ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Alcide UDDERgold Platinum Teat Dip

PuAR correct as of 09/01/2019 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0288/001/MR
Name, strength and pharmaceutical form	Alcide UDDERgold Platinum Teat Dip
Applicant	Ecolab GmbH & Co OHG Reisholzer Werftstrasse 38-42 40589 Dusseldorf Germany
Active substance	Base - Sodium chlorite Activator – Lactic acid
ATC Vetcode	QP53AB
Target species	Cattle
Indication for use	A post-milking teat dip for use as an aid in the control of mastitis in dairy cows caused by pathogens such as *Staphylococcus aureus, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus uberis or Escherichia coli.*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual recognition application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	30 April 2008
Date product first authorised in the Reference Member State (MRP only)	25 April 1994
Concerned Member States for original procedure	Belgium Denmark Greece Ireland Italy Netherlands Portugal Spain Germany

I. SCIENTIFIC OVERVIEW

Alcide UDDERgold Platinum Teat Dip is intended for veterinary medicinal use as a topical post-milking teat disinfection material, as an aid in the control of contagious mastitis-causing organisms, which arise primarily during the immediate post-milking period. The product comprises an activator and base which are mixed together prior to use. On average, approximately 7.5ml of product will be used per cow per milking.

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

II. QUALITY ASPECTS

A. Composition

The product comprises a base and an activator. The base concentrate contains the active substance sodium chlorite and excipients disodium edetate dihydrate, polysulfonic acid, sodium hydroxide and purified water.

The activator concentrate comprises the active substance lactic acid and excipients sodium benzoate (E211), tartrazine (E102), hydroxyethyl cellulose, glycerol, sodium dodecylbenzene sulfonate and purified water.

The base and activator are supplied separately and packed in pairs of high density polyethylene (HDPE) bottles/containers with polypropylene or HDPE screw caps holding 3.785, 10 or 20 litres of the base or activator component. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and presence of preservative are 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.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance in the base concentrate is sodium chlorite an inorganic non-pharmacopoeial substance widely used in drinking water treatment. An in house specification has been provided. Batch analysis data on three batches from each supplier have been presented.

The active substance in the activator concentrate is lactic acid and the substance complies with the supplier's specifications. Batch analysis data on several batches from each supplier have been presented.

The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the materials.

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
There are no intermediate products.

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

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

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.

H. Genetically Modified Organisms
Not applicable

J. Other Information
Shelf life of the veterinary medicinal product as packaged for sale:
Base: 2 years
Activator: 2 years

Shelf life of the ready-to-use solution (1:1 mixture of Base and Activator): 3 hours

A fresh solution should be prepared immediately before use and be used within 3 hours. Any unused material should be discarded.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing
The applicant has provided a number of published references which includes summary reports of the components of the product.

Pharmacological Studies
When the active substances of Alcide UDDERgold Platinum Teat Dip, lactic acid (activator) and sodium chlorite (base) are mixed in equal volumes, chlorous acid, chlorine dioxide and other oxychlorine compounds, are formed within the gel. Thus the chemical reaction between base and activator results in the production

of activated chlorite which also affects the activity of the product not just the specific substances included in the formulae. The chlorous acid/derived species system has a highly potent and broad spectrum of antimicrobial activity. The mechanism of action of this primary antimicrobial effect is thought to be via oxidative attack at susceptible sites on the microbial envelope.

Several references relating to pharmacokinetics have also been provided. Chlorine dioxide, sodium chlorite and sodium chlorate were all shown to be well absorbed by the oral route in rats by using radio-labelled compounds. The plasma elimination half lives[1] ranged from 35 to 44 hours. The main route of excretion for sodium chlorite and chlorine dioxide appeared to be via the kidneys, predominantly as chloride with some chlorite, and a little chlorate. For sodium chlorite, 83 % of the recovered dose was found in urine, and 13 % in faeces. For chlorine dioxide and sodium chlorate no radioactivity was detected in expired air.

