



**FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
AGENCE NATIONALE DU MÉDICAMENT VÉTÉRINAIRE**

Agence nationale du médicament vétérinaire
14 rue Claude Bourgelat – PA de la Grande Marche – Javené - CS 70611 – 35306 FOUGERES
Cedex - FRANCE

MUTUAL RECOGNITION (FORMERLY, UK AS RMS)

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Orbeseal (France)
Orbeseal Dry cow 2.6g intramammary suspension
Orbesealer Vet - Dry Cow 2.6g intramammary suspension (Denmark Only)

DATE: 15 JULY 2019

MODULE 1**PRODUCT SUMMARY**

EU Procedure number	New product n° FR/V/0341/001 (old procedure number UK/V/0172/001/E/001) Change of RMS: 18 December 2018
Name, strength and pharmaceutical form	Orbeseal 2.6 g bismuth subnitrate / 1.858 g bismuth Intramammary suspension
Applicant	ZOETIS FRANCE 10 rue Raymond David 92240 Malakoff, France
Active substance(s)	Bismuth subnitrate, heavy
ATC Vetcode	QG52X
Target species	Cattle (dairy cows at drying-off)
Indication for use	Prevention of new intramammary infections throughout the dry period. In cows considered likely to be free of sub-clinical mastitis, Orbeseal can be used on its own in dry cow management and mastitis control.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website <http://www.anmv.anses.fr/>

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	20 th February 2003. National phase (FR): 24 th February 2014
Date product first authorised in the Reference Member State (MRP only)	25 th June 2002
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Romania, Spain <i>UK added via RMS change.</i>

I. SCIENTIFIC OVERVIEW

Orbeseal Dry Cow Intramammary Suspension was first authorised in the UK in June 2002. The product contains 2.6 g bismuth subnitrate and is indicated for prevention of new intramammary infections in dairy cows during the dry period. The product is provided in 4 g syringes and should be administered at drying off at a dose rate of one syringe per udder quarter. The product is contraindicated in cattle where clinical or sub-clinical mastitis is present at drying off.

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.

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 SPC¹.

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. *Composition*

The product contains the active substance bismuth subnitrate, heavy and the excipients liquid paraffin, aluminium di tri stearate and silica, colloidal anhydrous.

The container/closure system consists of a low density polyethylene syringe with a smooth, tapered hermetically sealed nozzle containing 4 g of the product and packaged in cartons of 24, 60 or 120 syringes. 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.

B. *Method of Preparation of the Product*

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured by sterilising the aluminium stearate and liquid paraffin and mixing

¹ SPC - Summary of Product Characteristics

to form a base. The bismuth subnitrate and silica are also sterilised before adding to the base and mixing. Finally the 4 g syringes are filled with the product under aseptic conditions. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is bismuth subnitrate, heavy, an established substance described in the European Pharmacopoeia. An in-house specification was provided, which is in accordance with the European monograph. 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 comply with their respective Ph. Eur. monographs and an in-house specification is provided for aluminium di tri stearate. Testing is performed on receipt and certificates of analysis for each excipient were received from the finished product manufacturer.

D. 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.

E. Control on intermediate products

Not applicable.

F. 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. The tests include those for identification and assay of the active substance, deliverable mass, appearance, viscosity and sterility.

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.

G. Stability

Stability data on the active substance have not been provided which is in line with the European monograph. Bismuth subnitrate is considered a very stable compound and changes to the dry powder are unlikely. A retest interval of 5 years has been determined, when the product is protected from light and moisture content is tested immediately before manufacture.

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 have been provided for the product when stored for 36 months at 25°C/60%RH and for 12 months at 40°C/75%RH. A shelf life of 5 years has been established.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- The shelf life of the product as packaged for sale is 5 years.
- There are no special precautions for storage.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

The product works by forming a physical barrier to prevent the entry of mastitis causing pathogens during the dry period. The active substance, bismuth subnitrate, is used due to its high density and molecular weight, which confers the necessary density and viscosity to the product. The high density and viscosity of the product prevent the seal moving up into the udder cistern and prevent leakage of the product from the teat. The active substance is described as inert and no antimicrobial effects have been described against mastitis causing bacteria.

Pharmacokinetics

Bismuth subnitrate is not absorbed systemically from the mammary gland. The absorption of the active substance is not required as protection against mastitis

is caused by physically sealing the teat duct. The product remains in the teat until physically removed.

Toxicological Studies

There is limited data reported in the literature regarding bismuth compounds single dose, repeat dose and reproductive toxicity. Bismuth toxicity can result from overdose, however the toxic effects are not associated with bismuth salts, such as bismuth subnitrate. Bismuth toxicity is not considered a hazard for intramammary application where there is very limited systemic absorption.

