IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Novomate 277.8 mg/ml powder and solvent for suspension for injection for cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0613/001 (formerly UK/V/0539/1)
Name, strength and pharmaceutical form	Novomate 277.8 mg/ml powder and solvent for suspension for injection for cattle
Active substances(s)	Penethamate hydriodide
Applicant	Lohmann Pharma Herstellung GmbH, Heinz-Lohmann-Strasse 5, 27472 Cuxhaven, Germany
Legal basis of application	Hybrid application (Article 13(3) of Directive No 2001/82/EC)
Date of Authorisation	23 September 2015 (UK) 04 December 2015 (IE)
Target species	Cattle
Indication for use	Treatment of mastitis in lactating cows caused by *Streptococcus uberis, Streptococcus dysgalactiae, Streptococcus agalactiae* and *Staphylococcus aureus* (beta-lactamase non-producing), sensitive to penicillin.
ATCvet code	QJ01CE90
Concerned Member States	Austria, Belgium, Denmark, France, Ireland (now RMS), Netherlands, Poland, Portugal, Spain

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

Novomate 277.8 mg/ml Solvent and Suspension for Injection has been developed as a generic hybrid of Mamyzin 269.5 mg/ml Powder and Solvent for Suspension for Injection. The reference product has been authorised in the UK since March 2000. This is a hybrid application as a different strength has been used in this product compared to the reference product.

The product is indicated for the treatment of mastitis in lactating cows caused by penicillin sensitive bacteria. The suspension should be reconstituted prior to intramuscular injection at a dose of 15 mg penethamate hydriodide per kg bodyweight. The product is contraindicated in animals known to be hypersensitive to β-lactams, and/or any of the excipients. It should also not be administered intravenously.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated 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

II.A. Composition

The product contains penthamate (as penethamate hydriodide) as the active substance. Following reconstitution each ml of the solution contains 277.8 mg of the active substance. The excipients are methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate, sodium citrate, polysorbate 80, citric acid monohydrate and water for injections.

The container/closure system consists of colourless Type I and Type II vials closed with bromobutyl rubber stoppers and aluminium caps. The powder is supplied in 30 ml or 50 ml siliconized glass vials, whilst the solvent is supplies in 20 ml or 50 ml glass vials. The powder and solvent are supplied as a pair and packaged in cardboard cartons. The particulars of the containers and controls performed are provided and conform to the regulation.

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

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of filling the powdered active substance into vials under aseptic conditions. The solvent is made by mixing the excipients and adjusting the pH as necessary, before sterilising the solution which is finally filled into the glass vials. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is penethamate hydriodide, an established active substance not described in a Pharmacopoeia. Data on the active substance have been supplied in the form of an Active Substance Master file (ASMF). The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

The excipients are each manufactured in accordance with their respective European Pharmacopoeia (Ph. Eur.) monographs. Certificates of analysis have been provided.

II.C.4. Substances of Biological Origin

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

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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. Control tests on the finished product include those for identification and assay of the active substance, identification of impurities, pH, extractable mass, particle size and microbiological purity.

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

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A retest period of 3 years has been proposed for the substance when stored below 25°C and protected from light.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Data were provided for batches stored at 25°C/60%RH for up to 36 months, at 30°C/65%RH for 12 months and at 40°C/75%RH for 6 months.

In addition, data were provided for the reconstituted solution stored at 25°C/60%RH and at 5°C for up to 7 days. The vial was stored following reconstitution to form a homogenous solution and withdrawal of a dose. A further dose was removed part way through storage.

II. G. Other Information

Shelf life

Shelf life of the finished product as packaged for sale is 3 years.
Shelf life after reconstitution according to directions:
Storage in refrigerator (2°C - 8°C) is 7 days.
Storage below 25°C is 2 days.

Special precautions for storage

Powder and solvent:
Does not require any special storage conditions.

Reconstituted product:
Store the reconstituted product in the outer carton to protect from light.
Store the reconstituted product in a refrigerator (2°C - 8°C) or below 25°C.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As this is a generic hybrid application according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, results of pharmacological studies are not required.

Toxicological Studies

As this is a generic hybrid application according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, results of toxicological studies are not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the main routes of exposure are dermal through spillage onto skin, oral through hand-to-mouth contact, parenteral through accidental self-injection and inhalation of the powder. The risk to the user is low as the product will be used by trained professionals only. Bioequivalence to the reference product has been demonstrated therefore the risks to the user are considered to be the same. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-reactions to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious.
- People with known hypersensitivity to penicillins or any of the excipients should avoid contact with the veterinary medicinal product.
- Handle the product with great care to avoid exposure, taking all recommended precautions.
- If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the Doctor this warning. Swelling of the face, lips or eyes or difficulty breathing are more serious symptoms and require urgent medical attention.
- Wash hands after use.
- Care should be taken to avoid accidental self-injection. In case of accidental self-injection, seek medical advice immediately.

