EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 December 2012
EMA/794474/2012
Veterinary Medicines and Product Data Management

Withdrawal extension assessment report

ZOLVIX 25 mg/ml oral solution

International non-proprietary name: Monepantel (EMEA/V/C/000154/X/007)

Extension of the Community marketing authorisation to add goats as target species

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

Withdrawal at day 190

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Introduction

An application for an extension to the Community marketing authorisation for ZOLVIX has been submitted by Novartis Healthcare A/S to the European Medicines Agency (the Agency) on 27 February 2012 in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I point 2(c) thereof.

The already authorised product, ZOLVIX is a broad spectrum anthelmintic oral solution for the treatment and control of gastro-intestinal nematode infections and associated diseases in sheep including lambs, hoggets, breeding rams and ewes and was authorised for use in the Community on 4 November 2011.

This extension application is to add goats as the target species.

The applicant applied for the following indication "*ZOLVIX oral solution is a broad spectrum anthelmintic for the treatment and control of gastro-intestinal nematode infections and associated diseases in sheep and goats including lambs, kids hoggets, breeding rams, bucks, ewes and does.*

Spectrum of activity includes fourth larvae and adults of:

*Haemonchus contortus**
*Teladorsagia circumcincta**
*Teladorsagia trifurcata**
*Teladorsagia davtiani**
*Trichostrongylus axei**
Trichostrongylus colubriformis
Trichostrongylus vitrines
Cooperia curticei
Cooperia oncophora
Nematodirus battus
Nematodirus filicollis
Nematodirus spathiger
Chabertia ovina
Oesophagostomum venulosum

* including inhibited larvae

The veterinary medicinal product is effective against strains of these parasites resistant to (pro) benzimidazoles, levamisole, morantel, macrocyclic lactones and H. contortus strains resistant to salicylanilides".

ZOLVIX contains monepantel and is presented in aluminium bags or high density polyethylene (HDPE) bottles of 250 ml, 500 ml, 1 l, 2.5 l, and 5 l. The route of administration is oral. The proposed withdrawal period is 7 days for meat and offal for sheep and goats.

The dossier has been submitted in line with the requirements for submissions in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof (variations/extensions). Quality data have not been submitted as the formulation of the product remains the same. In relation to safety and efficacy where no new data were generated no further information has been submitted.

MUMS Status

The applicant requested minor use minor species (MUMS) status for this procedure by the CVMP, and the Committee confirmed at their November 2011 meeting that, where appropriate, the data requirements in the appropriate CVMP guidelines on MUMS data requirements would be applied when assessing the application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system which fulfils the requirements of Directive 2001/82/EC. 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.

Manufacturing authorisations and inspection status

The product is manufactured in approved GMP sites in line with GMP requirements; similarly batch release is in line with GMP requirements. As a result there is no need for any GMP inspections

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites were considered in line with legal requirements.

Part 2 – Quality

Quality data have not been submitted as the formulation of the product remains unchanged. Cross reference is made to the initial dossier assessment.

Part 3 – Safety

For the purpose of this extension to add goats as a new target species the applicant provided no new pharmacological or toxicological studies. The data from studies provided in the initial dossier relating to sheep which is a closely related species to goats were considered adequate. The absence of such studies was also acceptable given that goats are considered a minor species.

Safety documentation

Pharmacodynamics

No new pharmacological studies have been submitted for this extension. The data from the pharmacological studies described and assessed in the original application for sheep were considered adequate for the purpose of this procedure. In the original dossier no specific signs were observed even in high single and repeated dose studies in the various species (mouse, rat, rabbit, dog, sheep), in which studies were conducted. As a result it was concluded that monepantel is devoid of a relevant pharmacological activity in mammals.

Pharmacokinetics

The applicant conducted one GLP compliant study to demonstrate pharmacokinetics and basic metabolism of monepantel in goats. This study was combined with a dose-determination efficacy study, which is assessed under Part 4. The applicant also conducted one GLP-compliant tissue residue depletion study in goats (which is addressed under the Part 3 residue section).

