16 March 2017
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Novem to add a new strength 40 mg/ml solution for injection for cattle (EMEA/V/C/000086/X/0018)

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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Product profile

Invented name:	Novem
Active Substances:	meloxicam
Target Species:	Cattle and pigs
Pharmaceutical Form:	Solution for injection
Strength:	20 mg/ml and 40 mg/ml
Therapeutic Indication:	For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle and Cattle: For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle. For use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle. For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy. For the relief of post-operative pain following dehorning in calves. Pigs: For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation. For adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.
ATCvet code	QM01AC06
Pharmacotherapeutic group	Musculo-skeletal system
Applicant	Boehringer Ingelheim Vetmedica GmbH

Introduction

On 22 November 2016 Boehringer Ingelheim Vetmedica GmbH submitted an application for an extension to the marketing authorisation for Novem to the European Medicines Agency (The Agency) in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I point 2(c) thereof.

Novem 5 mg/ml and 20 mg/ml solution for injection are authorised for cattle and pigs and contain meloxicam, a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. Novem was authorised for use in the Union on 2 March 2004.

This extension application concerns the addition of a new strength (40 mg/ml) for subcutaneous use in cattle.

Within the initial marketing authorisation application of Novem the marketing authorisation holder, Boehringer Ingelheim Vetmedica, self-consented to the data contained in the original files for Metacam.

The addition of a new strength (Novem 40 mg/ml) for an existing pharmaceutical form (solution for injection) for subcutaneous use in cattle is already authorised for Metacam. Relevant data submitted within this extension to the marketing authorisation of Novem was already submitted and assessed for the addition of a new strength for Metacam (40 mg/ml) and a new route of administration (subcutaneous use) for an existing target species (cattle). Reference to the assessment of Metacam 40 mg/ml solution for injection for subcutaneous use for cattle is therefore made in this report.

The applicant applied for the following indications:

- For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle.
- For use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle.
- For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy.
- For the relief of post-operative pain following dehorning in calves.

Novem 40 mg/ml solution for injection is presented in packs containing 1 vial or 12 vials of 50 ml or 100 ml of product.

The rapporteur appointed is Frida Hasslung Wikström and the co-rapporteur is Ellen-Margrethe Vestergaard.

The dossier has been submitted in accordance with Article 19 of Commission Regulation (EC) 1234/2008 and Annex I thereof (extensions).

On 16 March 2017 the CVMP adopted an opinion and CVMP assessment report.

On 15 May 2017 the European Commission adopted a Commission Decision granting the extension to the marketing authorisation for Novem.

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 (dated November 2012) 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 manufacturer of the finished product is appropriately authorised for manufacture of the product in accordance with European Union (EU) Good Manufacturing Practice (GMP). A valid GMP certificate was provided. Batch release for the EU will be carried out by Labiana Life Sciences S.A., Spain.

A statement from the qualified person (QP) of the manufacturer of the finished product confirming that the manufacture of the active substance is performed in compliance with GMP was provided. This GMP certificate confirms that the manufacturing site complies with EU GMP for active substances used as starting materials.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The new presentation is an aqueous solution for intravenous injection containing meloxicam at a concentration of 40 mg/ml.

The excipients used in the formulation (poloxamer 188, macrogol 300, glycine, disodium edetate, sodium hydroxide, hydrochloric acid and meglumine) are the same as those used for the solution for injection already authorised in other strengths. They are all well-known and widely used in other medicinal products, including other solutions for injection. The proposed composition includes 150 mg/ml of ethanol as antimicrobial preservative and several solubilising agents are included as the active substance is practically insoluble in water.

Novem 40 mg/ml solution for injection is qualitatively identical to the 20 mg/ml solution and differs quantitatively only in the concentrations of the active substance (40 mg/ml vs. 20 mg/ml) and of

some excipients. The proportion between the active substance meloxicam and excipients has been appropriately justified.

Containers

The product is presented in colourless type I glass vials of 50 ml and 100 ml, closed with bromobutyl stoppers and aluminium caps. These are characteristic components for the primary packaging of solutions for injection.

