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Publicly Available Assessment Report for a Veterinary Medicinal Product

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Ubroseal Dry Cow 2.6 g intramammary suspension for cattle

PRODUCT SUMMARY

EU Procedure Number	IE/V/0437/001 (formerly UK/V/0648/001)
Name, Strength, Pharmaceutical Form	Ubroseal Dry Cow 2.6 g intramammary suspension for cattle
Active Substances(s)	Bismuth subnitrate, heavy
Applicant	Univet Limited Tullyvin Cootehill Co. Cavan. Ireland
Legal Basis of Application	Hybrid application (Article 13(3) of Directive No 2001/82/EC)
Target Species	Cattle
Indication For Use	Prevention of new intramammary infections throughout the dry period. In cows considered likely to be free of sub-clinical mastitis, the product can be used on its own in dry cow management and mastitis control. Selection of cows for treatment with the product should be based on veterinary clinical judgement. Selection criteria may be based on the mastitis and cell count history of individual cows, or recognised tests for the detection of sub-clinical mastitis or bacteriological sampling.
ATC Code	QG52X
Date of conclusion of the decentralised procedure	01 December 2017 (UK) 02 February 2018 (IE)
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned	Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark,

Member States for original procedure	Estonia, Finland France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden UK added via change of RMS.

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

This was an application for a generic 'hybrid' product, Ubroseal Dry Cow 2.6 g Intramammary Suspension for cattle, submitted in accordance with Article 13 (3) of Directive 2001/82/EC, as amended. The reference product is Orbeseal Dry Cow Intramammary Suspension, marketed in the UK since June 2002.
This was determined as a generic 'hybrid' application, because as bismuth subnitrate is essentially insoluble in water, bioequivalence could not be demonstrated or inferred through bioavailability studies or waivers.
The product is indicated for use in cattle, for the prevention of intramammary infections throughout the dry period. Administration of the product should be based on veterinary clinical judgement and either on the mastitis and cell count history of the cow, or the detection of sub-clinical mastitis by recognised tests or bacteriological sampling. The contents of one syringe are injected into each udder quarter immediately after the last milking of the lactation.
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.[1] 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 [2] 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.
[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITY ASPECTS

II.A. Composition

The product contains 2.6 g bismuth subnitrate, heavy, and the excipients paraffin liquid, aluminium di tri stearate and silica, (colloidal, anhydrous).
The container/closure system consists of a 4g polyethylene intramammary syringe consisting of a barrel with plunger and a polyethylene dual-cap. The product may be presented in a cardboard box of 20 syringes and 20 cleaning towels, a polyethylene bucket of 60 syringes and 60 cleaning towels, or a polyethylene bucket of 120 syringes and 120 cleaning towels.
The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the absence of a preservative are 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 the mixture of liquid paraffin and aluminium di tri stearate in a heating vessel, mixing in of the active substance, assessment of appearance of the product followed by filling into syringes and sterilisation.

II.C. Control of Starting Materials

The active substance is bismuth subnitrate, heavy, an established active substance described in the European Pharmacopoeia (Ph. Eur). 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. Suitable documentation, which was in accordance with EU requirements, was provided.
The following excipients are monographed within the Ph. Eur: liquid paraffin and colloidal anhydrous silica. Aluminium di tri stearate does not appear in any European pharmacopoeia, but is subject to an acceptable in-house specification.
Packaging for the active substance and finished product fulfils the necessary requirements.

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. 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. Control tests on the finished product include those for: appearance, identification test, assay, viscosity, deliverable mass, particle size and sterility.

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.
Studies were carried out on the finished product, under VICH conditions: 25^{o}C/60% RH (60 months), 30^{o}C/65% RH (60 months), and 40^{o}C/75% RH (6 months).

G. Other Information

Based on data provided, the following stability claim was agreed:
Shelf-life of the veterinary medicinal product as packaged for sale: 24 months.
Do not store above 25°C.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Due to the legal base of the application, no toxicological or pharmacological data were required, other than those submitted to support the user risk assessment.

Toxicological Studies

User Safety

A user risk assessment was provided in compliance with the relevant guideline. The proposed product is identical to the reference product with regard to pharmaceutical form, active substance, posology and excipients. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

- Wash hands after use.
- The cleaning towels provided with the intramammary product contain isopropyl alcohol. Wear protective gloves if skin irritation due to isopropyl alcohol is known or suspected. Avoid contact with eyes because isopropyl alcohol can cause eye irritation.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The product will be used to treat a small number of animals in a herd and as such environmental exposure will be low. The assessment stopped at Question 17 of the Phase I decision tree. A Phase II ERA was not required.

III.B.2 Residues documentation

Residue Studies

The applicant was not required to provide residue depletion studies due to the legal base of the application.

MRLs

The active substance is listed in Table 1 of Regulation 37/2010 as 'No MRL Required.' Provisions are: 'For oral use only' for all food-producing species and 'For intramammary use' only for bovines. 'No MRL required' is also seen in Table 1 for liquid paraffin, and 'Out of scope' is cited for anhydrous silica.

Withdrawal Periods

Based on the data provided, (and in emulation of the reference product), the following withdrawal periods were defined:
Meat and offal: Zero days.
Milk: Zero hours.

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Due to the legal base of the application, pharmacodynamic information was not required.

Pharmacokinetics

Certain studies were waived in line with the bio-waiver guideline as cited in EMA/CVMP/344/1999-Rev.2, (previously EMA/CVMP/EWP/141272/2011):

'Efficacy and tolerance studies may be waived for generic products that are fully identical to the reference product.
Efficacy studies may also be waived if the following conditions are fulfilled: the generic product has the same pharmaceutical form and contains qualitatively and quantitatively the same active substance(s) (same salts), the excipients of the generic are qualitatively and quantitatively very similar compared to the reference product, and the physicochemical properties (e.g. crystalline form, particle size distribution, viscosity, relative density, dissolution profile) of the generic product are similar to those of the reference product.'

The request for a biowaiver was accepted under section 6 of the guideline of conduct of efficacy studies for intramammary products for use in cattle 'EMA/CVMP/344/1999-Rev.2). No further data were required.

Tolerance in the Target Species

Tolerance studies were not required due to the legal base of the application.

IV.II. Clinical Documentation

The application has been made in accordance with Article 13 (3) of Directive 2001/82/EC as amended. The active substance is a locally-acting, inert teat sealant, and therefore *in vivo* bioequivalence cannot be demonstrated or inferred as per the guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2). A waiver from the requirement to conduct *in vivo* studies is permissible as outlined in section 6 of the guideline of conduct of efficacy studies for intramammary products for use in cattle (EMA/CVMP/EWP/141272/2011). No further data were required.

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 is favourable.