Pharmacokinetics and basic metabolism of monepantel in goats study

The applicant has conducted one GLP-compliant study to demonstrate pharmacokinetics and basic metabolism of monepantel in goats. This study was combined with a dose-determination efficacy study. Animals were dosed at 0, 1.25, 2.5, 3.75 and 5 mg/kg bw monepantel. Blood samples were analysed by LC-MS/MS to determine monepantel and its sulfone metabolite, and the analytical data were subjected to pharmacokinetic analysis. Data showed that monepantel is metabolised to the sulfone in goats, and that the elimination of monepantel sulfone is faster in goats than in sheep (T1/2: 2 days in goats and 5 days in sheep).

To determine an equivalent exposure of monepantel and its sulfone metabolite in goats the applicant has used the bioequivalence principle to find the dose in goats comparable to the recommended dose of 2.5 mg/kg bw for sheep.

The analysis showed that the bioavailability in goats after 3.75 mg/kg and sheep after 2.5 mg/kg bw is very similar, indicating that 3.75 mg/kg bw may be efficacious for treatment of gastro-intestinal worms in goats.

Toxicological studies

No new toxicological data were submitted for this application; the data provided for sheep which is a related species were considered adequate for this procedure. In the original dossier the results of single oral dose studies in rats indicated low acute toxicity of monepantel. Repeated daily administration of monepantel admixed to the diet was well tolerated in rats, mice and dogs even at high concentrations.

Tolerance in the target species of animal

A target animal safety study has not been conducted in goats. The absence of such a study can be accepted given that goats are a minor species, the product is known to be well tolerated at multiples of the recommended treatment dose in a related species (sheep) and no evidence of intolerance was observed in goats in various safety and efficacy studies conducted at doses up to 5.6 mg/kg. Please also see Part 4.

Reproductive toxicity

No new data were submitted. In the original dossier monepantel did not show any teratogenic potential under the conditions of the relevant study assessed.

Mutagenicity

Monepantel was tested in a comprehensive series of mutagenicity test systems with studies performed under GLP conditions and did not provide any evidence of mutagenic activity.

Carcinogenicity

Monepantel has no carcinogenic potential in mice and rats.

User safety

The applicant has not provided additional data to the sheep file for user safety. This was considered acceptable as it is acknowledged that addition of goats as a target species will not increase the risk to the user relative to the risk that exists for sheep. In the original dossier it was concluded that no unacceptable health risk to operators is associated with the use of monepantel in sheep.

As result the CVMP concluded that the product does not pose an unacceptable risk to the user when used in goats in accordance with the advice given in the draft Summary of Product Characteristics (SPC).

Environmental risk assessment

In the original dossier a comprehensive Phase II assessment of the environmental risk of monepantel and its major metabolites was conducted according to the VICH Guideline GL 38 (CVMP/VICH/90/03-Final) and the CVMP Guideline in support of VICH GL 6 and GL 38 (EMEA/CVMP/ERA/418282/2005-corr). The provided data fulfilled the requirements specified in those documents. The provided tests were conducted according to international standard guidelines and under the compliance of GLP, and test results were generally of a quality that enabled a full and complete assessment. Risk to ground water, fresh water organisms or soil organisms was not identified. A risk to dung fauna was identified: RQ values were above 1 for three, probably four days, but it was concluded that this was only the case for a relatively short period of time and that therefore no risk mitigation measures were deemed necessary.

Monepantel was proposed to be used at a higher dose in goats as compared to sheep. Therefore, the applicant provided additional information for the environmental risk assessment (ERA) related to the use of the product in goats.

The applicant considered the direct excretion on pasture as the only relevant exposure scenario, which is accepted. Although specific excretion data in goats is lacking, the applicant provided a conservative estimation of the faecal concentrations in goat's dung on the basis of the metabolism and excretion data in sheep in combination with the comparative kinetic and residue study in goats. This approach resulted in an estimated faecal peak concentration (total residues) of approximately 50 mg/kg wet weight, equivalent with 167 mg/kg dry weight in the first 24 hours after administration.

At 7-8 days after administration, faecal concentrations of the total residue were estimated to be reduced to approximately 3 mg/kg wet weight, equivalent to 10 mg/kg dry weight.