Development pharmaceutics

The development pharmaceutics is acceptable. The rationale for the proposed composition is discussed and is acceptable. The formulation development performed is acceptable. All excipients used are already used in the approved 20 mg/ml strength. The amounts of all excipients used are the same as in the 20 mg/ml strength except for meglumine. The 40 mg/ml strength contains twice as much meglumine as the 20 mg/ml strength. The proportion between the active substance meloxicam and meglumine has been justified.

The sterilisation method used is acceptable.

The container closure system for the finished product is characteristic for this pharmaceutical form. Materials in contact with the solutions fulfil the specifications of the relevant European Pharmacopoeia (Ph. Eur.) monographs for the type I glass and for the bromobutyl stoppers. Fragmentation and self-sealing test have been conducted on the stoppers.

Method of manufacture

The manufacturing process is a standard one.

The range proposed for commercial batch size is acceptable.

The justification that the proposed manufacturing process can be considered standard is in line with current guideline on process validation for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev.1). Validation data on 6 commercial batches has been provided. This is acceptable for a standard process.

Control of starting materials

Active substance

The active substance meloxicam is the subject of a Ph. Eur. monograph. Batch analyses include the tests of the monograph plus complementary tests for residual solvents and particle size.

Stability data are provided at 25 °C ± 2 °C /60% ± 5% RH up to 60 months and at 40 °C ± 2 °C/75% ± 5% RH for 6 months. All results comply with the specification. No trends are shown for assay, impurities or other parameters tested. The proposed retest period of 5 years is acceptable and considered justified by the stability data provided.

Excipients

The excipients used in the manufacture of the solution for injection are: Ethanol (antimicrobial preservative), poloxamer 188, glycine, meglumine, macrogol 300, disodium edetate, water for injections, hydrochloric acid and sodium hydroxide. All excipients are the subject of a monograph in the Ph. Eur. The amount of ethanol given in the composition of Novem 40 mg/ml corresponds to ethanol anhydrous.

Certificates of analysis of the excipients from the manufacturer of the finished product have been submitted and are satisfactory.

The data provided for the excipients are considered acceptable.

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

None of the starting materials used for the manufacture of 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).

The applicant has provided a declaration indicating that the product does not contain any substance of biological origin.

Control tests on the finished product

The proposed finished product specification at release is acceptable. Tests for pH (Ph. Eur.), relative density (Ph. Eur.), refractive index (Ph. Eur.), appearance and colour (visual), particulate matter (Ph. Eur.), identity and assay of meloxicam and ethanol (HPLC), any and total impurities (HPLC), extractable volume (Ph. Eur.) and sterility (Ph. Eur.) are performed. The methods used are validated when necessary.

The specifications proposed at release are appropriate to control the quality of the finished product.

Batch analysis results are provided for 6 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Results from stability studies have been provided at long term, intermediate and accelerated conditions on 6 commercial scale batches manufactured at the proposed manufacturing site of commercial batches. All batches were filled into 50 ml and 100 ml vials.

Three batches were tested at long-term and intermediate conditions up to 12 months and for 6 months at accelerated conditions. Two other batches were tested at long-term and intermediate conditions up to 9 months and for 6 months at accelerated conditions. Results of the third batch are provided up to 3 months at long-term conditions.

Stability data are provided for 3 non-commercial scale batches from the manufacturer initially approved for Metacam 40 mg/ml solution for injection. Data is provided for 36 months at long-term conditions and 6 months at accelerated conditions. All results comply with the specification.

The finished product is tested according to the specification at the end of shelf life and all results were within specification.

The proposed finished product specification at the end of shelf life is acceptable.

Based on the stability data provided, the proposed shelf life of 3 years is considered acceptable.

In-use stability data are available for two batches filled in vials of 50 and 100 ml, stored under uncontrolled conditions (climatic zone 1) for 9 months and 17 months and stored under long term conditions (25 °C/60% RH) for 36 months. Based on these results, an in-use shelf-life after first opening of the container of 28 days is considered acceptable.

The stability tests were performed in compliance with the respective VICH standards.

No photostability study was provided. Photostability testing should be conducted on at least one primary batch of the finished product according to the guideline on stability testing: Photostability testing of new veterinary drug substances and medicinal products (CVMP/VICH/901/00). However, taking into the account that the 20 mg/ml presentation is also packed in clear vials it is acceptable to omit the photostability study of the new strength (40 mg/ml).

