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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Kexxtone (EMEA/V/C/002235)

International non-proprietary name: Monensin sodium

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

An application for the granting of a community marketing authorisation of Kexxtone was submitted to the Agency on 28 September 2011 by Eli Lilly and Company Limited in accordance with Regulation (EC) No. 726/2004.

Kexxtone is a continuous release intraruminal device and presented in bags containing 1, 3 or 5 intraruminal devices. It is indicated for the reduction in the incidence of ketosis in the peri-parturient dairy cow/heifer which is expected to develop ketosis. The route of administration is intraruminal use. The target species is cattle (dairy cows and heifers).

The CVMP adopted an opinion and CVMP assessment report on 8 November 2012.

On 28 January 2013, the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

The applicant has provided a detailed description of the pharmacovigilance system which fulfils the requirements of Directive 2001/82/EC, as amended. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

The product is manufactured outside the EEA, and batch released in the UK. Valid manufacturing authorisations are in place for each site. Any additional inspection of these sites was not considered necessary. Appropriate declarations have been provided for the supplier of the active substance certifying that the active substance is manufactured in accordance with EU guidelines and is in compliance with GMP legislation.

The applicant received in June 2006 scientific advice by the CVMP on questions in regard to clinical development, and in March 2008 scientific advice in regard to questions on the pharmaceutical development, residue testing and target animal safety.

Part 2 - Quality

Composition

Kexxtone is presented as a cylindrical shaped intraruminal device containing a total of 32.4 g of monensin (as monensin sodium).

The core of the device is composed by a stack of twelve subunits (tablet cores) each containing 2.7 g of monensin (as monensin sodium). The monensin tablet-subunits are formulated in such way that they will, when exposed to water, form a gel that due to the pressure of the spring in the device on the tablet stack is progressively released. The tablet components contain monensin sodium as active substance; the excipients are sucrose fatty acid ester (gel forming agent), carbomer (gel forming agent), lactose monohydrate (binder/diluent), magnesium stearate (lubricant), silica, colloidal anhydrous (lubricant) and purified water (granulation agent).

The intraruminal device components are made of polypropylene (barrel, wings, plunger and orifice cap) and a spring (steel coil). A colouring agent (E110, sunset yellow) is employed for the polypropylene capsule components.

Container

One, three or five Kexxtone intraruminal device(s) are packaged in sealed aluminium foil bags.

Development pharmaceutics

The composition of this medicinal product has been properly justified on the basis of the nature of the active substance, the product is fit-for-purpose and the experience of the manufacturer in similar non-EU products. A number of *in-vivo* trials were carried out which involved a number of variations to the design of the intraruminal device and to the formulation. Detail has also been provided on the development of the manufacturing process and of the primary packaging. The method used to control monensin in the active substance and in the tablet cores is based on the HPLC method described in the USP. The method has proved to be also suitable to quantify the degradation products.

Method of manufacture

The manufacture of Kexxtone is considered a non standard process according to Annex II on Non Standard Process (CPMP/QWP/2054/03; EMEA/CVMP/395/03) to the Note for Guidance on Process Validation (EMEA/CVMP/598/99).

The finished product manufacturer has considerable experience in the manufacture of similar products, some of them marketed in EU. Limited validation data are submitted in the dossier.

Control of starting materials

Active substance

The active substance is milled monensin sodium. The active substance is a fermentation product which consists of a mixture of four factors (monensin sodium factors A - D), with factor A being the main component. A declaration that the European Pharmacopoeia (Ph. Eur.) monograph on "Products of Fermentation" has been adhered to has been attached.

The specification of the starting material is based on that of the USP monograph for monensin sodium, plus an additional requirement for particle size. It includes appearance, identification, loss on drying, assay of monensin content, determination of monensin A activity and monensin A + B activities, and particle size. The limits for monensin content are tighter than that of the United States Pharmacopoeia (USP) monograph, establishing a range of potency to ensure that assay limits of ±5% be achieved at the release of finished product. Additionally, a range for the related substances has been proposed by the applicant, are in line with the principles of VICH GL10.

Detail on the production of the active substance has been provided.

The stability studies on the active substance monensin sodium comprise tests on both un-milled and milled material. The stability testing does not include microbial testing or particle size analysis. During validation of tests for the finished product it was shown that monensin sodium does not support microbial growth. Milled material is fully tested by the finished product manufacture upon receipt to confirm compliance with the specification.

Excipients

All excipients, except the sucrose fatty acid ester, are subject to monographs in the Ph. Eur..

The components of the device (with the exception of the spring) are made from polypropylene complying with the Ph. Eur. monographs 3.1.3 and 3.2.2. The specifications and scientific data for the components used in the manufacture of the device are provided.

Primary packaging

Specifications and declarations of compliance have been provided for the primary packaging, the heat-sealed aluminium bag.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the starting materials used for the active pharmaceutical ingredient, monensin sodium, or for the excipients used in the finished product are risk materials as defined in Section 2 of the combined CPMP/CVMP "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMEA/410/01 Rev 2).

TSE certificates for other components (e.g. lactose monohydrate) are submitted accordingly.