Considering the PNEC of 15 mg/kg for dung organisms, it is concluded that there is a risk for dung organisms during a maximum period of a week. As this risk is present for a relatively short period (dung insects are expected to be present in dung droppings of goats previously at pasture which serve as a reservoir for insects to colonise droppings of treated animals within a week) no risk management measures are considered necessary.

Apart from the risks to dung fauna, the applicant calculated PECs for soil, groundwater and surface water, and related those to appropriate endpoints from relevant toxicity studies to arrive at the conclusion that there are no risks associated with the use of monepantel in goats for those environmental compartments.

Conclusions on the environmental risk assessment

Based on the data provided for the ERA Phase II ZOLVIX when used in goats is not expected to pose a risk for the environment when used according to the draft SPC.

Overall conclusions on the safety documentation

No new safety data were provided for the addition of goats as new target species besides one GLP study to demonstrate pharmacokinetics and basic metabolism of monepantel in goats. The above was considered acceptable as data from the initial dossier showed that monepantel possess a low toxicity

without reproductive or teratogenic potential and is not genotoxic. There is no additional user risk and environmental risk from the use of monepantel in goats is considered acceptable.

Residues documentation

Identification of the product concerned

No changes to the formulation of the product are proposed for extending the indication of ZOLVIX to goats. Therefore the description in the original dossier of the formulation of the product used in the residues studies is applicable.

Residue studies

The applicant conducted one GLP-compliant tissue residue depletion study in 20 goats. The dose was 5.6 mg monepantel per kg bw orally, which is higher than the recommended dose of 3.75 mg per kg bw. Goats were slaughtered at 4, 7, 10 and 13 days after treatment and samples of renal fat, liver, kidney and muscle were collected and analyzed for monepantel sulfone. Residues dissipated over time in all tissues with half-lives being 4.4, 5.3, 5.3 and 5.8 days for fat, liver, kidney and muscle, respectively. Comparing the actual day 7 residues in goat tissues with those of sheep, it was noted that the goat residues are slightly lower than those in sheep. A routine analytical method, based on HPLC with UV-detection, for the quantification of monepantel sulfone residues in edible goat tissues (fat, liver, kidney and muscle) is available and is the basis for the CVMP recommendation of the goat MRLs. The limit of quantification is 50 µg/kg. This method was used in the pivotal residue study. The study design and conclusions from this study were considered satisfactory.

Pharmacokinetics

Please see Safety Documentation.

Depletion of residues

The applicant conducted one GLP-compliant tissue residue depletion study in 20 goats which was described above. The study presented was adequate to determine a withdrawal period for goats.

MRLs

The active substance in ZOLVIX is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010, as amended:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Monepantel	Monepantel-sulfone	Ovine	700 µg/kg 7000 µg/kg 5000 µg/kg 2000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals producing milk for human consumption	Antiparasitic agents/ Agents acting against endoparasites

		Caprine	700 µg/kg 7000 µg/kg 5000 µg/kg 2000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals producing milk for human consumption	Antiparasitic agents/ Agents acting against endoparasites

The excipients listed in section 6.1 of the draft SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Withdrawal periods

In order to calculate the withdrawal period the recovery corrected residue data from the above goat study were subjected to log-linear regression. Applying the above MRLs, the calculated upper 95/95 confidence intervals intersect with the MRLs shows a withdrawal period of 8, 4, 0 and 4 days for fat, liver, kidney and muscle respectively. The overall withdrawal period therefore can be assigned as 8 days, based on longest withdrawal period observed for fat. However, the withdrawal period has been set to 7 days in sheep based on fat tissue. At Day 7 tissue concentrations are lower in goat than in sheep and it is therefore illogical to set the withdrawal period in goats to 8 days. Assuming the same marker/total residue ratios as observed in sheep is applied to goats the calculated consumer intake of goat meat at Day 7 after monepantel administration at a high dose of 5.6 mg/kg is only 29% of the ADI. Furthermore all tissue residues are below MRL in goat at day 7. It therefore appears that it is reasonable to maintain the 7 days withdrawal period for goat as set for sheep.