The proposed in-use stability of 28 days is justified by the stability data provided.

Overall conclusions on quality

The data provided in part 2 of the dossier are in line with VICH and Ph. Eur. requirements and are acceptable. The product is a solution for injection which utilises standard pharmaceutical excipients. The proposed formulation for the 40 mg/ml strength has been satisfactorily justified and it has been shown that significant differences in the quality profile respect to the reference solution 20 mg/ml are not expected. The method of manufacture is a standard process and the specifications of the finished product are satisfactory for the proposed composition and dosage form. The active substance is monographed in the Ph. Eur.; both active substance and the finished product are considered to be stable.

The composition of the new strength is justified and critical issues are discussed sufficiently.

Part 3 – Safety

A detailed and critical summary of the safety documentation is based primarily on the published scientific literature. The applicant has submitted a satisfactory dossier including peer-reviewed literature. Meloxicam is a well-known substance in veterinary medicines for many years and therefore this approach is considered acceptable.

Within the initial marketing authorisation application of Novem the marketing authorisation holder, Boehringer Ingelheim Vetmedica, self-consented to the data contained in the original files for Metacam.

The addition of a new strength (Novem 40 mg/ml) for an existing pharmaceutical form (solution for injection) for subcutaneous use in cattle is already authorised for Metacam. Relevant data submitted within this extension to the marketing authorisation of Novem was already submitted and assessed for the addition of a new strength for Metacam (40 mg/ml) and a new route of administration (subcutaneous use) for an existing target species (cattle). Reference to the assessment of Metacam 40 mg/ml solution for injection for subcutaneous use for cattle is therefore made in the safety part.

The safety of the product has been assessed already by the CVMP during the initial marketing authorisation application and later variations and extension applications of Metacam. Appropriate measures to ensure the safe use of the product are included in the product information.

Safety documentation

Pharmacodynamics

No new studies have been submitted. The pharmacodynamic characteristics of meloxicam have been described in connection with previous applications. The omission of pharmacodynamic data is acceptable for this type of application, i.e. an extension for the addition of a new strength (40 mg/ml) for Novem solution for injection in the existing target species cattle.

Pharmacokinetics

No new pharmacokinetic data was submitted apart from two bioequivalence studies (one pilot and one pivotal study). The pivotal bioequivalence study showed the bioequivalence of Meloxicam 40 mg/ml solution for injection and Meloxicam 20 mg/ml solution for injection following subcutaneous injection of the recommended dose of meloxicam to cattle. For details and assessment of the studies, see Part 4.

Toxicological studies

Except for an injection site tolerance study in the target species, no new studies have been submitted. With regard to toxicology data in laboratory species, this information has been presented in previous applications for this product. The toxicological profile of all excipients of the product is well known, they are not expected to raise toxicological concerns for the animal safety nor for human or environmental safety. The omission of toxicological data for meloxicam in laboratory species for Novem 40 mg/ml solution for injection in the target species cattle is acceptable.

Tolerance in the target species of animal

With regard to systemic safety, tolerance information has been presented in previous applications for the current species. Since no change to the authorised dose is proposed, previously assessed data is sufficient to ensure systemic safety. By contrast, given that the current application concerns subcutaneous administration of Novem 40 mg/ml solution for injection, the required information on local tolerance has been provided.

For details and assessment, see Part 4.

User safety

A user safety assessment has been presented and conducted in accordance with CVMP Guideline EMEA/CVMP/543/03-Rev.1.

Identified relevant exposure scenarios were accidental self-injection and dermal exposure. The worst case scenario is accidental self-injection of 0.5 ml containing 20 mg of meloxicam which resulted in a calculated internal exposure level of 0.33 mg/kg for a 60 kg person. The margin of

exposure (MOE) to the repeated dose internal NOEL of 0.2 mg/kg (established in a 52-week feeding study in rats as well as after intravenous treatment for 4 weeks in rats) is 0.6. For the dermal scenario, using a dermal bioavailability of 30%, the internal exposure to a droplet (volume of 50 µl) was calculated to be 0.01 mg/kg for a 60 kg person. MOEs to the repeated dose NOEL were calculated to be 20 without gloves. The MOEs after dermal exposure and after accidental self-injection are below 100. However, it is acknowledged that the NOEL of 0.2 mg/kg bw is derived from repeated dose studies. It is expected that any professional using the product is aware of the user safety aspects of this product and follows good veterinary practice, which includes correct procedures for administration (e.g. wash hands). Moreover, in humans a daily oral dose of 0.125 or 0.25 mg/kg bw/day is recommended. Therefore, the risk for the non-pregnant professional is considered acceptable.