Control tests during production

In this medicinal product the tablet core before assembly in the intraruminal device is defined as intermediate product. The compliance of the product with the "Note for Guidance on the Start of Shelf-life of the Finished Dosage Form" is confirmed.

Control tests on the finished product

The finished product is the assembled intraruminal device containing twelve tablet cores. Specification is stated for both the assembled intraruminal device and the tablet cores inside the device as stated below:

Assembled Device

Appearance (intraruminal device components and embossing of batch number), wing span, 12 tablet cores , orifice diameter and microbiological quality (total aerobic microbial count (TAMC) and combined total yeast and mould count (TYMC)).

Tablet cores

Appearance, identification of monensin (by both HPLC retention time and UV absorbance spectrum), average tablet weight, uniformity of mass (Ph. Eur. 2.9.5), uniformity of dosage units (Ph. Eur. 2.9.40), tablet thickness, tablet diameter, tablet hardness, loss on drying, friability, assay, and gel extrusion. Monensin content is referred as the carboxylic acid and not the sodium salt.

Related substances specifications for the finished product have been proposed in line with VICH GL11.

Certificates of commercial batches of the intraruminal devices will be provided.

Stability

Different shelf life/stability specification is stated for Kexxtone tablet cores for the limits in tablet thickness, diameter, hardness, as well as loss on drying, assay of monensin, related substances and gel extrusion test. The applicant will revise the proposed limits when more data are available.

VICH stability testing was carried out in batches with a larger orifice size than the one proposed in the commercial Kexxtone intraruminal device, as a larger orifice providing more contact with air is considered to provide a "worst case scenario" for stability. A bracketing design has been used for stability testing and all batches were tested with both one and five intraruminal devices per aluminium foil bag, representing the smallest and largest pack sizes. Results up to 6 months at real time, intermediate and accelerated conditions were originally provided for three batches where one intraruminal device is added per foil bag and for three batches where five intraruminal devices have been added per foil bag. All test parameters comply with the specifications set.

As updated stability data provided indicate that the product is very stable, and 12 months data has been provided for the long-term conditions, a maximum shelf-life of 2 years is allowable. A new protocol has been sent with the inclusion of an assay for the related substances, and the applicant agrees to review the proposed limits for some of the parameters according to the data obtained.

Data have been performed to establish the stability of the intraruminal devices in broached bags from T = 0 to T = 6 months supporting the proposed in-use shelf-life of 6 months. No special storage conditions are required, and no storage conditions are required with respect to freezing.

Overall conclusions on quality

The composition of this medicinal product has been properly justified on the basis of the nature of the active substance, the suitability-for-purpose of the product and the experience of the manufacturer in similar non-EU products (continuous release intraruminal devices).

The only active ingredient, monensin sodium, is a fermentation product consisting of a mixture of four factors, with factor A as the main component. Compliance of the active ingredient manufactured by Elanco with the standard as described in the USP and with the Ph. Eur. monograph on products of fermentation was demonstrated.

The manufacture of Kexxtone is considered a non standard process according to Annex II on Non Standard Process (CPMP/QWP/2054/03; EMEA/CVMP/395/03) to the Note for Guidance on Process Validation (EMEA/CVMP/598/99). The finished product manufacturer has considerable experience in the manufacture of similar products, some of them marketed in EU, so partial validation data are submitted in the dossier, but as the manufacturer has already produced batches of commercial scale, complete validation data should be available prior to the marketing of the product to confirm compliance with the currently proposed specifications.

The method used to control monensin in the active substance and in the tablet cores are based on the HPLC method described in the USP. The applicant has developed a method capable of quantifying the degradation products to be in line with the future guideline on setting specifications for impurities in antibiotics. The applicant agrees to revise the release and stability specifications once sufficient data are available.

The active ingredient is fully tested by the finished product manufacturer upon receipt to confirm compliance with the specification.

All excipients, except the sucrose fatty acid ester, are subject to monographs in the Eur. Ph.. The container closure system chosen is suitable for the dosage form and product. The finished product specification provides an assurance of the quality of the product and the tests comply with the requirements of the Ph. Eur. for the dosage form. In general, the analytical methods are considered adequate, and their validation data confirm their suitability. Stability studies have been performed according to VICH guidelines. The proposed cumulative re-test period of the active substance is 3 years, with no special storage conditions. For the finished product, the primary stability studies are on-

going. In view of the limited stability data, a shelf-life of 2 years is at this moment acceptable for the finished product.

Part 3 – Safety

Most of the safety information provided by the applicant had been previously assessed by the CVMP in the context of the application for the establishment of MRLs for monensin. A detailed description and assessment of the studies is included in the respective "Monensin European public MRL assessment report (EMEA/CVMP/185123/2007-FINAL). No additional studies have been performed regarding pharmacological or toxicological properties of monensin or the finished product.

Safety documentation

Pharmacodynamics

Pharmacodynamic properties of monensin are addressed in Part 4 of this report.

Pharmacokinetics

Pharmacokinetics properties of monensin are addressed in Part 4 of this report.

