9 July 2015
EMA/469449/2015
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Novaquin (EMEA/V/C/003866/0000)

International non-proprietary name: meloxicam

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

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Introduction

On 27 January 2014 Le Vet Beheer B.V. submitted an application for a marketing authorisation to the European Medicines Agency (EMA) for Novaquin through the centralised procedure falling within scope of Article 3(3) of Regulation (EC) No 726/2004 (a generic application).

The eligibility to the centralised procedure was agreed upon by the CVMP on 10 October 2013. The rapporteur appointed was D. Murphy and co-rapporteur J. Bureš.

The applicant is registered as an SME pursuant the definition set out in Commission Recommendation 2003/361/EC.

Novaquin is an oral suspension that contains 15 mg/ml meloxicam as active substance. The product is intended for oral use and the target species is horses. The product will be available in bottles containing 125 ml and 336 ml, together with a 20 ml polypropylene measuring syringe for dosing.

The proposed indication is the 'alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses'.

The dossier has been submitted in line with the requirements for submissions under Article 13(1) of Directive 2001/82/EC. The reference product is Metacam 15 mg/ml oral suspension for horses.

The CVMP adopted an opinion and CVMP assessment report on 9 July 2015.

On 8 September 2015, the European Commission adopted a Commission Decision granting the marketing authorisation for Novaquin.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (version 2013/04-04, with an effective date of 29 August 2014) 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 active substance is manufactured outside the European Union (EU).

The finished product is manufactured in the EU. Batch release for the European Union (EU) is carried out by Produlab Pharma B.V., Forellenweg 16, 4951 SJ Raamsdonksveer, The Netherlands.

A manufacturing authorisation for Produlab Pharma B.V. issued on 10 April 2012 by the Ministerie van Economische Zaken, Landbouw en Innovatie, The Netherlands is provided. The manufacturing authorisation lists the date of last inspection to be 25/01/2012.

The GMP declaration for the active substance manufacturing site provided by the qualified person at the dosage form manufacturing site is based on an audit of the active substance site by a third party. This audit was conducted on 7 January 2015. The declaration provided is considered acceptable.

Overall conclusions on administrative particulars

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

Part 2 - Quality

Composition

The product contains 15 mg/ml meloxicam and has been formulated as a generic of Metacam 15 mg/ml oral suspension for horses which is authorised via the centralised procedure. The excipients used in the formulation are sodium benzoate as preservative, glycerol, polysorbate 80, hydroxyethylcellulose, silica, colloidal anhydrous, disodium phosphate dodecahydrate, citric acid monohydrate, sodium cyclamate, sorbitol, liquid, sucralose, anise aroma and water, purified. These excipients are standard excipients for the dosage form and all comply with their respective European Pharmacopoeia (Ph. Eur.) monographs except for one of the flavouring agents which is a non-pharmacopoeial material.

Container

The product is supplied in white opaque high density polyethylene (HDPE) bottles with a HDPE screw cap. Fill volumes are 125 ml (in a 136 ml bottle) and 336 ml (in a 347 ml bottle). A 20 ml polypropylene measuring syringe is provided for dosing. The syringe is marked in increments of 50 kg from 50 kg to 600 kg. Each 100 kg mark is also marked with the corresponding volume in ml. Appropriate specifications and declarations of compliance with Ph. Eur. monographs for containers are provided for the containers and syringes.

Development pharmaceutics

The dossier does not give a complete review of the formulation development. Initial formulations using a flavour combination similar to the reference product caused problems in the analytical methods and other flavour combinations were therefore investigated. No details of the different flavours investigated are given but the flavouring complex of sodium cyclamate, anise and sorbitol is stated to be effective in masking the bitter taste of meloxicam. It is not clear how this was established and the final formulation also includes sucralose as a flavouring agent. It is unclear at what stage of development or why this was added. The justification for the chosen formulation is based on reference to 'identical meloxicam formulations'. No specific details are provided. The product has been demonstrated to be bioequivalent to

the reference product and on that basis the CVMP accepts it as a generic product albeit that the rationale for inclusion of the individual components within the formulation has not been provided as expected in the development pharmaceutics section of the dossier.