Meloxicam is considered to be maternotoxic/embryotoxic as observed from animal studies resulting in a LOEL of 0.125 mg/kg (MRL summary reports, EMA). When considering the scenario of accidental self-injection a MOE of 0.4 (0.125/0.33) can be calculated. When considering the scenario of dermal exposure a MOE of 12.5 (0.125/0.01) or with gloves of 125 (0.125/0.001) can be calculated. Although the MOE when wearing gloves appears to be above 100, it should be noticed that this MOE was calculated using a LOEL without applying an additional safety factor (for extrapolation from a LO(A)EL to a NO(A)EL).

It cannot be excluded that some of the observed reproductive effects could also be induced by a single exposure. No risk reduction measures can limit the risk of accidental self-injection.

When considering women of childbearing potential the exposure of 0.33 mg/kg is compared to the LOEL of 1 mg/kg/day derived from the fertility and early embryonic study in rats. A MOE based on a NO(A)EL could not be derived, but is considered to be definitely lower than 3, which is not acceptable. However, taking into account that the LOEL is derived from a repeated dose study whereas the accidental exposure is considered as a single exposure and with a low probability of occurrence, the inclusion of following warning phrase in section 4.5 of the SPC, is considered adequate to mitigate the risk for pregnant woman and woman attempting to conceive.

"In view of the risk of accidental self-injection and the known adverse class-effects of NSAIDs and other prostaglandin inhibitors on pregnancy and/or embryo-foetal development, the veterinary medicinal product should not be administered by pregnant women or women attempting to conceive."

This warning and the other user safety warnings in the already authorised Metacam 40 mg/ml solution for injection are appropriate also for Novem 40 mg/ml solution for injection and have been included in the SPC.

The product is not considered to pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

The new strength of Novem, 40 mg/ml solution for subcutaneous injection to cattle is assumed to not affect the environment differently compared to the previously authorised administration route for Metacam 40 mg/ml solution for injection. A Phase I environmental risk assessment (ERA) was provided according to the VICH guideline GL6 - Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products (VMPs) - Phase I (CVMP/VICH/592/98-FINAL).

The environmental risk assessment can stop in Phase I and no Phase II assessment is required

because Novem 40 mg/ml solution for injection will be used to treat a small number of animals in a flock or herd and to treat calves for post-operative pain relief following dehorning for which initial predicted environmental concentration in soil is less than 100 µg/kg.

Based on the provided data, Novem 40 mg/ml solution for injection is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

MRLs

The MRL status of the constituents of Novem 40 mg/ml solution for injection for cattle is as follows:

The active substance in Novem 40 mg/ml solution for injection for cattle 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/Nonsteroidal 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.

Analytical method

As Metacam 40 mg/ml solution for injection and Novem 20 mg/ml solution for injection are already approved for use in cattle, then no further consideration of the analytical methods is required in relation to this application for the addition of a new strength of solution for Novem (40 mg/ml) for subcutaneous administration to the target species cattle.

Residue studies

Pharmacokinetics

As Novem 40 mg/ml solution for injection will be used at the same dosage and dose frequency and for the same indications as for currently registered products, Novem 5 and 20 mg/ml solution for injection, the pharmacokinetic information is unchanged. No new studies except for two bioequivalence studies, one pilot and one pivotal were submitted. The pivotal study indicated that Metacam 40 mg/ml solution for injection was bioequivalent to Metacam 20 mg/ml solution for injection following subcutaneous injection of 0.5 mg meloxicam/kg to cattle. This is acceptable.

The results of the pivotal bioequivalence study indicate that the pharmacokinetics of meloxicam administered subcutaneously, in terms of rate and extent of absorption from the injection site, distribution, metabolism and excretion, are similar between Metacam 40 mg/ml solution for injection

and Metacam 20 mg/ml solution for injection. Extrapolation of the established withdrawal periods for Novem 20 mg/ml solution for injection and subcutaneous administration to cattle for milk (5 days) and meat (except for the injection site) and offal (15 days) to Novem 40 mg/ml solution for injection and subcutaneous administration to cattle is therefore considered acceptable.