In the absence of an MRL, the product is not for use in animals producing milk for human consumption.

Overall conclusions on the residues documentation

Monepantel is rapidly metabolised and cleared by goats, such that about 50% more monepantel is required to achieve the comparable plasma profiles in goats as compared to sheep. The half-life of monepantel sulfone in goat (2 days) is less than half than that observed in sheep (5 days). In a goat residue depletion study conducted at the maximum recommended dose rate of 5.6 mg/kg monepantel, the marker residue (monepantel sulfone) was localised primarily in fat and liver, but residues depleted quickly.

As an extension of the use of ZOLVIX to a minor species (goats), a withdrawal period of 7 days for goats as set for sheep is proposed. The estimated consumer intake, based on maximum observed residues, at day 7, leads to only 29% consumption of the maximum daily permitted intake.

Part 4 – Efficacy

Pharmacodynamics

See safety section.

Development of resistance

The anticipated impact of resistance development in view of the effective use of the product in goats, taking into account posology is not expected to be greater than that of sheep.

Pharmacokinetics

Dose determination / justification

Two dose determination studies and two dose confirmation studies were conducted respectively in goats..

First dose determination study

Goats were infected with motile third larvae of *Nematodirus spathiger*, benzimidazole resistant *Teladorsagia circumcincta* and *Haemonchus contortus, Trichostrongylus axei*, levamisole resistant *Trichostrongylus colubriformis* and *Cooperia curticei* (total of 3000). After 9 days animals were treated with monepantel at doses of 1.25, 2.5, 3.75 and 5 mg per kg bw while one group was left untreated. About three weeks later, faecal eggs were counted and all goats were subjected to a helminthological necropsy.

All worm counts in the treated groups were statistically significantly different from those in the untreated group with the exception of the *N. spathiger* numbers of group 1.25 mg/kg. Nematodirus egg counts after treatment were not different statistically in the treated groups versus the untreated group but non-Nematodirus egg counts were.

Second dose determination study

In the second study goats with natural infections (200 to 6000 eggs per gram of faeces) of *H. contortus, T. circumcincta, Teladorsagia trifurcata, T. axei, T. colubriformis, Trichostrongylus vitrinus, Nematodirus abnormalis, Chabertia ovina, Oesophagostomum venulosum* and *Trichuris ovis* were treated with monepantel at doses of 2.5 or 3.75 mg/kg bw while one group was left untreated. Two weeks later, faecal eggs were counted and all goats were subjected to a helminthological necropsy. All worm counts in treated groups were statistically significantly different from those in the untreated group with the exception of the *T. circumcincta* larvae, *N. abnormalis* and *T. ovis*.

After treatment, faecal egg counts of the treated groups were statistically significantly different from those of the untreated group.

The minimum effective dose rate in this study was 2.5 mg/kg for adults of *H. contortus, T. circumcincta, T. trifurcata, T. axei, T. colubriformis, T. vitrinus, C. ovina* and *O. venulosum*. The presence of inhibited stages of larvae in this study was highly unlikely, when considering the presence of developing stages of larvae as it usually takes more than 2 weeks to allow inhibition.

The presence of inhibited stages of larvae in this study was considered unlikely, when considering the presence of developing stages of larvae as it usually takes more than 2 weeks to allow inhibition.

First dose confirmation study

In the first dose confirmation study 8 months old goats were inoculated with motile third larvae of *O. venulosum, N. spathiger, T. circumcincta, and H. contortus* resistant to (pro)benzimidazoles, levamisole, macrocyclic lactones, salicylanilides and derquantel), *T. axei, T. colubriformis* (resistant to (pro)benzimidazoles and levamisole) and *C. curticei* at day -16 to - 6. On day 0, when the worms were fourth larvae one group was treated once orally with monepantel at 3.75 mg/kg bw while the other group was left untreated. Two weeks later, faecal eggs were counted and all goats were subjected to a helminthological necropsy.

Data showed that the worm counts in the treated group were statistically significantly different from those in the untreated group for *H. contortus, T. circumcincta*. In all other species the infection was

statistical inadequate. Therefore this study confirmed the efficacy of the proposed dose in goats for *H. contortus, T. circumcincta*.