The CVMP considered that the combination of the active substance specification and the finished product release specification is sufficient to ensure that routine batches are equivalent to the one used in the satisfactory bioequivalence study.

With respect to polymorphism the applicant has confirmed that all batches of active substance were the same polymorphic form and a test for this parameter is also included on the active substance specification.

Method of manufacture

Manufacture of the finished product involves the preparation and combination of a number of solutions and suspensions. The process is adequately described and a flow chart is provided. Appropriate in-process controls are established at different stages of the manufacturing process. Satisfactory process validation has been provided for three full scale batches. However, the proposed holding period needs to be confirmed on production scale batches post-authorisation.

Control of starting materials

Active substance

The active substance is meloxicam and is the subject of a Ph. Eur. monograph. Documentation in support of the active substance is provided in the form of a Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM). In addition to the Ph. Eur. monograph and CEP requirements the specification for the active substance includes limits for particle size, polymorphism and a residual solvent. Details of the test for polymorphism and its specificity for the polymorphic form in this product are provided and are acceptable.

Satisfactory stability data for the active substance according to the CVMP Guideline on stability testing of existing active substances and related finished products (EMEA/CVMP/QWP/846/99-Rev.1) is provided to support the proposed retest period of 60 months. No specific storage precautions are required.

Excipients

The excipients used in Novaquin are standard excipients for the dosage form and all comply with their respective Ph. Eur. monographs except for one of the flavouring agents, anise aroma, which is a non-pharmacopoeial material.

The anise aroma is provided by 2 different suppliers with different compositions. Specifications and certificates of analysis from both suppliers are provided for this non-pharmacopoeial excipient.

One of the suppliers provides the same flavouring agent (i.e. same composition) as that used in a veterinary medicinal product already authorised for the same target species and the quantity used for the manufacture of Novaquin is less than that used in the already authorised product. The CVMP therefore considers acceptable the use of this excipient and its quantity within this medicinal product.

The anise aroma from the other supplier contains traces of estragole which is genotoxic and carcinogenic. A limit for estragole of 1000 ppm is included in the specification for the anise aroma from this second supplier and this is acceptable with respect to target animal and consumer safety (see part 3 below).

Certificates of analysis of each of the pharmacopoeial excipients have been provided and the results are satisfactory.

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

None of the starting materials used for the active substance meloxicam or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 Rev.3).

TSE statements for the Novaquin components are submitted accordingly.

Control tests during production

Not applicable.

Control tests on the finished product

A tabulated release specification covering both bottle sizes, including all parameters, limits (with units) and reference to analytical methods is provided. The tests conducted are satisfactory (appearance, colour, homogeneity, odour, pH, absolute density, extractable volume, uniformity of mass of delivered doses from multidose containers, identification and assay of active substance, identification and assay of preservative, related substances, dissolution and microbiological quality). The measuring syringe has been tested with respect to dosing accuracy according to the requirements of Ph. Eur. and, as indicated above, this test is included in the release specification.

Analytical methods and appropriate validation in line with VICH GL2 on validation of analytical procedures are provided for determination of the active substance, the preservative and related substances. This is considered acceptable.

Stability

The shelf-life specification is the same as that proposed for release with the following exceptions:

- A test for uniformity of mass of delivered doses from multidose containers is not included.
- The shelf-life limits for individual and total related substances are different from those at release.

The specification at end of shelf-life is considered acceptable.

Stability data is provided for four full scale batches. 24-month data under real time (25 °C/60% RH) and 6-month data under accelerated (40 °C/75% RH) conditions is presented.