Depletion of residues

A study to confirm that the withdrawal period approved for Metacam 20 mg/ml solution for injection and subcutaneous injection to cattle (15 days for meat and offal) are applicable also for Metacam 40 mg/ml solution for injection and Novem 40 mg/ml solution for injection (which is identical to Metacam 40 mg/ml solution for injection) with respect to residues at the injection site was submitted.

Two male and 2 female healthy cattle with an age of 12–19 months and a body weight of 347-424 kg were given 2 subcutaneous injections of 0.5 mg meloxicam (0.0125 ml solution)/kg body weight on Day 0 (left neck) and Day 2 (right neck). Appropriate injection site samples (cylinder shaped core samples) were taken at sacrifice on Day 15, i.e. 15 (left neck) and 13 (right neck) days after administration, after removal of the overlying skin. Appropriate steps, including verification by a photograph, were taken to ensure sampling of the injection site.

No residues of meloxicam were found at the injection site 13 or 15 days following a subcutaneous administration of Metacam 40 mg/ml solution for injection. For all injection site samples (core and surrounding samples) there were no meloxicam concentrations above the lower limit of quantification (LLOQ) of 10.0 µg/kg (i.e. half the MRL of 20.0 µg/kg in muscle). Due to an adequate collection of the injection site and bovine muscle tissue QC samples which confirmed the performance of the analytical method, the lack of quantifiable meloxicam concentrations in the injection site samples do not raise any concern regarding the validity of the study results.

These results are in line with the approved withdrawal period of 15 days for meat following subcutaneous administration of Metacam 40 mg/ml solution for injection and Novem 20 mg/ml solution for injection to cattle. The same withdrawal period in meat (including injection site) for subcutaneous administration of Novem 40 mg/ml is also supported by the demonstrated bioequivalence between Metacam 40 mg/ml and Metacam 20 mg/ml which indicate similar plasma pharmacokinetics, including rate and extent of absorption from the injection site, for the two formulations following subcutaneous injection to cattle (see Part 4).

Withdrawal periods

The proposal to extrapolate the withdrawal periods established for subcutaneous injection of Novem 20 mg/ml solution for injection to cattle at the dose of 0.5 mg meloxicam/kg (i.e. 5 days for milk and 15 days for meat including the injection site and offal) to the subcutaneous route of administration of Novem 40 mg/ml solution for injection to cattle at the same dose is acceptable.

Metacam 40 mg/ml solution for injection was shown to be bioequivalent to Metacam 20 mg/ml solution for injection after a subcutaneous injection of 0.5 mg meloxicam/kg to cattle which indicate similar plasma pharmacokinetics, including rate and extent of absorption from the injection site, for the two formulations following subcutaneous injection to cattle. Furthermore, there were no residues of meloxicam in the injection site 13 or 15 days after a subcutaneous injection of Metacam 40 mg/ml solution for injection at a dose of 0.5 mg meloxicam/kg which confirmed that the rate of absorption, i.e. depletion of meloxicam from the injection site, was not slower for Metacam 40

mg/ml solution for injection than for Metacam 20 mg/ml solution for injection.

Overall conclusions on the safety and residues documentation

A detailed and critical summary on the safety documentation is based largely on published scientific literature. A satisfactory dossier has been submitted including peer-reviewed literature. Meloxicam is a well-known substance and used in veterinary medicines for many years and therefore this approach is considered acceptable. The new strength was formulated to be pharmaceutically identical to Novem 20 mg/ml solution for injection and the dosing regimen will be the same, i.e. a single intravenous injection at a dosage of 0.5 mg meloxicam/kg bw and 0.6 mg meloxicam/kg bw in cattle.

The available data and evaluations concerning the safety for Novem 5 and 20 mg/ml solution for injection for the approved subcutaneous route of administration are considered to be valid also for Novem 40 mg/ml solution for injection for cattle. A conclusion on local tolerance is available in Part 4.

A user safety assessment was provided concluding on sufficient warnings and safety measures. As meloxicam is considered to be maternotoxic/embryotoxic a precautionary warning is included in section 4.5 of the SPC and other product information.