An evaluation of the pharmacokinetics, following dermal administration to rats using radio-labelled compounds of a product which generates the same active antimicrobial substances as Alcide UDDERgold Platinum Teat Dip was also provided. The product was applied dermally at a dosage level of 2.0 g/kg for a period of 10 consecutive days. The maximum absorption of ^{36}Cl into plasma was observed after 72 hours when a concentration of 69.4 µg/ml ^{36}Cl was reached. The elimination half-life of radio-labelled material was 64 hours and highest levels of radioactivity were found in whole blood. The urinary excretion of radioactivity was greatest in the first 24 hours and consisted of approximately equal parts of chloride and chlorite. No radioactivity was detected in either faeces or expired air at any time point studied.

Toxicological Studies

Single Dose Toxicity

References have been provided relating to the acute toxicity of chlorite ion, chlorate, chloride dioxide and lactic acid in a number of different species at different dose rates. For chlorite ions the worst case scenario was found in rats administered orally giving rise to a LD_{50} value of 140 mg/kg. For chlorine dioxide the worst case scenario was found in rats administered orally giving rise to a LD_{50} value of 292 mg/kg. The LD_{50} values of lactic acid indicate that it is classified as non-toxic. This is also demonstrated by its listing as a food additive within the European Union (E 270).

Repeated Dose Toxicity

Repeat-dose toxicity tests with chlorine dioxide, sodium chlorite and sodium chlorate gave rise to similar dose-related toxic effects in a number of different animal species. The main effect was on haematological parameters which were observed in rats and mice. Inhibition of thyroid hormone synthesis was observed in rats and African green monkeys with chlorine dioxide (9 mg/kg bwt/day in drinking water), which was dose-related and reversible on cessation of treatment. A NOEL[2] of 3 mg/kg/day was established for chlorine dioxide which

[1] Half life - The biological half-life of a substance is the time it takes for a substance (drug, radioactive nuclide, or other) to lose half of its pharmacologic, physiologic, or radiologic activity

did not affect serum thyroxine levels, whereas both sodium chlorite and sodium chlorate had no effect on thyroid function in monkeys at doses of 60 mg/kg bw/day for 30-60 days.

Reproductive Toxicity, including Teratogenicity:
Studies with chlorine dioxide, sodium chlorite and sodium chlorate suggest that they are not teratogenic in mice, rats or rabbits. At high doses of chlorine dioxide and sodium chlorite (100 mg/l of drinking water) the number of implants and live foetuses per mother tended to be reduced, and foetal weight and length birth weight were decreased. At lower doses (10 mg/l of drinking water) there were no effects on female fertility, gestation length, litter size and weight.

Male fertility was unaffected by chlorine dioxide, but sperm development was affected after treatment with 100 mg/l of sodium chlorite. Exposure to both chlorine dioxide and sodium chlorite resulted in reduced thyroid hormone levels and inhibition of locomotor activity, suggesting delayed neuro-behavioural development in young animals.

Mutagenicity
Conflicting results have been produced in the mutagenicity tests conducted with chlorine dioxide, sodium chlorite, and sodium chlorate. These conflicting mutagenicity results were considered of limited relevance.

Carcinogenicity:
Classical carcinogenicity studies were not been conducted with sodium chlorite, however chronic studies were performed where sodium chlorite was administered via drinking water at doses up to 0.05 % in mice for 80 weeks and 0.06 % in rats for 85 weeks. The survival rate and incidence of tumours were not significantly different between treated and control groups. Conventional carcinogenicity studies were not been conducted with chlorine dioxide or sodium chlorate, however, the data that are available do not suggest a significant carcinogenic hazard.

A number of references were submitted for the chlorite ion, chlorate ion and chlorine dioxide. Although some tumour incidences were reported, the results were generally equivocal or negative.

Other Studies
The acute dermal toxicity of the base and activator together with the acute oral toxicity of the mixed product were determined. All were found to be of low toxicity with LD_{50} >2000 mg/kg[3].

Eye irritation studies in rabbits were conducted for the activator and the mixed product. Conjunctival redness was reported in animals but the score was not sufficient to require the labelling “Irritating to eyes”. The base can, however, be considered as irritating to eyes.