Second dose confirmation study

In the second study 9 months old goats were used. Each goat was orally inoculated with motile third larvae *Nematodirus spp., T. axei, T. colubriformis* (resistant to (pro)benzimidazoles and levamisole) and C*. curticei* at –9 to -6. On day 0, when the worms were fourth larvae one group was treated once orally with monepantel at 3.75 mg/kg bw while the other group was left untreated. Two weeks later, faecal eggs were counted and all goats were subjected to a helminthological necropsy.

The worm counts in the treated group were statistically significantly different from those in the untreated group for *T. circumcincta, T. axei, T, colubriformis, C. curticei and N. abnormalis* and thus confirmed the efficacy of the proposed dose for those parasites in goats. The infection was inadequate for *T. trifurcate and N. filicollis*.

The dose determination studies can be used for dose confirmation because they were conducted under label conditions (e.g. final formulation, recommended route of administration, goats representative for the patients in the field etc.). An overall review of all four studies is justified because they followed very similar protocols (study designs) and were conducted under similar experimental conditions that were considered satisfactory.

Conclusions on dose determination and dose justification studies

These studies were well conducted under GCP or GLP and followed essentially VICH and WAAVP guidelines.

All genera and ten out of 14 parasite species for which an efficacy claim is included in the SPC of the sheep product are covered in effectiveness studies with goats. The effectiveness against the three major species *H. contortus, T. circumcincta and T. colubriformis* was examined using adults and fourth larvae. The effectiveness against other species was studied with adults and fourth larvae (i.e. *T. axei, O. venulosum*), with fourth larvae (i.e. *C. curticei* and *N. spathiger*) or with adults (i.e. *T. trifurcata, T. vitrinus* and *C. ovina*).

Efficacy (i.e. adequate infection statistically significantly reduced by 90 % or more using geometric means) was demonstrated in all cases studied but for *T. ovis* and *T. axei*. The *T. ovis* infection was statistically adequate but the worm reduction was 63.5 % and statistically not significant i.e. efficacy was in fact not demonstrated, as for sheep. In contrast, the infections with fourth *T. axei* larvae were statistically adequate and the worm reductions statistically significant and 99.0 % (1.25 mg/kg), 99.4 % (2.5 mg/kg), 99.8% and 87.5% (3.75 mg/kg). The efficacy against fourth *T. axei* larvae is therefore confirmed. Thus, efficacy of the proposed dose against all ten species tested in goats of the 14 species claimed on the approved label of the sheep product was demonstrated. The four species not examined in any efficacy trial and therefore cannot be included in the claim are *Teladorsagia davtiani*, *Cooperia oncophora, Nematodirus battus* and *N. filicollis*. *T. davtiani.*

Moreover the presence of inhibited stages of larvae in a second dose determination study was highly unlikely, when considering the presence of developing stages of larvae as it usually takes more than 2 weeks to allow inhibition.

Therefore, the above submitted studies were not considered to demonstrate the efficacy against inhibited larval stages. Furthermore, a difference in $T_{1/2el}$ between goat and sheep was observed. As the time of exposure to active substance (monepantel, its metabolite or both) needed to kill larvae seems to be a matter of days, the extrapolation of efficacy from sheep to goat cannot not considered justified. As a result of the above the indication against inhibited larvae stages was not considered appropriate for goats.

Target animal tolerance

No tolerance study has been carried out in goats. However no adverse events were observed which could be attributed to monepantel in the residue study, dose determination and dose confirmation studies or in the field studies. Combining this information with the tolerance data reported for sheep, there is no reason to expect intolerance in the goat.

Field trials

Three field studies were conducted, one in Europe, one in New Zealand and one in Australia. The non European studies were considered relevant to the EU conditions as the target animal species was the same, the target nematode species were the same and the susceptibility of the nematodes encountered to treatment was the same or very similar. Finally many methods used in the 3 field studies were identical or very similar.