The environmental risk assessment can stop in Phase I. Novem 40 mg/ml solution for injection is not expected to pose a risk for the environment when used according to the SPC.

Metacam 40 mg/ml solution for injection was shown to be bioequivalent to Metacam 20 mg/ml solution for injection after a subcutaneous injection of 0.5 mg meloxicam/kg to cattle which indicate similar plasma pharmacokinetics, including rate and extent of absorption from the injection site, for the two formulations. Furthermore, there were no residues of meloxicam in the injection site 13 or 15 days after a subcutaneous injection of Metacam 40 mg/ml solution for injection at a dose of 0.5 mg meloxicam/kg which confirmed that the rate of absorption, i.e. depletion of meloxicam from the injection site, was not slower for Metacam 40 mg/ml solution for injection than for Metacam 20 mg/ml solution for injection.

In conclusion, the withdrawal periods established for Novem 20 mg/ml solution for injection and subcutaneous injection of 0.5 mg meloxicam/kg to cattle, i.e. 5 days for milk and 15 days for meat (including the injection site) and offal, are considered safe and adequate also for subcutaneous injection of Novem 40 mg/ml solution for injection to cattle at the same dose level.

Part 4 – Efficacy

Pharmacodynamics

Within the initial marketing authorisation application of Novem the marketing authorisation holder, Boehringer Ingelheim Vetmedica, self-consented to the data contained in the original files for Metacam.

The addition of a new strength (Novem 40 mg/ml) for an existing pharmaceutical form (solution for injection) for subcutaneous use in cattle is already authorised for Metacam. Relevant data submitted within this extension to the marketing authorisation of Novem was already submitted and assessed for the addition of a new strength for Metacam (40 mg/ml) and a new route of administration (subcutaneous use) for an existing target species (cattle). Reference to the assessment of Metacam

40 mg/ml solution for injection for subcutaneous use for cattle is therefore made in the efficacy part.

The pharmacodynamic characteristics of meloxicam have been described in connection to the previous application for marketing authorisation of Metacam. No additional information has been supplied, which is acceptable.

Pharmacokinetics

As Metacam 20 mg/ml solution for injection is already approved for the subcutaneous route of administration in the target species cattle, bioequivalence between Metacam 40 mg/ml solution for injection and Metacam 20 mg/ml solution for injection in cattle following single subcutaneous administration was investigated in a pilot and a pivotal bioequivalence study. The pilot study was designed in order to assess local tolerability in only 8 animals, and since the bioequivalence results for AUC_{0-t} were at the lower end of the acceptance range an additional pivotal study was conducted with an appropriate number of animals.

Pivotal bioequivalence study:

This was a two-period, two-sequence, single dose cross-over trial performed in bovines (24 animals aged 4–8 months, weight 121–255 kg) with a 14 days washout period between doses. Metacam 40 mg/ml was compared to Metacam 20 mg/ml solution for injection. The administered dose in each period was 0.5 mg/kg body weight given subcutaneously. The study design is satisfactory. Blood samples were collected pre-dose and up to 168 hours after dose. Plasma concentrations of meloxicam were determined with an adequately validated HPLC method with UV detection.

For AUC_{0-t} and C_{max}, the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80–125%:

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max}, median, range) for meloxicam, n=24

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	67642.36±19172.26	2494.39±393.05	4.00 (2.00-8.00)
Reference	65385.86±15712.82	2321.10±318.18	5.00 (4.00-8.00)
*Ratio (90% CI)	1.021 (0.947-1.101)	1.071 (1.017-1.128)	-
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Pilot bioequivalence study and local tolerance study:

The pilot study had the same design as the pivotal study but with only 8 animals. For C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80–125%, and for AUC_{0-t} the results were at the lower limit of the acceptance range. However, in the larger pivotal bioequivalence study results for both AUC and C_{max} were within the conventional acceptance criteria.

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for meloxicam, n=8

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	58697.71±13949.26	2422.06±317.95	3.50 (3.00-5.00)
Reference	66753.70±11995.56	2409.88±261.67	5.00 (4.00-7.00)
*Ratio (90% CI)	0.872 (0.799-0.952)	1.002 (0.893-1.124)	-

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Conclusion

Based on the submitted bioequivalence studies, Metacam 40 mg/ml solution for injection is considered bioequivalent with Metacam 20 mg/ml solution for injection in cattle following subcutaneous injection.