The stability batches are full scale batches manufactured using different batches of active substance and packaged in their proposed commercial container (2 batches in the 136 ml size bottles and 2 batches in the 347 ml size bottles). All batches were tested fully in accordance with the specification. In addition,

preservative efficacy within the in-use testing is reported at 6, 12 and 24 months after production (i.e. at the 5-month timepoint of the in-use testing). The data demonstrate no adverse trends and little variability over time for any parameter tested. Individual impurities are above the reporting threshold of 0.05% at the latter timepoints only and there is a slight increase in total impurities. Assay values fluctuate a little but not significantly. All results remain within specification. The study is scheduled to continue to 36 months at 25 °C/60% RH.

An in-use stability study was conducted as part of the on-going stability study. Slightly higher levels of individual and total impurities are seen at these in-use testing points but both remain within the specification. The latest in-use testing point is at 24 months after production and therefore close to the proposed end of shelf-life. The data is considered acceptable to support the proposed in-use shelf-life of 5 months.

A freeze/thaw study was conducted as part of the on-going stability study. No adverse effect or out-of-specification results are observed and therefore it is concluded that low temperature storage does not have any adverse impact on the quality of the product.

A photostability study in line with VICH GL5 on photostability testing of new veterinary drug substances and medicinal products confirms that the product is not sensitive to light.

Based on extrapolation of the 24-month real time data a shelf-life of 3 years with the no specific storage precautions is supported.

Overall conclusions on quality

Novaquin is a suspension for oral use for horses that contains 15 mg/ml meloxicam as active substance.

The excipients, apart from the anise aroma, are commonly used in veterinary medicines and comply with Ph. Eur. monographs. The quantity used and the specifications set for the anise aroma from both suppliers ensure adequate target animal and consumer safety. The rationale for inclusion of the individual components within the formulation has not been fully addressed. However, the product has been demonstrated to be bioequivalent to the reference product and on that basis the CVMP accepts it as a generic product.

Documentation in support of the active substance is provided in the form of a CEP from EDQM. Additional tests for particle size, polymorphism and a residual solvent are performed by the finished product manufacturer.

Stability data show that the active substance is stable and a re-test period of 60 months with no specific storage conditions is appropriate.

Manufacture of the finished product involves the preparation and combination of a number of solutions and suspensions. Satisfactory process validation has been provided for three full scale batches.

No materials of animal origin are used in the manufacture of the product.

The product is packed in appropriate HDPE bottles containing 125 ml or 336 ml of suspension. A 20 ml measuring syringe is provided for dosing. Appropriate specifications and declarations of compliance with Ph. Eur. monographs for containers are provided for the containers and the syringe.

The finished product specifications include appropriate tests and limits for a suspension. The analytical methods have been satisfactorily validated. Certificates of analysis have been provided which demonstrate compliance with the proposed release specification.

Stability data is provided for four full scale batches of the finished product packaged in their proposed commercial container. 24-month data under real time (25 °C/60% RH) and 6-month data under accelerated (40 °C/75% RH) conditions is presented.

An in-use stability study was conducted as part of the on-going stability study where, besides the other parameters, the preservative efficacy was tested. The latest in-use testing point is at 24 months after production (i.e. at the 5-month timepoint of the in-use testing) and therefore close to the proposed end of shelf-life. The data is considered acceptable to support the proposed in-use shelf-life of 5 months.

A freeze/thaw study and a photostability study demonstrated that low temperature storage does not have any adverse impact on the quality of the product and that the product is not sensitive to light, respectively.

Based on extrapolation of the 24-month real time data a shelf-life of 3 years with the no specific storage precautions is supported.

The applicant is recommended to provide the following data post-authorisation:

- During process validation of further batches, and before release of batches subjected to a holding period, the holding period should be validated under production conditions.