Field study in Europe

A field study in Europe includes 266 Alpine does, dry and presumed pregnant, and four bucks on three sites selected for highly abundant infection with gastrointestinal nematodes. Does producing or intended to produce milk for human consumption within 35 days, goats to be slaughtered for human consumption with 28 days and goats treated with an anthelmintic within six weeks of day 0 were excluded.

On day 0, faeces were sampled from 207 selected goats. 165 of these animals were administered monepantel at 3.75 mg/kg bw orally once. The remaining 42 goats were untreated controls. On day 7 and 14, faeces were sampled again. All faecal samples were used for determining coccidian oocysts and nematode eggs, for coprocultures and consistency scoring. The primary egg count reduction was calculated for each post-treatment sampling based on the pretreatment egg counts modified for the egg count change in the untreated controls from pretreatment to post-treatment using geometric means and the Henderson-Tilton formula: effectiveness % = 100 x (1 – [tA x uD0] / [tD0 x uA]) (t = treated group, u = untreated group, D0 = Day 0, A = each sampling day after dosing). The secondary egg count reduction was calculated for each goat as an egg count reduction based on the pretreatment egg count and for each group calculating the arithmetic mean of the individual effectiveness values. Efficacy was defined as statistically significant egg reduction of 90 % or higher. The actual dose rate range was 3.69 to 6.2 mg/kg. Six “efficacy and safety goats” were excluded from all effectiveness calculations due to lack of faecal sample or lack of eggs in the faecal sample on day 0.

All egg count reductions were statistically significant. There were no differences in egg counts before dosing between treated and untreated group. The secondary effectiveness was also higher than 99%. *Haemonchus, Cooperia, Chabertia* and/or *Oesophagostomum, Teladorsagia* and also *Trichostrongylus* were present. There was no difference in faecal score between groups before dosing and after dosing, with the exception that faecal scores on site MEN-06 on day 7 and overall faecal scores on day 14 were statistically significantly lower in treated goats. There was no difference in the presence of coccidian oocysts between the groups before and after dosing.

In this field study monepantel (3.75-5.625 mg/kg bodyweight) was effective against natural infections with *H. contortus, Teladorsagia, Cooperia* and *Chabertia/Oesophagostomum*. Because Nematodirus infections were not diagnosed in the selected herds, no conclusions could be made about this nematode species. *Trichostongylus spp* eggs were found at a very low percentage (this nematode species produces less eggs than Haemonchus contortus).

Field study in New Zealand

A field study in New Zealand was conducted on three sites selected for highly abundant infection with gastrointestinal nematodes. Boer, Angora and Angora x Cashmere cross wethers, bucks and does (presumably not pregnant, in lactation or dry), six months to 10 years old and weighing 16 to 61 kg were used. Two weeks before day 0, all goats were weighed, inspected by a veterinarian and their faeces were sampled for consistency scoring, for examination for coccidian oocysts, tapeworm and nematode eggs and for coprocultures. Goats treated within six weeks of day 0 with an anthelmintic with residual efficacy were excluded from the study.

On day 0, the goats were randomly allocated to two groups balancing nematode egg counts, weights, and also age. Group 1 (n = 55) was left untreated and group 2 (n = 209) received monepantel at 3.75 mg/kg according to the dosing table weight class of their individual weight orally once.

The goats were observed by the veterinary investigator or a designated assistant on days 0, 10, 14 and 21 at which time also faecal samples were taken for examinations. After three weeks sites 1 and 3 were closed with a nematodicidal dose for all goats.

All egg count reductions were statistically significant. There were no differences in egg counts before dosing between the treated and untreated group disregarding the statistically significantly lower egg count in the untreated group on site 3 on day 0. *Teladorsagia* and also *Trichostrongylus, Chabertia* and/or *Oesophagostomum, Haemonchus, Cooperia* and *Nematodirus* were present.

There was no difference in faecal score between groups before and after dosing on sites 2 and 3, but faecal scores on site 1 and overall faecal scores were statistically significantly lower in treated goats after treatment. There was no difference in the presence of coccidia oocysts and tapeworm eggs between the groups before and after dosing disregarding the significantly lower prevalence of tapeworm eggs in treated goats on days 14 and 21 on site 1 and day 10 on site 3.