Target animal tolerance

Local tolerance of subcutaneous administration of Metacam 40 mg/ml was evaluated in the two bioequivalence studies and was also investigated through necropsy in a residue depletion study.

Pilot bioequivalence and local tolerance study

This study included 8 animals and was designed as a randomized two-period, two-sequence, single dose cross-over trial. In the two treatment periods (i.e. on days 0 and 14) either the test article Metacam 40 mg/ml solution for injection or the reference article Metacam 20 mg/ml solution for injection was given by single subcutaneous injection at the recommended dose of 0.5 mg meloxicam/kg body weight. For investigation of local tolerance, isotonic saline was also administered to each animal on the contralateral side at a volume equivalent to the test/reference article. For investigations of local tolerance, observations during treatment and clinical assessments according to predetermined scoring system of the injection sites were conducted at 1, 2, 4 and 8 h after treatment and thereafter on daily basis to 7 days after treatment.

Swelling was found at the injection site between 1 and 4 h after treatment with both the reference and test article. At 8 h after treatment, swelling could not be observed anymore. Maximum mean diameter of the test article was 24.6 mm and 28.7 mm for the reference article, this occurred 1 h after treatment. No redness, elevated temperature or pain was observed after treatment with the test article or the reference article in any of the animals. No swelling, redness, elevated temperature or signs of pain were observed after treatment with the negative control at any of the time points.

Pivotal bioequivalence study

This was a two-period, two-sequence, single dose cross-over trial performed in cattle (24 animals). In the two treatment periods (i.e. on days 0 and 14) either the test article Metacam 40 mg/ml Solution for injection or the reference article Metacam 20 mg/ml Solution for injection was given by single subcutaneous injection at the recommended dose of 0.5 mg meloxicam/kg body weight. Inspection of the injection site occurred every hour up to 10 h post treatment and thereafter daily up to 7 days after treatment.

Subcutaneous injection resulted in swelling with a diameter ranging from 1-5 cm at the injection site, in 16/24 animals treated with the test article and in 21/24 animals treated with the reference article. No swelling was observed later than 7 h after treatment.

Tissue residue depletion study

Local tolerance was assessed in this study which had the primary aim to determine the residues and concentration of meloxicam in edible tissues and included four animals. Subcutaneous administration of Metacam 40 mg/ml solution for injection with the recommended dose of 0.5 mg meloxicam/kg body weight was performed twice with two days interval. No clinical signs were observed from the time of treatment until slaughter. Necropsy was performed of the injection sites 13 and 15 days after respective treatment. 3/8 injection sites showed findings such as a reddish/reddish-yellowish/yellowish, partly gelatinous focus/swelling in the subcutaneous tissue. The findings had a maximal extension of the alteration of 2–3 cm. In 1/8 injection sites subcutaneous reaction with a size of 8x2.5 cm was identified.

Conclusions regarding local tolerance

It is noted that the bioequivalence and local tolerance study included limited numbers of animals (in total 36 animals). However, there is no indication from these studies that the local tolerance pattern is divergent from what have been observed for Metacam 20 ml/ml solution for injection. The clinical examinations performed in the bioequivalence studies revealed only mild transient swelling at the injection site after subcutaneous administration. In the tissue residue depletion study, no local clinical signs were noted from the time of subcutaneous injection until slaughter. At necropsy, changes of limited size was noted in 3/8 injection sites. In 1/8 injection sites, pathological changes of larger size were detected, likely caused by the needle that was used for the subcutaneous injection. Relevant information regarding local adverse events is included in the product information.

The CVMP concluded that subcutaneous administration is generally well-tolerated in cattle. Relevant information regarding the slight transient swelling at the injection site observed in most animals in laboratory studies, has been added to section 4.6 of the SPC in the product information.

Field trials

No clinical data from field trials are required.

Overall conclusion on efficacy

Based on the submitted bioequivalence studies, Metacam 40 mg/ml solution for injection is considered bioequivalent with Metacam 20 mg/ml solution for injection in cattle following subcutaneous injection. This supports the subcutaneous use of Novem 40 mg/ml solution for injection in cattle.