Part 3 – Safety

The dossier has been submitted in line with the requirements for submissions under Article 13(1) of Directive 2001/82/EC concerning a generic medicinal product. The chosen reference product is Metacam 15 mg/ml oral suspension for horses. In support of this application an in vivo bioequivalence study was provided. This is summarised and commented on in part 4 of this assessment report. Given that bioequivalence is documented, cross-reference to the safety and efficacy dossier of reference product is considered appropriate.

Pharmacodynamics

With reference to the pharmacodynamic properties of the reference product, meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class which acts by inhibition of prostaglandin synthesis, thereby exerting anti-inflammatory, analgesic, anti-exudative and antipyretic effects. It reduces leukocyte infiltration into the inflamed tissue. To a minor extent it also inhibits collagen-induced thrombocyte aggregation. Meloxicam also has anti-endotoxic properties because it has been shown to inhibit production of thromboxane B2 induced by intravenous *E. coli* endotoxin administration in calves and pigs.

Pharmacokinetics

With reference to the pharmacokinetic properties of the reference product the following apply:

Absorption

When the product is used according to the recommended dosage regime the oral bioavailability is approximately 98%. Maximal plasma concentrations are obtained after approximately 2–3 hours. The accumulation factor of 1.08 suggests that meloxicam does not accumulate when administered daily.

Distribution

Approximately 98% of meloxicam is bound to plasma proteins. The volume of distribution is 0.12 l/kg.

Metabolism

The metabolism is qualitatively similar in rats, mini-pigs, humans, cattle and pigs although quantitatively there are differences. The major metabolites found in all species were the 5- hydroxy- and 5-carboxy-metabolites and the oxalyl-metabolite. The metabolism in horses was not investigated. All major metabolites have been shown to be pharmacologically inactive.

Elimination

Meloxicam is eliminated with a terminal half-life of 7.7 hours.

Toxicological studies

No data was presented which is considered acceptable for this generic application.

Genotoxicity

The anise flavouring agent from one of the suppliers contains traces of estragole as an impurity which is genotoxic and carcinogenic. A limit of 1000 ppm for estragole in the specification of the anise aroma from this supplier has been included. It is argued that quantities of the impurity below the limit proposed will not pose an unacceptable risk. In support of this position, reference is made to the Committee on Herbal Medicinal Products (HMPC) Public statement on the use of herbal medicinal products containing estragole (EMA/HMPC/137212/2005-Rev 1), wherein it is stated that in the evaluation of herbal medicinal products the acceptable daily dose (ADD) for human exposure is 10 µg estragole/kg/day (0.5 mg/person/day for a 50 kg adult). The human ADD of 0.01 mg/kg bw is based on the benchmark dose ($BMDL_{10}$) of 10 mg/kg/day (based on induction of hepatomas by estragole in female mice) and the application of an uncertainty factor of 1000. Assuming that estragole is present in the flavour at the limit of 1000 ppm, a horse would be maximally exposed to 0.06 µg/kg bw/day (>100 times lower than the human ADD). Given that the worst-case exposure for the target animal is 0.06 µg/kg bw/day, it can be reasonably expected that any consumer exposure will be much less and much lower than the established ADD. When potential exposure is viewed against the ADD established by HMPC as referred to above, the CVMP considers reasonable to conclude that the risk to both the target animal and the consumer arising from estragole as an impurity (up to a limit of 1000 ppm) in anise aroma is negligible.

Studies of other effects

Meloxicam is used in human medicine for treatment of rheumatoid arthritis and osteoarthritis. Daily oral doses of 7.5 mg or 15 mg per person are recommended, corresponding to approximately 0.125 or 0.25 mg/kg bw/day.

Information on the safety of the various excipients as detailed in Handbook of pharmaceutical excipients (Rowe, 2009) is provided. All excipients are commonly used as food additives or in pharmaceuticals and/or cosmetics and their toxicological profile is well known. Indeed, in common with Novaquin oral suspension, the following excipients are included in the reference product: sodium benzoate, sorbitol, glycerol, silica colloidal anhydrous, hydroxyethyl cellulose and citric acid. All excipients at the quantities included in Novaquin can be regarded as essentially non-toxic.