Toxicological studies

Single dose toxicity:
Monensin has a high potential for producing acute toxic effects in a wide range of species, though susceptibility for these effects are remarkably different between species. Acute toxicity signs were found to be death, anorexia, hypoactivity, skeletal muscle weakness, ataxia, diarrhoea and decreased weight gain. Oral LD_{50} were available for a range of species including rats, dogs, rabbits, mice, monkeys, horses, pigs, cattle, sheep, goats, guinea fowl, chickens and turkeys and were very variable, ranging from 1.3 - 3 mg/kg bw in horses to 346 - 416 mg/kg bw in turkeys. A warning has been included not to allow certain non-target species access to the device, as monensin might be fatal in these species.

Repeat dose toxicity:
Subchronic and chronic toxicity studies carried out in rodents and dogs showed clinical and clinico-pathologic signs of muscle related toxicity among other typical toxicological findings (decrease in body weight gain and organ weights, ataxia, anorexia, etc). In most of these studies the determination of a NOEL was not possible because of effects observed in the lowest dose groups. Based on the results of a one-year GLP compliant chronic oral dog study, the NOEL was considered to be 1.25 mg/kg bw.

Tolerance in the target species of animal:
Tolerance studies are addressed in Part 4 of this report.

Reproductive toxicity:
Monensin treatment had no effect on the reproductive parameters in two multigeneration reproduction studies carried out on three generations of rats, nor in a non-GLP compliant teratology study performed in rabbits. The apparent NOEL for maternal and embryo/foetotoxicity in this last study carried out in rabbits was 0.76 mg/kg bw (the highest dose tested).

Mutagenicity/genotoxicity:
Monensin was tested in a standard battery of genotoxicity tests and is concluded not to be genotoxic.

Carcinogenicity:
Carcinogenicity studies were performed in rats and mice. Monensin was not carcinogenic in these species.

Studies of other effects

The potential for crystalline monensin and the feed premix formulation to induce skin sensitisation was evaluated in CBA/J mice using the local lymph node assay. No clinical signs of toxicity, mortality, cutaneous reactions, or clinically significant increases in ear thickness were observed. However, there were dose-related increases in indices for lymphoproliferative response. It was concluded that monensin induced delayed contact hypersensitivity in the local lymph node assay, and would be classified as a weak sensitizer by skin exposure.

Monensin is not used in human medicines and there is very limited data on effects following direct exposure of humans to monensin. Allergic symptoms including urticaria, swelling of the face or tongue, pruritus, nasal congestion, contact dermatitis and local respiratory irritation have been reported in workers handling monensin.

The assessment of risks related to exposure of the human gut flora to residues in food was previously evaluated and a microbiological ADI of 14.46 µg/kg bw determined. Microbiological properties of monensin and development or resistance are further addressed in Part 4 of this report.

User safety

The applicant has submitted a User Risk Assessment following the guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1).

The likelihood of exposure is limited given the pharmaceutical form of the product. The only possible contact of the user with the active ingredient would be via the intraruminal device's orifice. The subunits have low potential for friability or dust generation. Therefore, during pre-application and application phases, only very small amounts of monensin are likely to come into contact with the user. During the post-application phase the animals may regurgitate the intraruminal device and the content may be externalised as a gel.

The risk of oral and ocular exposure is accepted to be negligible.

As stated above, monensin is classified as a weak sensitizer by skin exposure and allergic symptoms have been reported in workers handling monensin. Therefore, an allergenic hazard following dermal exposure to the product cannot be ruled out. As result of the user safety assessment appropriate warnings for the user have been included in the SPC and product literature.

The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

The environmental risk assessment was performed according to the guideline on environmental impact assessment for veterinary medicinal products (Phase I - CVMP/VICH/592/98-FINAL) as well as the guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL 6 and GL 38 (EMEA/CVMP/ERA/418282/2005). The primary route of environmental exposure to monensin (the active substance) or relevant metabolites will be from cattle manure applied to agricultural land, or excreted directly from animals at pasture. A phase I assessment has

been conducted taking into consideration the intended indication, use patterns, and various production scenarios.

For the purposes of this assessment it has been considered that up to 26% of animals in a herd could be classed as at risk of developing ketosis.

Calculations have been made following the equations and default values presented in the guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL 6 and GL 38 (EMEA/CVMP/ERA/418282/2005). The worst case $PEC_{soil\ initial}$ was below the threshold of 100 µg/kg and therefore a Phase II assessment was not required, in line with the VICH guidelines.

Conclusions of the environmental risk assessment

The initial Predicted Environmental Concentration in soil ($PEC_{soil,\ initial}$) is lower than 100 µg/kg. Based on the data provided, Kexxtone 32.4 g intraruminal device for cattle is not expected to pose a risk for the environment when used in accordance with the SPC.

Overall conclusions on the safety documentation

The pharmacological and toxicological profiles of monensin have been previously assessed by the CVMP during the MRL assessment procedure, and are considered to be acceptable.

Various studies addressing the tolerance and the potential for resistance development have been provided and are assessed in Part 4 of this assessment report.

