injection site reactions are common following administration of the candidate product, a variety of additional data are provided which indicates that the product is well tolerated under field use.

The product literature accurately reflects the type and incidence of adverse effects which might be expected. It is proposed that the product is safe for use during pregnancy, lactation and in breeding animals when administered at the recommended treatment dose. The applicant provided literature reports relating to six studies conducted to evaluate the effect of injections of a trace mineral solution containing copper, selenium, zinc and manganese during pregnancy, lactation and in breeding females. The studies were conducted in a large number of heifers/cows of different breeds. The findings of these studies with respect to various reproductive parameters do not provide any indication that the administration of Zn, Mn, Cu and Se in combination by the subcutaneous route, and at doses close to the RTD for Multimin, is associated with adverse effects on breeding and/or pregnancy. Accordingly, the advice that the product can be used during pregnancy and lactation, proposed for inclusion in section 4.7 of the SPC, can be accepted.

IV.B Clinical Studies

The purpose of the product is to correct or prevent deficiencies where there is an increased physiological need. It is accepted that the correction of subclinical deficiencies, as may arise at a time of increased physiological demand, is a legitimate treatment objective. In addition, the indication states that the combination is to be used in situations where all four minerals are considered necessary (albeit not for the treatment of a distinct clinical condition).

It is noted that trace mineral supplementation of production animals at times of physiological need is common practice. For the most part such supplementation is by the oral route. However, as highlighted by the applicant, parenteral administration offers advantages over oral supplementation in that it may improve availability (does not have the same variability associated with oral intake) and rules out the potential for interference (in absorption) by other dietary constituents.

In support of the proposed indication, the applicant provides detailed bibliography which shows that:

1. Selenium, copper, manganese and zinc are essential nutrients;
2. Subclinical trace mineral deficiencies have a negative impact on animal health and production;
3. Copper, manganese, selenium and zinc are all considered important to the functioning of the enzymatic antioxidant system and are therefore important to combat oxidative stress. Combating oxidative stress is necessary to support adequate immune, reproductive and metabolic function in cattle;
4. Despite widespread oral trace mineral supplementation in Europe, the occurrence of herds of low trace mineral status is common;
5. Periods of oxidative stress occur at key stages in the production and breeding life cycle. The physiological demand for these trace minerals can be increased during periods of stress. In times of stress, oral supplementation may not effectively address the animals trace mineral needs due to variation in mineral intake;
6. Multimin administration is associated with increased levels of key antioxidants; and
7. For each of the minerals included in Multimin, the maximum doses do not exceed international and scientifically accepted limits.

Based on the totality of information presented, it is accepted that there is a need for supplementation of cattle with essential trace minerals during periods of stress at key stages in the production and breeding life cycle. At such times, supplementation by the oral route may not adequately address the animals' needs.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the HPRA website.

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Quality Changes

Summary of change (Application number)	**Approval date**
Change to composition of the veterinary medicinal product (IE/V/0322/001/DX/001)	6th February 2019