Local effect studies (dermal irritation/sensitisation, ocular irritation) using the formulation proposed for marketing would normally be expected in order to adequately characterise the risk to the user in the

event of dermal or ocular exposure. Such studies have not been presented for this product. In this case, the CVMP accepts the absence of such studies given that this information is available for the active substance (meloxicam is neither an irritant nor a sensitiser) and that the excipients, at the quantities included in the formulation, are not expected to be associated with adverse effects.

User safety

A user safety assessment was conducted in accordance with the current guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-FINAL-Rev.1).

The exposure, and therefore risk to the user, is expected to be the same for both test and reference products as the main constituent to consider in this user safety assessment is meloxicam (no risk to the user due to exposure to the excipients is anticipated), and Novaquin is identical to the reference product in terms of meloxicam content, and will be used in the same manner.

Therefore, it is appropriate that the user safety statements approved for the reference product be applied to Novaquin. The following user safety statements were proposed and can be accepted:

"People with known hypersensitivity to NSAIDs should avoid contact with the veterinary medicinal product.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician."

In addition, the warning "keep out of sight and reach of children" will appear on the label and package leaflet of the product.

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

A phase I environmental risk assessment was provided in line with line with the VICH guideline GL 6 - Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products (VMPs) - Phase I (CVMP/VICH/592/98-FINAL). Given that the product is used to treat an individual or a few animals in a flock or herd, the environmental risk assessment can stop at phase I.

The CVMP concluded that the product will not pose an unacceptable risk for the environment when used as recommended.

Overall conclusions on the safety documentation

Given the nature of the application (a generic) and the fact that bioequivalence with the authorised reference product, Metacam 15 mg/ml oral suspension for horses, is documented (see part 4) cross-reference to the safety and pre-clinical studies of the reference product is acceptable.

The risk for the target animal arising from estragole as an impurity (up to a limit of 1000 ppm) in anise aroma is negligible.

Based on the user safety assessment provided, it can be concluded that Novaquin will have the same risks to the user as the reference product and the same safety warnings apply.

The data provided are sufficient to conclude that the product is not expected to pose a risk for the environment when used as recommended.

Residues documentation

Identification of the product concerned

Novaquin contains 15 mg/ml meloxicam and has been formulated to be similar to Metacam 15 mg/ml oral suspension for horses.

Residue studies

No residue depletion studies were provided and cross-reference is made to the dossier of the reference product. Given the comparable plasma pharmacokinetic profile (see part 4), it is assumed that residue depletion from tissues will be the same for both test and reference product. As bioequivalence between Novaquin and Metacam 15 mg/ml oral suspension for horses has been shown, this is considered acceptable.

Pharmacokinetics

In support of this application an in vivo bioavailability study in horses was submitted to compare the plasma pharmacokinetic profile of meloxicam between Novaquin 15 mg/ml oral suspension for horses and the reference product Metacam 15 mg/ml oral suspension for horses, as described in part 4 of this report.

MRLs

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

Pharmacologically active substance	**Marker residue**	**Animal species**	**MRL**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Meloxicam	Meloxicam	Bovine, caprine, porcine, rabbit, Equidae	20 µg/kg 65 µg/kg 65 µg/kg	Muscle Liver Kidney	NO ENTRY	Anti-inflammatory agents/Non-steroidal anti-inflammatory agents
		Bovine, caprine	15 µg/kg	Milk		

The excipients listed in section 6.1 of the 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 are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Withdrawal periods

Given that bioequivalence with Metacam 15 mg/ml oral suspension for horses is documented, the same withdrawal period approved for the reference product was proposed to be applied to Novaquin. The following text is proposed for inclusion in section 4.11 of the SPC:

'Meat and offal: 3 days'.