The applicant has presented a User Safety Risk Assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/543/03-FINAL-Rev.1. The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

The environmental risk assessment was performed according to the relevant guidelines. Using a herd treatment factor of 26%, the PECs for the various scenarios are less than the trigger for phase II assessment, 100 µg/kg. Therefore, based on the data provided, Kexxtone 32.4 g intraruminal device for cattle is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

Some studies were already provided with the respective MRL application dossier for monensin, and detailed descriptions and assessments of the studies are included in the respective "Monensin European public MRL assessment report" (EMA/CVMP/78198/2012).

Identification of the product concerned

The residue depletion study submitted to support the proposed withdrawal period was conducted with an experimental formulation of a monensin continuous release intraruminal device (slightly different from the final product in terms of tablet formulation and aperture diameter of the intraruminal device).

An *in vivo* "bridging" study was provided using the experimental and the final formulation to be marketed (to compare similarity of monensin release rate). This approach was accepted by the CVMP during a scientific advice procedure (EMEA/CVMP/19613/2008).

The bridging study compared the monensin release payout of several intraruminal devices with different aperture sizes containing the final product formulation in 36 rumen fistulated dairy cows. The *in vivo* study submitted identified the appropriate sized aperture for the final formulation intraruminal device to provide statistically similar monensin release rates to the previous experimental

intraruminal device used in the residue depletion study, the target animal safety study and in the clinical field study.

Pharmacokinetics

See part 4.

Depletion of residues

MRLs for monensin for use in veterinary medicinal products were initially established by Commission Regulation (EC) No 1353/2007. In March 2012 the CVMP recommended a modification of the MRLs for monensin, increasing the limits for liver and kidney (EMA/CVMP/804330/29012 - CVMP Opinion). The residue data submitted aims to demonstrate depletion to below the values recommended in March 2012.

Since the intraruminal device cannot be retrieved from the animal once administered, a depletion phase is not practical. Therefore, tissues and milk were assayed for marker residue concentrations at steady-state to confirm that the marker residue concentrations are constantly below each tissue MRL during and after treatment. The design is appropriate to determine whether a zero-day withdrawal period can be accepted.

The applicant conducted a GLP depletion study with 23 dairy cows, which were administered one monensin intraruminal device. Milk was collected twice daily at 12 hour intervals from just before the administration and for 28 consecutive milkings (up to 336 hour post-application). Liver, kidney, loin muscle and fat were collected from 10 animals slaughtered 14 days after the administration, when it was considered that monensin concentrations had reached a steady-state phase.

Milk and tissue samples were analysed for monensin A using a validated HPLC analytical method with tandem mass spectrometry (LC – MS/MS). Marker residue assay values in each tissue commodity and milk were all below their respective MRLs.

MRLs

MRLs for monensin for use in veterinary medicinal products were initially established by Commission Regulation 1353/2007. In March 2012, the CVMP recommended the following modification of the MRLs for monensin:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Monensin	Monensin A	Bovine	2 µg/kg 10 µg/kg 50 µg/kg 10 µg/kg 2 µg/kg	Muscle Fat Liver Kidney Milk		Anti-infectious agents/ Antibiotics

The excipients in Kexxtone, 32.4 g intraruminal device for cattle, are included in table 1 of Commission Regulation (EU) No 37/2010 of 22 December 2009 with a "No MRL required" classification, or considered as not falling within the scope of Regulation (EC) No 470/2009 of the European Parliament and of the Council.

Withdrawal periods

For the calculation of the withdrawal period the MRLs recommended by CVMP in March 2012 were used.

Standard methods of calculating withdrawal periods were deemed inappropriate as all the individual values were below the MRLs, and most of them were below the LOQ. Hence, the upper tolerance limit (UTL) was calculated for the 95% percentile of residue concentrations with 95% confidence considering a normal distribution of the samples for each tissue. The residue concentrations and the UTL values were all below the MRLs recommended by the CVMP in March 2012.

Based on the results of the above study a zero day withdrawal period is considered appropriate for both meat and offal, and for milk under the proposed conditions of use of the product.

Overall conclusions on the residues documentation

A monensin residue depletion study was submitted by the applicant. The study was conducted following GLP and in accordance with Volume 8. It is considered that the design of the study is appropriate and that the data support a zero day withdrawal period for cattle tissues and milk. The study was conducted with an experimental formulation of the product. However, a bridging study has been submitted to demonstrate the similarity of the intraruminal device release profiles of the experimental and the intended market formulations.

A LC-MS/MS analytical method and its validation have been presented following the guidance of Volume 8.

According to the results obtained in the residue depletion study, and based on the recommended MRLs, a zero day withdrawal period is considered appropriate for meat and offal, and for milk of dairy cows/heifers.

Part 4 – Efficacy

Pharmacodynamics

In the early post calving period, the increased demand for glucose and precursors for lactose synthesis for milk production triggers hyperketonaemia in cows of high milk production. This hyperketonaemia has several consequences: decline in bodyweight and milk production, loss of appetite, hypoglycaemia, hyperketonaemia, elevated NEFa1, and fat deposition in the liver.