Observations in Humans

There is more information available on the adverse effects of bismuth in humans as large amounts are used worldwide, often in uncontrolled situations. Bismuth toxicity results from excessive dosage, usually from ingestion of bismuth over prolonged periods of time or administration via intramuscular injections. The adverse effects include nephrotoxicity, osteoarthropathy, encephalopathy, hepatotoxicity, stomatitis and gingivitis. Insoluble inorganic bismuth compounds have been associated with reversible encephalopathy. The risk of bismuth related toxicity is very low.

Microbiological Studies

Bismuth has been used for many years in human medicine to treat peptic and duodenal ulcers. Bismuth coats the ulcer and protects it from gastric acid. There is also some evidence to indicate bismuth subnitrate can inhibit colonic bacteria.

The applicant also submitted an in vitro study to investigate the effect of the product on dairy starter cultures. The effect of the product on the growth of the bacterial strains and the acid production in milk was measured. The results showed the product caused no significant reductions in growth rate of the bacteria and no significant effects were seen to the acidification rates when used at a higher dose than the maximum recommended dose. It was concluded the product has no effect on dairy starter cultures.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the main route of exposure would be through accidental spillage onto the skin. In this situation the amount absorbed is expected to be less than 1%, therefore exposure is considered to be very low. Specific warnings are not required and the precautions listed on the product literature are adequate to ensure safety to users of the product.

- Wash hands after use.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The applicant has provided PEC^2_{soil} calculations which determined the value was $<100 \mu\text{g/kg}$. No Phase II assessment was required based on the low PEC_{soil} value and as bismuth subnitrate is insoluble in water it will not reach groundwater or surface waters. The applicant concluded the risk of exposure to the environment is minimal and is further reduced by the disposal advice included on the SPC and product literature.

- Any unused product, seal stripped from an animal at calving or waste materials should be disposed of in accordance with national requirements.

III.B Residues documentation

Residue Studies

The applicant has provided a GLP compliant study to determine the concentration of bismuth in the blood of cattle following treatment with the product as directed. In the study 8 cows received the test product whilst 2 received a control product containing no bismuth subnitrate. Blood samples were taken before administration of the product and at regular intervals following treatment. The results showed none of the animals that had received the test product had bismuth concentrations higher than the control animals. Each of the samples taken had a bismuth level less than the limit of detection. The applicant concluded that bismuth is not absorbed systemically following intramammary administration.

The CVMP report, following assessment of pharmacokinetic data, agreed that oral absorption of bismuth subnitrate in target animals is negligible. It was concluded that the presence of bismuth residues in edible products of target animals is extremely unlikely.

A meat residue depletion study was not conducted as bismuth subnitrate is not absorbed from the udder. A milk residue depletion study has been conducted. Cows were treated with the product at drying off and the bismuth levels were measured in their milk. The concentrations in the milk were independent of the drying-off period.

MRLs

Bismuth subnitrate is listed in Annex II of Council Regulation 2377/90. No MRL has been established for bismuth subnitrate after intramammary use. This is

² PEC – Predicted Environmental Concentration

because treatment is infrequent and animals are unlikely to be sent to slaughter immediately after treatment. Bismuth is also a normal component of the human diet and systemic availability following intramammary administration is unlikely.

Withdrawal Periods

Based on the above information the withdrawal periods have been established:

- Meat and offal: Zero days
- Milk: Zero hours

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The product works by forming a physical barrier to prevent the entry of mastitis causing pathogens during the dry period. The active substance, bismuth subnitrate, is used due to its high density and molecular weight, which confers the necessary density and viscosity to the product. The high density and viscosity of the product prevent the seal moving up into the udder cistern and prevent leakage of the product from the teat. The active substance is described as inert and no antimicrobial effects have been described against mastitis causing bacteria.

Pharmacokinetics

Bismuth subnitrate is not absorbed systemically from the mammary gland. The absorption of the active substance is not required as protection against mastitis is caused by physically sealing the teat duct. The product remains in the teat until physically removed.

Tolerance in the Target Species of Animals

The applicant has conducted controlled target animal tolerance studies using multiples of the recommended dose in the target species. The first randomised, partially blinded study aimed to investigate the intramammary tolerance to the test product in lactating dairy cows. Cows were given either a single dose of the test product (1 syringe per teat) or a double dose (2 syringes per teat on one occasion) and a negative control group remained untreated. Milk samples were taken from individual quarters for somatic cell count (SCC) assay and bacteriology at milkings prior to administration. Following treatment clinical examinations were made including udder appearance, milk and behaviour. Milk

samples were analysed using the California Mastitis Test (CMT) or SCC assay for at least six milkings after treatment.