Environmental Safety

An Environmental Risk Assessment (ERA) has been submitted in support of the application. The ERA was conducted in accordance with VICH and CVMP guidelines.

Phase I:

The product will only be used to treat a small number of individual animals within a herd. As such environmental exposure will be low.

The initial predicted environmental concentration (PEC) in soil for intensively reared dairy cattle was also calculated. The PEC_{soil} was shown to be less than 100 µg/kg. A Phase II ERA was not required.

III.B.2 Residues documentation

Residue Studies

The applicant has conducted a confirmatory residue depletion study using the final formulation in dairy cattle. A dose of 20 mg/kg penethamate hydriodide was injected intramuscularly for 5 consecutive days. Samples of muscle were taken at necropsy, from the last injection site and surrounding muscle tissue, 6 days and 10 days after the last administration. The marker residue was benzyl penicillin.

Results show that residues depleted to below the MRL in the surrounding muscle by 6 days post-treatment, whilst for the core muscle sample the residues were all below the MRL by day 10 and most were below the MRL by day 6. The alternative method was used to set the withdrawal period as statistical analysis was not appropriate.

The analytical method was GLP-compliant, high-performance liquid chromatography coupled with mass spectrometry (UPLC-MS/MS). The method was fully validated.

MRLs

Penethamate is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues and milk. The marker substance is benzylpenicillin.

MRLs are listed below:

	All mammalian food producing species
Muscle	50 µg/kg
Liver	50 µg/kg
Kidney	50 µg/kg
Fat / skin	50 µg/kg
Milk	4 µg/kg

Withdrawal Periods

Based on the data provided, withdrawal periods have been established for meat and milk.
Meat and offal: 10 days
Milk: 96 hours

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Bioequivalence with the reference product has been demonstrated therefore no data are required regarding the pharmacodynamics.

Pharmacokinetics

An *in vivo* bioequivalence study was supplied to compare the test product with the reference following single intramuscular injection in lactating dairy cows. The study was GLP compliant and involved a two-period, two-sequence, single dose cross over design with a 7 day washout period.

Twenty healthy lactating dairy cows (3-8 years, 510 – 810 kg) were divided into 2 groups. None of the cows had received antibiotics 8 days prior to the study start. Animals received a dose of 10 mg/kg penethamate hydriodide of either the test or reference product administered via intramuscular injection divided between 2 sites. Animals were observed daily for general signs and injection sites were checked. Blood samples were taken before the injection and at regular intervals up to 48 hours post-treatment.

Pharmacokinetic parameters, including AUC[1], C_{max}[2] and T_{max}[3], were calculated. Analysis of variance was performed on log transformed data and 90% confidence intervals were calculated for AUC and C_{max}. The acceptance limits were 80-125% for AUC and 70-143% for C_{max}.

The results showed that similar pharmacokinetic profiles were produced following injection with the test or reference product. The pharmacokinetic parameters that were measured were broadly similar. The 90% confidence intervals fell within the acceptance limits for C_{max} (1.071–1.254%) and AUC (0.851–0.912%). Therefore, bioequivalence with the reference product was accepted.

Tolerance in the Target Species

Information was provided on the tolerance of the product in the target species. A specific study was not performed but evidence supporting the tolerance was identified from literature, the residue depletion study and the bioequivalence study. As bioequivalence with the reference product has been demonstrated, tolerance to the active substance can be assumed. In addition, the excipients have been used in veterinary medicine previously and data demonstrating systemic tolerance was identified in the literature.

Local tolerance was investigated during the residue depletion study. Dairy cows received intramuscular injections of the test product for 5 consecutive days. Physical examination and clinical observations were performed. The injection sites were monitored for swelling and redness, and if this was accompanied by pain or temperature; evaluation was performed using a scoring system. The only observations made following administration were some slight swelling of the injection site, which resolved without treatment. The product was generally well tolerated by the cattle, however on a few occasions animals were struggling with movements, although it was not determined if this was related to injection of the product. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

As this is a generic hybrid application according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, resistance data is not required. Adequate warnings and prudent use recommendations are included on the SPC and product literature.

IV.II. Clinical Documentation

As this is a generic hybrid application according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, results of clinical studies are not required

[1] AUC – Area under the curve
[2] C_{max} – Maximum plasma concentration
[3] T_{max} – Time to maximum concentration

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 of the product(s) is favourable.