Monensin is a monovalent ion-selective carboxylic ionophore, acting at a cellular level and interfering with important ion gradients necessary for nutrient transport and movement of protons and monovalent cations. Due to its highly lipophilic nature monensin inserts in cell membranes impairing cellular gradients. By restoring these gradients, gram-positive bacteria use energy, this decrease of bacterial ATP finally results in lysis of the bacterial cell. Gram-negative bacteria are not affected by this process and are not inhibited by monensin.

When given by oral administration to cattle (dairy cow), monensin exerts a shift in ruminal bacterial population eliminating and inhibiting gram-positive ruminal bacteria. This results in an increase in the proportion of propionic acid and a decline in the proportion of acetate and butyrate volatile fatty acids (VFA) produced in the rumen. This shift in ruminal VFA production impacts on glucose metabolism as propionic acid is a precursor molecule of glucose.

Several authors investigated the antiketogenic effects of monensin in early lactation. In one study, monensin was fed at a rate of 0, 15, 30 g/ton of dry matter from one to three weeks pre-partum: the addition of 30 g of monensin/ton of feed decreased hyperketonaemia in 50% of cows. In addition acetate: propionate ratios were decreased in the high dose monensin group.

Development of resistance

Several studies demonstrate that ionophore resistance of ruminal bacteria is not readily spread from one bacterium to another; the applicant concluded that some ruminal bacteria exhibit non-inheritable rather than acquired resistance. Several studies pointed out those traditional mechanisms of antibiotic resistance are not a good model for ruminal ionophore resistance. The idea that ionophores demonstrate reversible tolerance is a phenotypic selection rather than mutation or acquisition of foreign genes is further supported by three additional studies. It is agreed that for ionophores the risk for an emergence or spread of resistance is not likely to have a significant impact on the transfer of antibiotic resistance from animals to man.

Pharmacokinetics

Pharmacokinetics in the target species are summarised below:

Absorption:
Monensin is rapidly absorbed following oral administration in cattle.

Distribution:
In the pivotal radiometric residue study in cattle, the results indicate that the total residues in milk reached steady-state after 5 days of administration, following twice daily oral doses of 0.9 mg ^{14}C-monensin/kg bw in gelatine capsules via rumen fistula over a period of 9.5 days (approximately 3 times the daily dose from the control release device).

Non-esterified ("free" or unsaturated) fatty acids (**NEFAs**)

Metabolism:
Monensin is extensively metabolised (mainly in liver). Metabolites were found to be produced by either single or combined demethylation, decarboxylation, and hydroxylation at various positions along the ionophore backbone, resulting in a number of mainly unknown polar metabolites in low concentrations. Unchanged monensin represented a limited fraction of the monensin-related compounds in liver and faeces (less than 10%) and only 2% in milk. The data provided indicate a loss of activity for major monensin metabolites of 75% or more, and confirm previous results that major metabolic pathways (oxidative modification) of monensin significantly modify the polarity or complexing ability of the molecule, and thus impair the biological properties. A conservative estimate based on all available information is that major monensin metabolites retain no more than 50% of the pharmacological and microbiological activity of the parent compound.

Excretion:
Biliary excretion in cattle was reported to be about 35% of the oral dose. Orally dosed radioactivity (^{14}C-monensin) was nearly completely recovered in faeces, whereas urinary excretion was negligible.

Target animal tolerance

Adverse events related to monensin intoxication are well reported and consistent throughout the reviewed published literature and the proprietary studies. Target species tolerance to monensin has been described in several toxicologiy and preclinical studies, in a pivotal target animal safety study, and the pivotal clinical study.

In the first toxicological studies, high monensin doses (from 1 to 10 mg of monensin/kg bw/day were given orally for short periods (one or two weeks) to heifers and steers. Typical signs of intoxication include anorexia, diarrhoea, ataxia and depression. Fatality has been reported at high monensin doses (above 4 mg of monensin/kg bw/day). Signs of toxicity have been reported at doses as low as 1.6 mg/kg bw/day where treatment was continued for more than one week. At higher doses, signs of toxicity will become apparent sooner. The dose tolerated without adverse events was 1 mg/kg bw/day.

In another study, monensin was given at a rate of one or two intraruminal devices per animal (mean delivery of 255 mg monensin/day each). The higher dose resulted in weight loss, loose faeces and scouring in smaller heifers and steers. The dose of 1 intraruminal device (255 mg monensin daily, equivalent to 1.3 mg/kg bw of monensin daily) showed no adverse events.

It was concluded that the highest tolerated dose is between 1 mg and 2 mg monensin/kg bw/day.

In a pre-clinical study using development intraruminal devices, signs consistent with monensin toxicity (diarrhoea and appetite reduction/loss) were observed following administration of two intraruminal devices (twice the recommended dose). This provides an indication of the narrow safety margin of monensin in cattle. The text proposed for inclusion in section 4.10 of the SPC ('Overdose') details the adverse events that may be expected following administration of more than one intraruminal devices. The text proposed reflects what has been observed following administration of 2 intraruminal devices and is considered appropriate.