As no MRL for horse milk is established, the following sentence is included: Not authorised for use in horses producing milk for human consumption.

The CVMP accepts that a withdrawal period of 3 days authorised for the reference product can be applied to Novaquin.

Overall conclusions on the residues documentation

Based on the outcome of the bioequivalence study, the same withdrawal period approved for the reference product (meat and offal: 3 days) is applicable to Novaquin. The proposed withdrawal period can be accepted. Additionally, as no MRL for horse milk is established, the following sentence is included: Not authorised for use in horses producing milk for human consumption.

The risk for the consumer arising from estragole as an impurity (up to a limit of 1000 ppm) in anise aroma is negligible.

Part 4 – Efficacy

Pharmacodynamics

See part 3.

Development of resistance

Not applicable.

Pharmacokinetics

In support of this application, the applicant conducted an in vivo bioavailability study according to the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) in order to compare the plasma concentration profile of meloxicam when administered as Novaquin 15 mg/ml oral suspension for horses (test product) and the Metacam 15 mg/ml oral suspension for horses (reference product). The choice of reference product is considered acceptable.

This was a GLP compliant study using 20 horses. The study was designed as a cross-over study with two treatment periods (I and II) and a wash out period of 7 days between treatment periods. Animals were acclimatised for 7 days before administration of the test articles. Animals were randomly assigned to one of two groups (10 animals in each group) using a blocking system based on gender and weight.

Following weighing, all animals were administered the test/reference products at a dose rate of 0.6 mg meloxicam/kg bodyweight (based upon nominal meloxicam concentrations) once during each period of the study.

Blood samples for plasma meloxicam determination were collected from the jugular vein on 16 occasions in each period of the study; once pre-treatment and then at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours after administration.

Samples were assayed for the determination of meloxicam content using a LC-MS/MS method validated in the concentration range 5 – 5000 ng/ml. The plasma concentrations of meloxicam were used to calculate the pivotal pharmacokinetic parameters C_{max}, T_{max}, AUC_t, AUC_∞ and $t_{1/2}$. Determination of bioequivalence was based on the pivotal parameters C_{max} and AUC_t. Demonstration of bioequivalence was specified as having been achieved if the 90% confidence intervals (CIs) for AUC_t are within the ratio of the test mean to control mean of 0.8 to 1.25 and if the 90% CIs for C_{max} are within the ratio of 0.7 to 1.43. The wider limits for C_{max} were justified primarily on the basis of the higher expected variance at C_{max}. Notwithstanding the fact that wider limits were pre-specified for C_{max}, the results of the comparative bioavailability study indicate that the 90% confidence intervals for the estimate of the ratio of the means for both parameters, AUC and C_{max}, lie within the narrower limits of 80% to 125%.

Mean plasma meloxicam concentrations peaked at 2010 ± 550 ng/ml (t_{max} = 1.5 ± 0.5) and 1810 ± 600 ng/ml (t_{max} = 2.1 ± 1.1) for test and reference products, respectively. The observed terminal elimination half-lives ranged from 3.3 h to 9.1 h.

The ratio estimate for AUC_{0-t} is 104.8%. The associated 90% CI, i.e. 100.8 to 108.9% is included within the bioequivalence range of 80% to 125%. The ratio estimate for C_{max} is 112.5%. The associated 90% CI, i.e. 104.9% to 120.7% is included within the bioequivalence range of 70% to 143%.

Based on the calculations of confidence intervals for C_{max} and AUC, the confidence intervals for both parameters were within the allowable ratio of the test mean to the control mean. Therefore, based on the results presented it is concluded that the two products are bioequivalent.

Dose determination/justification

The product is an oral suspension containing 15 mg/ml meloxicam to be administered orally to horses at a dose rate of 0.6 mg/kg once daily for up to 14 days. The posology is justified by reference to the reference product and this is considered acceptable.