The results of the study showed mastitis occurred at a rate of 0% for the negative control group, 1.7% for the single treatment group and 5% for the double treatment group. Any affected quarters were excluded from SCC assays. No significant effects on the milk yield were seen between the three groups. The appearance of the milk and the udder quarters remained normal throughout the study, with the exception of the quarters which developed mastitis. A statistically significant difference was seen between the CMT and SCC immediately after treatment. Treatment, particularly with a double dose, was seen to increase CMT scores and SCC's. By the 6th milking all cows had normal SCC scores. Although increased SCC scores were seen, due to the rapid return to normal it was concluded that the teat seal was well tolerated.

A second study was conducted to investigate the effect of the product on calves which may ingest the remains of the product. Eight newborn calves (5 male, 3 female) which had been born to cows not treated with the product at drying off were used. The calves were allowed to suckle for the duration of the study. Within 5 hours of birth the product was administered to the calves by mixing the contents of 4 syringes with approximately 200 ml of colostrum from an untreated cow and administered using a long necked glass bottle. The calves were observed twice daily for 7 days for feeding and general health.

The results showed all the calves continued to feed normally and remained in good health throughout the study. No adverse effects were observed. The dose administered to the calves is likely to be in excess of the amount a calf would receive in the field and systemic effects are unlikely as bismuth subnitrate is very poorly absorbed. It was concluded that the ingestion of any product remaining in the udders would not have any clinically significant adverse effects on calves.

IV.B Clinical Studies

Laboratory Trials

Clinical studies have been conducted and reports provided for the test product. One study was conducted in New Zealand and reported as a published paper. A further two studies were conducted in the UK using dairy cows on commercial farms.

The study in New Zealand investigated the effect of the test product compared to another product and the use of test product with preceding antibiotic therapy. Dairy cows had at least three uninfected quarters at drying off. One of four treatments was randomly assigned to each quarter (in cows with 1 infected quarter the antibiotic treatment was assigned to this quarter); no treatment, Cevavin Dry Cow, test product, test product preceded by cloxacillin.

The study demonstrated that treatment with Cepravin and the test product, with or without antibiotic treatment, reduced the incidence of new intramammary infections during the dry period and at calving by ~90% ($P < 0.01$). No significant differences were seen between the three treatments. Most of the infections were caused by *S. uberis*. It was also reported during the study that treatment resulted in a 50% lower incidence of clinical mastitis over several months after calving.

The results of the above study may not apply directly to a European situation and the challenge faced by the animals may have been less than expected in Europe. Further studies were conducted in the UK and the results are reported in the below tables.

Study title	Negative control, randomised clinical field effectiveness study to determine the incidence of new intramammary infections during the dry period following intramammary infusion of teat seal.
Objectives	<ol style="list-style-type: none"> 1. To demonstrate the effectiveness of the test product in preventing new intramammary infections during the dry period in healthy dairy cows. 2. To compare the incidence of clinical mastitis in treated and control groups.
Test site(s)	Multi-centre, commercial farms, UK.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Orbeseal (bismuth subnitrate) aseptically administered to all 4 quarters at drying off.
Control product/placebo	Negative control. Animals received no treatment at drying off.
Animals	Dairy cows approaching the end of lactation with SCC's below 200,000 cells per ml were used from 7 commercial farms. The test product group contained 106 cows and the control group contained 105 cows.
Outcomes/endpoints	Samples were taken for bacteriological examination and all cows were observed for signs of clinical mastitis during the dry period and after calving.
Randomisation	Randomised.
Blinding	Single blind; blinding was not possible at administration but the person performing bacteriology was blinded to the animal treatment.
Method	Milk samples were taken from each quarter before drying off for bacteriology. The test product was administered to the cows in the test group at drying off. After calving the teats were stripped (for the test animals) and milk samples taken from each quarter of all the cattle. A second milk sample was taken from