A pilot study with five empty predevelopment intraruminal devices was performed to assess the effect on safety of empty intraruminal devices remaining in the rumen from previous lactations. No findings at the clinical veterinary examinations were considered attributable to the administration of empty intraruminal devices.

The pivotal target animal safety study was carried out using 0 (3 empty intraruminal devices), 1x and 2x the recommended therapeutic dose (RTD) administered 3-4 weeks pre-calving. Doses of 1x or 2x RTD monensin intraruminal devices or three empty intraruminal devices was well tolerated in the peri-

parturient dairy cow. The only clinically evident treatment-related effect was a decreased faecal score in the 2x group (670 mg/day) relative to controls, i.e. loose faeces/diarrhoea.
Other, statistically significant changes (compared with the control group) were a decrease in β-hydroxybutyrate (BHB), and increases in lactate dehydrogenase, gamma-glutamyl-transferase and sorbitol dehydrogenase (Study Day 94 only) in both treatment groups.

In the clinical field study (treatment phase only), the administration of a single treatment intraruminal device appears to have been well tolerated: while diarrhoea was reported as an adverse effect for a small number of animals during the study, there were no clear cases of monensin toxicity. In this study, animal rate of retained placenta and interdigital dermatitis was higher ($P<0.10$) in the test group compared to placebo. Nevertheless, the overall analysis of multiple studies in the literature indicates that there is no causal relationship between monensin and retained placenta rate. Furthermore, the finding of a higher animal rate of interdigital dermatitis in the treated group is considered to be a chance finding, and not believed to have any relevance to the safety of the product.

In conclusion, the CVMP considered that oral administration of monensin intraruminal devices at the recommended therapeutic dose was generally well tolerated in the peri-parturient dairy cow.

Laboratory studies

Dose determination/dose justification

The optimum dose range for monensin for reducing mean ketone levels and the proportion of cows with elevated ketones after calving appears to be 300-400 mg/day. This conclusion is based on data generated with monensin administered in feed (at doses of 0, 150, 300 and 450 mg/day) and the results from large-scale field trials in Canada using a continuous release intraruminal device (release rate of approximately 335 mg/day).

Field trials

Dose-confirmation

The effect on prevalence and incidence of subclinical ketosis in peri-parturient cows was evaluated in several Canadian field studies (two large-scale studies involving around 1000 dairy cows each and conducted under GCP principles). Monensin was administered by a continuous release intraruminal device 3-4 weeks before calving (delivering an average dose of approximately 335 mg/day of monensin for 95 days). A reduction of 50% in incidence and prevalence of subclinical ketosis (defined as serum β-hydroxybutyrate (BHB) concentrations greater than 1.2 mmol/l) was experienced. Other studies use lower thresholds such as 0.9 and 1.0 mmol BHB/l (referenced in Sauer, 1989). The rate and duration of payout of the intraruminal device (delivering approx 335 mg/day of monensin for 95 days) is within the efficacious dose range of monensin in in-feed administration studies (300-450 mg/day of monensin), and was accepted by the CVMP in a scientific advice given to the applicant in 2006 (EMEA/V/SA/023/2006).

Based on available data, the applicant proposed that the target daily dose be 335 mg monensin per day to be paid out over 95 days. The administration of the intraruminal device is during the dry period. The period of risk for metabolic diseases in dairy cows is generally accepted as occurring between one and two weeks pre-calving, up to two months after calving. Taking into account that calving can occur one and two weeks before or after the expected calving date, it is deemed appropriate to treat individuals at risk of ketosis approximately three to four weeks before expected calving to ensure treatment during the total period of risk. A similar treatment regime was applied in the Canadian field studies (two to four weeks before expected calving).

Pivotal field study

The applicant submitted a multicentered, blinded, blocked randomised, placebo controlled, European study (involving farms in United Kingdom, France and Germany). The effects of monensin continuous release intraruminal device in periparturient cows were examined. 1312 dry cows were enrolled, 661 and 651 were given an oral administration of a single intraruminal device with monensin or placebo tablets, respectively, at enrolment between 21 to 28 days before expected calving.

The pivotal field study was conducted in two phases: a treatment phase (time of treatment up to 19 weeks post treatment) and a post-treatment phase (19 weeks up to one year following treatment).

Trial sites (29 farms) were selected based on risk of developing ketosis (e.g. based on previous site health history or sites with a high proportion of cows with high body condition score).

The primary objective was to evaluate the effect of the intraruminal device on the cumulative incidence rate ('animal rate') of clinical ketosis in peri-parturient dairy cows under typical European practical farm conditions. The statistical unit was the individual dairy cow. It should be noted that the design of the study was the subject of a request for CVMP scientific advice.