Target animal tolerance

A product specific target animal safety study has not been presented. The absence of a product specific study is justified on the basis that:

- Bioequivalence with the reference product has been confirmed; therefore, the expected risks to the target animal associated with the active substance are similar for both the test and the reference products, and
- The excipients in the test product are commonly used as food additives or in pharmaceuticals and/or cosmetics. All excipients at the quantities included in the formulation, are not expected to pose a risk to the target animal following oral administration.

The risks posed to the target animal by the test product are expected to be similar to those posed by the authorised reference product, Metacam 15 mg/ml oral suspension for horses. Therefore, it is appropriate that the precautionary measures relating to use in the target animals that appear on the reference product be applied to Novaquin.

Field trials

No clinical efficacy studies were provided. Given the nature of the application (generic) and the fact that bioequivalence with an authorised reference product is documented, this is considered acceptable.

Overall conclusion on efficacy

In support of the application a GLP comparative in vivo bioequivalence study was provided. Based on the study data presented, the CVMP concluded that bioequivalence between Novaquin (test product) and Metacam 15 mg/ml oral suspension for horses (reference product) has been demonstrated.

Therefore, it can be expected that both Novaquin and reference product will have a similar efficacy profile. The CVMP considers that the bioequivalence study supports the indication "For the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses" as authorised for the reference product.

Part 5 – Benefit-risk assessment

Introduction

Novaquin is an oral suspension that contains 15 mg/ml meloxicam as active substance. The product will be available in HDPE bottles of 125 ml or 336 ml, together with a 20 ml polypropylene measuring syringe for dosing. The product is intended for oral administration directly into the mouth of the horse or mixed with food.

The product is indicated for the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses. The proposed withdrawal period is 3 days for meat and offal.

The dossier has been submitted in line with the requirements for submissions under Article 13(1) of Directive 2001/82/EC, a generic application.

Benefit assessment

Direct therapeutic benefit

The benefit of Novaquin is its efficacy in the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses.

The evidence for the direct therapeutic benefit is considered established on the basis of bioequivalence to the reference product.

The active substance is a well-known non-steroidal anti-inflammatory drug (NSAID) in veterinary medicine. The primary mode of action of meloxicam is inhibition of cyclooxygenases in the arachidonic acid inflammatory pathway.

Additional benefits

Novaquin increases the range of available treatment possibilities for the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses.

Risk assessment

Main potential risks have been identified as follows:

Quality:

The formulation and manufacture of the finished product are well described and the specifications set will ensure that product of consistent quality will be produced. However, the applicant is recommended to validate the holding period under production conditions during process validation of further batches and before release of batches subjected to a holding period.

For the target animal:

The risks posed to the target animal are expected to be similar to those posed by the authorised reference product. Additionally, the CVMP considered that the anise flavour does not pose a risk to the target animal.

Novaquin is not expected to pose a risk for the target animal when used as recommended.

For the user:

The CVMP concluded that the user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the consumer:

The proposed withdrawal period for meat and offal of 3 days is accepted as bioequivalence with the reference product is demonstrated. The product is not authorised for use in lactating animals producing milk for human consumption.

The CVMP considered that the excipient anise flavour does not pose a risk to the consumer.

For the environment:

Novaquin is not expected to pose a risk for the environment when used as recommended.

Risk management or mitigation measures

Appropriate information is included in the SPC to inform on the potential risks of this product relevant to the target animal, the user, the consumer and the environment, and to provide advice on how to prevent or reduce these risks.

Additionally, the following sentence is included in section 4.11 of the SPC: 'Not authorised for use in horses producing milk for human consumption'.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders in horses.

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

Novaquin is well tolerated by the target animal and presents an acceptable risk for users and the environment when used as recommended. A sufficient withdrawal period has been set.

Appropriate warnings and precautionary measures have been included in the SPC and other product information.

The product has been shown to have a positive benefit-risk balance overall.

Conclusion on benefit risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Novaquin is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.