Monepantel (3.75 mg/kg or higher) was very effective (>95%) against *Haemonchus, Trichostrongylus, Ostertagia, Cooperia and Oesophagostomum/Chabertia spp* under field conditions. efficacy against *Nematodirus* could not be investigated due to a very low infection rate (only 1 animal positive).

No adverse events, potentially related to treatment, were observed.

Field study in Australia

In the Australian study three sites were selected for highly abundant infection with gastrointestinal nematodes. Boer and Angora wethers and does (not pregnant or pregnant up to eight weeks), six months to eight years old and weighing 16 to 76 kg, were used.

Two weeks before day 0, all goats were weighed, inspected by a veterinarian and their faeces were sampled for consistency scoring, for examination for coccidian oocysts, tapeworm and nematode eggs and for coprocultures. Goats treated within six weeks of day 0 with an anthelmintic with residual efficacy were excluded.

On day 0, goats were randomly allocated to four groups. Group 1 (n = 62) was left untreated, group 2 (n = 214) received monepantel at 3.75 mg/kg according to the dosing table weight class of the heaviest goat in the (sub)group, group 3 (n = 57) received abamectin (Caprimec) at nominally 0.2 mg/kg, and group 4 (n = 56) oxfendazole at nominally 4.53 mg/kg. The goats were observed by the veterinary investigator on days 0, 10, 14 and 21/22 at which time also faecal samples were taken for examinations. After three weeks the study was terminated Efficacy was defined as statistically significant nematode egg count reduction of statistically adequate nematode egg shedding by at least 90 %.

All egg counts of untreated groups were statistically adequate. All pretreatment egg counts did not differ statistically significantly between untreated and treated groups. All egg count reductions were statistically significant. *Trichostrongylus, Haemonchus, Teladorsagia and also Cooperia, Nematodirus* and *Chabertia* and/or *Oesophagostomum* were present.

At site 1, 28 of 68 goats were dosed at 3.68-5.49 mg/kg i.e. approximately within the dose rate range defined by the dosing table, and the remaining 40 received a higher dose. The respective numbers for site 2 were 48/77 and 29/77, and for site 3, 45/67 and 22/67. There was no statistically significant difference in efficacy between both groups on each site disregarding the higher efficacy on day 10 in the goats receiving the proper dose on site 3.

Monepantel, administered orally at a minimum dose of 3.75 mg/kg bw resulted in a reduction in FEC (faecal egg count) over 95%, which is sufficient according to the VICH guidelines (VICH GL7 and VICH GL14). Resistance was observed against other anthelmintics at all sites.

Other studies

No other efficacy studies were submitted for this extension.

Overall conclusion on efficacy

Three large GCP field studies with a suitable study design were conducted resulting in an anthelmintic efficacy above 97%. This confirms that the recommended dose rate of 3.75 mg/kg is appropriate. Efficacy for goats was demonstrated for ten out of the 14 claimed species. The four species for which efficacy was not examined, and thus cannot be included in the indication for goats, are *Teladorsagia davtiani*, *Cooperia oncophora, Nematodirus battus* and *N. filicollis*. Moreover, the efficacy against the inhibited larvae stages was not adequately demonstrated and, therefore, cannot be included in the indication for goats.

Part 5 – Benefit/risk assessment

Introduction

ZOLVIX oral solution is a broad spectrum anthelmintic for the treatment and control of gastro-intestinal nematode infections and associated diseases in sheep including lambs, hoggets, breeding rams and ewes. The active substance is monepantel which is an anthelmintic belonging to the amino-acetonitrile derivative (AAD) class of molecules. Monepantel acts on the nematode specific nicotinic acetylcholine receptor sub-unit Hco-MPTL-1. This is the first biological function to be described for the Hco-MPTL-1 receptor and therefore monepantel is effective against nematodes resistant to other anthelmintic classes. The application was submitted as an extension to add goats as a new species. Goats are a minor species and therefore the data requirements in the appropriate CVMP guidelines on “minor use minor species (MUMS) data requirements” were applied when assessing the application.