Clinical ketosis (primary or secondary) was based on the investigator observations in combination with a confirmatory β-hydroxybutyrate (BHB) threshold value of 1.0 mmol/l. An additional analysis was made for the higher threshold of 1.4 mmol/l for hyperketonaemia at herd level. So two cut-off values or threshold levels for hyperketonaemia (BHB) serum levels were used, a low one of 1 mmol/l, and a conservative one of 1.4 mmol/l, both referenced in relevant literature. Clinical signs that should be registered (one or more): drop in milk yield, reduced feed intake and/or appetite, low rumen fill, reduced activity or demeanour (i.e. dullness, listlessness), excessive loss of body condition, constipation/reduced faecal output or hard/dry faeces, ketone odour in breath/milk, nervous signs (i.e. weakness, mania, apparent blindness, pica).

Secondary objectives were: cumulative incidence rate of primary and secondary ketosis separately; prevalence of hyper-ketonaemia (elevated β-hydroxybutyrate blood levels) during the second week (7 to 14 days) post-partum; prevalence of elevated non-esterified fatty acid (NEFA) blood levels prior to calving; cumulative incidence (animal) rate of energy-deficiency associated diseases (clinical ketosis, retained placenta, metritis/endometritis and displaced abomasum); other abnormal health observations; fertility parameters, including calving ease, interval of calving to first oestrus, interval of calving to conception, pregnancy rate and number of services per pregnancy; milk yield, milk composition; cow removal and reasons for removal until 1 year after initial treatment with the intraruminal device; and regurgitation rate.

The approach to diagnosis of ketosis and criteria for selecting farms at risk of developing ketosis have been recommended by a panel of EU veterinary dairy /practitioners experts and agreed by the CVMP in a scientific advice given to the applicant in 2006 (EMEA/V/SA/023/2006).

The results showed that both groups (test and placebo), at enrolment, were comparable, regarding age, mean parity, milk yield and milk composition (from previous lactation).

Regarding the primary efficacy parameter, cumulative animal ketosis rate was 11.5% of cows in the test group, versus 25.6% in the placebo group (simple mean values). Least Square Mean (LSM) values were 6.2% and 18.3% for the test and placebo groups, respectively ($P<0.001$). Similar treatment effects were found in the overall population and in the primiparous and multiparous cows separately. Using the more conservative BHB threshold level of 1.4 mmol/l, in combination with confirmed presence of clinical signs, cumulative animal ketosis rates were 6.3% and 18.4% (simple mean values), with animal rate LSM-values of 3.3% and 12.3% of cows for the test and placebo groups, respectively

(P<0.001). Further, the prevalence of hyperketonaemia in the overall cow population (7-14 days after calving; secondary study objective) was significantly reduced, with 8.2% and 32.1% of cows in the test and placebo groups respectively exceeding BHB 1.0 mmol/l, and 3.0% and 19.6% of cows in the test and placebo groups, respectively, exceeding 1.4 mmol/l (P<0.001).

For energy metabolism related diseases such as retained placenta, metritis, endometritis and displaced abomasa, no effect of treatment was detected between treatment and placebo group. Specifically regarding the parameter "displaced abomasums", which was initially proposed by the applicant as another indication, no statistical difference between placebo and treated group could be seen (rates of 2.3% and 2.8% were obtained (p value = 0.678) for LSM values). Administration of monensin did not have a negative impact on parameters of milk production. No differences were found between placebo and monensin intraruminal device administration regarding parameters related to calf viability for both primiparous and multiparous cows, or for calving ease.

A 6.7% vs 6.5% regurgitation rate was obtained for test and placebo groups, respectively, during the 19 week treatment phase. No differences in regurgitation rate were found between groups. A high percentage of regurgitated devices showed intraruminal device damage (e.g. broken wing(s), damaged casing). In addition to the intraruminal device regurgitations that could be traced to a specific animal, reports from farm sites were also submitted of regurgitated intraruminal device components (e.g. separated caps, plungers, springs or wings) without identification. Additional design modifications have since been implemented for the final market presentation of the intraruminal device improving the durability and retention characteristics. See section on durability below.

Based on observations in the post-treatment phase, it was concluded that administration of the monensin intraruminal device had no adverse effects on the subsequent fertility of the study animals. No apparent effects on the disposition of the study animals as a result of the monensin intraruminal device treatment were found.

In conclusion, the findings of this study support the proposed indication 'For the reduction in incidence of ketosis in the peri-parturient dairy cow/heifer.' The product, when administered at the recommended treatment dose, was well tolerated.

No potential interactions between intraruminal device treatment and concomitant medication were reported.

Durability of the intraruminal device

In order to address the intraruminal device breakages reported in the field study, the following modifications were made for the purpose of improving the attachment of the cap and strengthening the wings against breakage: an alternative resin was used; the wings of the intraruminal device were strengthened with an alternative rib design and thickening around the wing/capsule joint; and the cap attachment to the intraruminal device body was redesigned and reinforced.

The durability of the intraruminal device was first evaluated in three 28 week studies: a field study with cull cows and two studies using rumen fistulated cows. The findings of these initial durability studies raised concerns in relation to: incidence of regurgitations, and disassembly of the intraruminal devices. Disassembly appeared to be an issue after the pay-out period of the intraruminal device (appeared to be an issue with the empty intraruminal device). The principle concern appeared to be orifice cap detachment. To address these findings, the applicant made further modifications to the intraruminal device design and generated additional supportive durability data using the final market-image intraruminal device design. Based on the findings of these additional studies, it is accepted that the newly modified intraruminal device successfully increased intraruminal device retention rate and

that the intraruminal device proposed for marketing is not as prone to orifice cap detachment as previous versions of the intraruminal device.