The local tolerance has been evaluated in three studies that in total included 36 animals. Only limited transient clinical signs were associated with subcutaneous injection of Metacam 40 mg/ml solution for injection in cattle, which suggests that subcutaneous administration is well tolerated. However, one animal showed more significant pathological changes at the injection site, likely related to the needle used for the subcutaneous injection.

Part 5 – Benefit-risk assessment

Introduction

Novem 5 mg/ml and 20 mg/ml solution for injection are authorised for cattle and pigs and contain meloxicam, a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. This extension application for Novem is to add a new strength 40 mg/ml solution for injection for subcutaneous use for the existing target species cattle.

The applicant applied for the same indications as those authorised for Novem 20 mg/ml solution for injection for cattle:

- For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle.
- For use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle.
- For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy.
- For the relief of post-operative pain following dehorning in calves.

The product was developed to be essentially similar to the authorised strength Novem 20 mg/ml solution for injection. Support has been provided through bioequivalence, local tolerance and residue depletion data.

Benefit assessment

Direct therapeutic benefit

The therapeutic benefit assessment for the new strength remains the same as that established for Novem 20 mg/ml solution for injection for cattle already authorised.

The benefit of Novem 40 mg/ml solution for injection would be its efficacy in the treatment of:

Cattle: For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs; for use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle; for adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy and for the relief of post-operative pain following dehorning in calves.

Support for the subcutaneous administration route is provided through bioequivalence and local tolerance data. The studies demonstrate that subcutaneous administration of Novem 40 mg/ml solution for injection at the recommended dose provides comparable exposure to Novem 20 mg/ml solution for injection.

Additional benefits

The volume of the solution for injection to be administered for Novem 40 mg/ml will be 50% lower than the volume needed with Novem 20 mg/ml solution for injection, providing an additional benefit for the treatment of larger animals.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Main potential risks have been identified as follows:

For the target animal:

In conclusion, the new strength represents the same risks to target animals as those for Novem 20 mg/ml when used in accordance with the SPC. The local tolerance for Novem 40 mg/ml solution for injection in the proposed use is acceptable. Relevant information regarding clinical findings that may occur after subcutaneous administration has been added to the product information (SPC section 4.6).

For the user:

The use of Novem 40 mg/ml solution for injection in accordance with the user safety warnings is expected to mitigate the potential risks (hypersensitivity reactions, known adverse class-effects of NSAIDs and other prostaglandin inhibitors on pregnancy and/or embryofoetal development) related to meloxicam. The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations.

For the environment:

An ERA performed in accordance with applicable guidelines showed that the assessment for Novem 40 mg/ml solution for injection can be stopped in Phase I. The use of Novem 40 mg/ml solution for injection is not expected to pose any risk to the environment when used as recommended.

For the consumer:

The withdrawal periods established for Novem 20 mg/ml solution for injection and subcutaneous injection of 0.5 mg meloxicam/kg to cattle, i.e. 5 days for milk and 15 days for meat (including the injection site) and offal, are considered adequate also for subcutaneous injection of Novem 40 mg/ml solution for injection to cattle at the same dose level.

It is accepted that the new strength will represent the same risks to consumers as those for Novem 20 mg/ml when used in accordance with the SPC.

Risk management or mitigation measures

The same appropriate precautionary measures as for Novem 20 mg/ml are included in the SPC and product information to prevent risks for the target animals, the user and for the environment.

In addition, a precautionary measure is included in section 4.5 of the SPC to prevent a risk to pregnant women and women attempting to conceive.

The same withdrawal periods as those of Novem 20 mg/ml solution for injection can be applied to Novem 40 mg/ml solution for injection to ensure the safety for the consumer.

Evaluation of the benefit-risk balance

Novem 40 mg/ml solution for injection has been shown to have a positive benefit-risk balance overall.

The product has been shown to be efficacious for the indication:

Cattle: For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle. For use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle. For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy. For the relief of post-operative pain following dehorning in calves.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and does not present an unacceptable risk for users and the environment when used as recommended. Appropriate precautionary measures including withdrawal periods have been included in the SPC and other product information.

Conclusion

Based on the original data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Novem 40 mg/ml solution for injection for cattle is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Commission Regulation (EC) No 1234/2008 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the extension to the marketing authorisation for Novem.