Benefit assessment

Direct therapeutic benefit

The benefit of ZOLVIX would be its efficacy in the treatment of goats, which was shown in four laboratory and three field studies. The active substance is a well-known and safe substance as the product was authorised for use in sheep in 2009.

Well conducted controlled clinical trials demonstrated that the product is efficacious in a wide spectrum of nematodes including. (*Haemonchus contortus, Teladorsagia circumcincta, T. trifurcate, T. davtiani, Trichostrongylus axei, Tr. colubriformis, Cooperia curticei, Nematodirus filicollis, N. spathiger, Oesophagostomum venulosum).*

However, the efficacy was not demonstrated for four species (*Teladorsagia davtiani*, *Cooperia oncophora, Nematodirus battus* and *N. filicollis*) out of the fourteen parasites for which the product is authorised in sheep. Moreover the efficacy against the inhibited larvae stages was not adequately demonstrated in goats.

Additional benefits

Goats are a minor species and therefore this extension increases the range of available treatment possibilities for this species.

Risk assessment

Following the use of the product in goats there is a risk for dung organisms during a maximum period of a week. As this risk is present for a relatively short period (dung insects are expected to be present in dung droppings of goats previously deposited on pasture which serve as a reservoir for insects to colonise droppings of treated animals after a week) no risk management measures are considered necessary.

No additional risks for the user, or the consumer other than those mentioned in the original dossier have been identified following the addition of goats as a new target species in the indication of ZOLVIX. A withdrawal period of 7 days for meat and offal has been established for goats. In the absence of an MRL for milk, the product is not for use in animals producing milk for human consumption.No classical tolerance study exists for goats. However it is known that sheep which is a closely related species to goats tolerate an overdose of 10 times the recommend dose of 2.5 mg/kg. The recommended dose for goats is 3.75 mg/kg. No evidence of intolerance was observed in goats in various safety and efficacy studies conducted at doses up to 5.6 mg/kg. Therefore the omission of the tolerance study can be considered acceptable as there is no reason to expect intolerance in this species.

Risk management or mitigation measures

No other additional risk management measures than those mentioned in the original dossier have been identified in the context of this extension of the product to goats.

The CVMP proposes that the periodic safety update report (PSUR) cycle be restarted for submission of 6 monthly reports (covering all authorised presentations of the product) for the next two years, followed by yearly reports for the subsequent two years and thereafter at 3 yearly intervals. This is considered necessary in view of the extension of the indications to a new target species.

The risk management and mitigation measures stated in the original application of ZOLVIX are also applicable for this extension.

Evaluation of the benefit / risk balance

The CVMP has agreed that the product has been shown to be efficacious for goats for the following indication(s):

"*ZOLVIX oral solution is a broad spectrum anthelmintic for the treatment and control of gastro-intestinal nematode infections and associated diseases in goats including lambs, kids hoggets, breeding rams, bucks, ewes and does.*

Spectrum of activity includes fourth larvae and adults of: Haemonchus contortus, Teladorsagia circumcincta, Teladorsagia trifurcate, Trichostrongylus axei, Trichostrongylus colubriformis, Trichostrongylus vitrinus, Cooperia curticei, Nematodirus spathiger, Chabertia ovina, Oesophagostomum venulosum."

However, the efficacy was not demonstrated for four other species (*Teladorsagia davtiani*, *Cooperia oncophora, Nematodirus battus* and *N. filicollis*) out of the fourteen parasites for which the product is already authorised in sheep. Moreover, the efficacy against the inhibited larvae stages was not adequately demonstrated in goats.

The formulation and manufacture of ZOLVIX is well described and specifications set will ensure that product of consistent quality will be produced.

It presents a low risk for users and the environment and appropriate warnings has been included in the draft SPC. A sufficient withdrawal period has been set.

The product has been shown to have a positive benefit/risk balance overall in goats for the above indication.

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 ZOLVIX are considered to be in accordance with the requirements of Directive 2001/82/EC, as amended. The overall benefit/risk evaluation is deemed positive for this extension application for the (reduced) indication recommended above for goats with a sufficiently clear and complete SPC and product literature.