	<p>each quarter of all cows between days 7 and 14 after calving.</p> <p>Cows were observed for signs of clinical mastitis throughout the study and for a minimum of 60 days after calving. If mastitis was suspected samples were taken for testing prior to administration of treatment.</p>
Statistical method	A X^2 test was used to compare the control and test group incidence of new infections and clinical mastitis cases. A P value of 0.05 was set.
RESULTS	
Outcomes for endpoints	<p>There were 6 cases of clinical mastitis reported in the control group and 1 case of clinical mastitis in the test group during the dry period. An incidence of 1.4% and 0.2% respectively. Bacteriological sampling was only performed for two cows and bacteriology indicated both cows were infected with <i>Strep. uberis</i>.</p> <p>Bacteriological sampling after calving demonstrated 73 infections occurred in the control group and 29 in the test group during the dry period. The commonly identified pathogens were <i>Strep. uberis</i>, <i>Staph. aureus</i>, and <i>E. coli</i>.</p> <p>In the first 60 days of lactation 29 cases of clinical mastitis were observed in the control group and 7 cases in the test group. The isolated pathogens were <i>Strep. uberis</i>, <i>Staph. aureus</i>, <i>E. coli</i> and <i>Strep. dysgalactiae</i>.</p> <p>The incidence of new intramammary infections during the dry period was calculated. For the negative control group the incidence was 36.1% whilst the incidence was 19.5% for the test group ($P < 0.001$). The incidence of clinical mastitis was also calculated for each group. For the control group during the dry period this was 1.4% and for the test group was 0.2% ($P > 0.05$). In the first 60 days after calving the incidence in the control group was 6.8% whilst for the test group it was 1.7% ($P < 0.001$).</p>
DISCUSSION	The applicant concluded that the use of the teat seal significantly reduced the incidence of new intramammary infections during the dry period and significantly reduced the incidence of clinical mastitis during early lactation.
Study title	Positive control, randomised, blinded clinical field effectiveness study to determine the incidence of new intramammary infections during the dry period following

	intramammary infusion of teat seal.
Objectives	<ol style="list-style-type: none"> 1. To demonstrate the effectiveness of the test product in preventing new intramammary infections during the dry period in healthy dairy cows. 2. To compare the incidence of clinical mastitis in treated and control groups.
Test site(s)	Multi-centre, commercial farms, UK.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Orbeseal (bismuth subnitrate) aseptically administered to all 4 quarters at drying off.
Control product/placebo	Positive control. Cepravin Dry Cow administered to all 4 quarters at drying off.
Animals	Dairy cows approaching the end of lactation with SCC's below 200,000 cells per ml were used from 16 commercial farms. The test product group contained 232 cows and the control group contained 237 cows.
Outcomes/endpoints	Samples were taken for bacteriological examination and all cows were observed for signs of clinical mastitis during the dry period and after calving.
Randomisation	Randomised.
Blinding	Single blind; blinding was not possible at administration but the person performing bacteriology was blinded to the animal treatment.
Method	<p>Milk samples were taken from each quarter before drying off for bacteriology. The test product was administered to the cows in the test group at drying off. After calving the teats were stripped and milk samples taken from each quarter of all the cattle. A second milk sample was taken from each quarter of all cows between days 7 and 14 after calving.</p> <p>Cows were observed for signs of clinical mastitis throughout the study and for a minimum of 60 days after calving. If mastitis was suspected samples were taken for testing prior to administration of treatment.</p>
Statistical method	A χ^2 test was used to compare the control and test group incidence of new infections and clinical mastitis cases. A P value of 0.05 was set.
RESULTS	
Outcomes for endpoints	<p>There were 2 cases of clinical mastitis reported during the dry period, both in cows from the control group. Bacteriological sampling was only performed for one cow and bacteriology indicated the causative pathogen was <i>Enterococcus</i> spp.</p> <p>Bacteriological sampling after calving demonstrated 122</p>

	<p>infections with major pathogens occurred in the control group and 65 in the test group during the dry period. The commonly identified pathogens were <i>Strep. uberis</i> and <i>E. coli</i>.</p> <p>In the first 60 days of lactation 25 cases of clinical mastitis were observed in the control group and 19 cases in the test group. The commonly isolated pathogens were <i>Strep. uberis</i> and <i>E. coli</i>.</p> <p>The incidence of all new intramammary infections during the dry period was calculated. For the negative control group the incidence was 53.2% whilst the incidence was 44.2% for the test group ($P>0.05$). The incidence of clinical mastitis was also calculated for each group. For the control group during the dry period this was 0.2% and for the test group was 0% ($P>0.05$). In the first 60 days after calving the incidence in the control group was 2.7% whilst for the test group it was 2.1% ($P>0.05$).</p>
DISCUSSION	<p>The applicant concluded that there was no statistical significance between the products. Therefore the test product was at least as effective as Cepravin Dry Cow at preventing new intramammary infections and cases of clinical mastitis during the dry period.</p>

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.

MODULE 4**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 veterinary Heads of Agencies website (www.hma.eu).

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.

No significant changes in safety or efficacy data have been made after the original procedure.

The following changes in administrative or quality data were approved:

Summary of change (Application number)	Section updated in Module 3	Approval date
Change in the DDPS - UK/V/0172/001/IA/017/G	N/A	27/04/2015
Change in the DDPS - UK/V/0172/001/IA/021/G	N/A	19/09/2018
Modification relating to the active substance UK/V/0172/001/IB/018	N/A	11/09/2015
Update of the quality dossier for harmonisation UK/V/0172/011/WS/020	N/A	22/08/2017
Updates to the SPC/PI – FR/V/0341/001/IB/022	N/A	16/05/2019