Overall conclusion on efficacy

Several studies demonstrate that ionophore resistance of ruminal bacteria is not readily spread from one bacterium to another; the conclusion was that some ruminal bacteria exhibit non-inheritable reversible tolerance rather than acquired resistance.

Based on the findings of the pivotal target animal safety study, the oral administration of 1x or 2x RTD monensin intraruminal devices or three empty intraruminal devices was well tolerated in the peri-parturient dairy cow.

Based on data generated with monensin administered in feed (at doses of 0, 150, 300 and 450 mg/day), the optimum dose range for monensin for reducing mean ketone levels and the proportion of cows with elevated ketones after calving is 300-400 mg/day.

For the study primary efficacy parameter (cumulative animal ketosis rate during the 19-week treatment phase, as based on the investigator observations in combination with confirmatory BHB assay value), a significant difference ($P<0.001$) between the treatment groups was found for the low threshold of 1.0 mmol/l of BHB and for the conservative threshold (1.4 mmol/l). The product is potentially valuable for the reduction in the incidence of ketosis in the peri-parturient dairy cow/heifer.

An additional indication, proposed by the applicant, for reduction in the incidence of displaced abomasum was not accepted by the CVMP because there was no statistical difference between the groups.

Part 5 – Benefit-risk assessment

Introduction

Kexxtone is presented as a cylindrical shaped intraruminal device containing a total of 32.4 g of monensin (as monensin sodium). The core is composed of a stack of twelve subunits (tablet cores) each containing 2.7 g of monensin (as monensin sodium). The monensin tablet cores are formulated in such a way that they, when exposed to an aqueous environment, form a gel. The tablet cores are held against the orifice at the end of the intraruminal device by a spring. Due to the pressure of the spring on the tablet stack, the gel containing the monensin is extruded through the orifice and progressively released at an approximate average dose of 335 mg of monensin per day for approximately 95 days.

Kexxtone is intended for use in cattle for the reduction in the incidence of ketosis in the peri-parturient dairy cow/heifer which is expected to develop ketosis. The proposed withdrawal period (meat and offal, milk) is zero days.

Benefit assessment

Direct therapeutic benefit

For the study primary efficacy parameter (cumulative animal ketosis rate), a significant difference ($P<0.001$) between the treatment groups was found: cumulative animal ketosis rate was 11.5% in cows in the test group, versus 25.6% in the placebo group (simple mean values). Therefore, the CVMP concluded that the product has a significant effect in the reduction of the incidence of ketosis in the peri-parturient dairy cow/heifer, which is expected to develop ketosis.

However, an additional indication proposed by the applicant, for reduction in the incidence of displaced abomasum, was not accepted by the CVMP because there was no statistical difference between placebo and test groups.

Additional benefits

N/A

Risk assessment

The applicant has presented a User Safety Risk Assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/543/03-FINAL-Rev.1. The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

The environmental risk assessment was performed according to the relevant guidelines. Based on the data provided, Kexxtone 32.4 g intraruminal device for cattle is not expected to pose a risk for the environment when used according to the SPC.

A zero day withdrawal period can be established for both, meat and offal and milk without posing a risk to the consumers of animal foodstuffs.

Antimicrobial resistance has been addressed and discussed in the report. It is agreed that for ionophores the risk for an emergence or spread of resistance is not likely to have a significant impact on the potential of transfer of antibiotic resistance from animals to man. Several studies demonstrate that ionophore resistance of ruminal bacteria is not readily spread from one bacterium to another; the conclusion was that some ruminal bacteria exhibit non-inheritable reversible tolerance rather than acquired resistance.

All of the clinical pathological changes of importance found in the tolerance studies were consistent with acute monensin toxicity. Most relevant dose-related toxicity signs were anorexia, ataxia, diarrhoea and decreased weight gain. All of these appeared at higher doses than those recommended for Kexxtone. Studies demonstrated that the administration of one or two monensin intraruminal devices was well tolerated by dairy cattle. No risk is expected for the target animal if the instructions of use recommended in the SPC are followed. However, monensin toxicity differs between species, and a warning has therefore been included on the SPC advising against use in certain non-target species.

Risk management or mitigation measures

A number of management measures have been proposed to be included in the SPC to mitigate possible risks to the user, target animal, other animal species and the environment.

Evaluation of the benefit-risk balance

Sufficient data have been presented to support the indication of reduction in the incidence of ketosis in the peri-parturient dairy cow/heifer which is expected to develop ketosis.

A number of management measures/warnings have been proposed to be included in the SPC. The CVMP concluded that when used in accordance with the SPC, the product does not pose a risk to the user, animals or the environment.

Based on these data, the CVMP considered that the product has a positive benefit-risk balance.

Conclusion

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Kexxtone is in accordance with the requirements of Directive 2001/82/EC, as amended, and that the benefit-risk balance is favourable.