[2] No observed effect level
[3] LD_{50} median lethal dose – These figures are frequently used as a general indicator of a substance's acute toxicity

The Activator, Base and Mixed product were also investigated for their sensitisation potential. The results showed all the components to be non-sensitisers in a test model.

Observations in Humans

A number of references were submitted as hypochlorite, chlorite and chlorine dioxide are widely used as water purifying agents. Chlorite ion was generally found to be of low toxicity to humans whereas the chlorate ion can be toxic to humans depending on the dose. Adverse reactions from chlorate ion exposure were similar affecting mainly the haemopoetic system, liver and kidneys. Chlorine dioxide was, however, found to be of low toxicity to man.

Data were provided from a clinical trial in humans exposed to 0.036 mg/kg bw daily for 12 weeks, and from a study where individuals were exposed for three months to chlorinated water with a mean chlorite concentration of 5 mg/l, and compared with non-exposed individuals. In both studies there was no evidence of any overt toxicity.

Chlorine dioxide, sodium chlorite and sodium chlorate are all present in drinking water which has been disinfected by chlorination processes.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which considered the main routes of exposure.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

The applicant submitted some information accompanied by published literature in order to address the residue aspects of the dossier. A full residue depletion study for this product was not necessary.

MRLs

Lactic acid and sodium chlorite are listed in Annex II of Council Regulation 2377/90 and therefore do not need an MRL to protect the safety of the consumer.

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days for meat and for milk are justified.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics was established for the active as well as is possible for a product of this nature. Good germicidal activity was demonstrated against relevant mastitis pathogens *in vitro* in two studies. Information provided supports the gel forming properties of the dip and its status as a barrier type dip.

Pharmacokinetic data was not provided for this product due to the nature of its action by topical disinfection, and the fact that no systemic absorption occurs; hence there is no distribution or metabolism within the animal or excretion from the animal.

Tolerance in the Target Species of Animals

The applicant provided a good body of evidence demonstrating target species tolerance and although it is not possible to do this in line with current guidelines for a product of this nature, the data presented are adequate. The tolerance is well supported by the periodic safety update report (PSUR) supplied. The data presented in conjunction with the clinical trials where only delayed healing of damaged teats was noted demonstrated the local tolerance of the product. Suitable warnings regarding these effects of the product in the healing of damaged teats have been included in the SPC.

Resistance

No formal studies on the potential for development of resistance in mastitis causing organisms were conducted with the proposed formulation. However evidence to support the notion that antimicrobial resistance[4] is not relevant to a product of this nature. It is very unlikely that resistance could occur to a chemical toxin. The mode of action was discussed by the applicant and appears to be complex, involving a disruption of intracellular protein production, a loss of permeability control, with non-specific oxidative damage to the outer membrane leading to destruction of the trans-membrane ionic gradient.

It was accepted that antimicrobial resistance is not truly applicable to a product of this nature. This was also supported by the PSUR data, since there have been no recorded events of lack of efficacy.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

Dose determination and dose confirmation are problematic in a product of this type, as no fixed dose per animal per teat can effectively be ascertained. Studies were provided which show that the formulations used have effective and rapid germicidal action at the concentrations that are recommended in the clinical situation. The MIC data generated indicated that a lower level of chemical

[4] antimicrobial resistance describes the ability of a micro-organism to resist the action of antimicrobial drugs

inclusion would not be as effective in the prevention of intramammary infections, and consequently justified the concentration recommended.

Field Trials

The applicant demonstrated significant clinical efficacy in a range of different climatic conditions in reducing the numbers of new intramammary infections occurring under field conditions. One of the clinical trials provided was based on the final formulation, and provided evidence of the efficacy of Uddergold as a post milking teat dip under field conditions. Good target species tolerance was also shown under field conditions. A significant level of efficacy has been shown against a wide range of mastitis related pathogens, comparable to other disinfectant teat dips and the efficacy statement “A post milking teat dip for use as an aid in the control of mastitis in dairy cows” is justified.

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 risk benefit 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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)