



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Metacam new route of
administration (subcutaneous use) for 40 mg/ml solution
for injection for cattle
(EMA/V/C/000033/X/0119)

International non-proprietary name: meloxicam

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



Product profile

Invented name:	Metacam
Active Substances:	meloxicam
Target Species:	Cattle
Pharmaceutical Form:	Solution for injection
Strength:	40 mg/ml
Therapeutic 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.
ATCvet code	QM01AC06
Pharmacotherapeutic group	Anti-inflammatory and antirheumatic products, non-steroids (oxicams)
Applicant	Boehringer Ingelheim Vetmedica GmbH

Introduction

On 26 October 2015, an application for an extension to the Community marketing authorisation for Metacam was submitted by Boehringer Ingelheim Vetmedica GmbH to the European Medicines Agency (the Agency) falling within Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I-2(e) Change or addition of a new route of administration thereof.

The already authorised product, Metacam was authorised for use in the Community on 7 January 1998.

This extension application is for Metacam 40 mg/ml solution for injection to include subcutaneous administration in cattle.

The indication of the product remains unchanged:

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 appointed rapporteur is Frida Hasslung Wikström and the co-rapporteur is Christian Friis.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC as a "known active substance".

On 16 June 2016, the CVMP adopted an opinion and CVMP assessment report.

On 12 August 2016, the European Commission adopted a Commission Decision granting the marketing authorisation for Metacam.

Scientific advice

Not applicable.

MUMS Status

Not applicable.

Part 1 – Administrative particulars

Detailed description of the pharmacovigilance system

The pharmacovigilance system (dated November 2012) has been detailed and it fulfils the requirements of Directive 2001/82/EC. The required 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 are available. The CVMP considered the pharmacovigilance system satisfactory.

Manufacturing authorisations and inspection status

The current application concerns the previously authorised product Metacam 40 mg/ml solution for injection. No additional information is required.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements. Manufacturing information remains adequate as previously addressed.

Part 2 – Quality

The current application refers to an authorised product, Metacam 40 mg/ml solution for injection. There are no changes with regard to the quality of the product within the scope of this application and reference is made to the approved quality documentation. This approach is considered acceptable.

Part 3 – Safety

Safety documentation

Pharmacodynamics

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

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 Metacam 40 mg/ml solution for injection and Metacam 20 mg/ml solution for injection following subcutaneous injection of the recommended dose of meloxicam to cattle. This is sufficient for an application for extension with addition of a new route of administration (subcutaneous) for Metacam 40 mg/ml solution for injection in the target species 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 this type of application, i.e. an extension with addition of a new route of administration (subcutaneous) for Metacam 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 a new administration route for Metacam 40 mg/ml solution for injection, the required information on local tolerance has been provided.

For details and assessment, see Part 4.

User safety

The new administration route of Metacam 40 mg/ml solution will not affect the previously performed user safety assessment. No new information has been presented which is acceptable. The user safety warnings in the SPC (Section 4.5) for the already authorised Metacam 40 mg/ml solution for injection for the intravenous route of administration are considered appropriate and applicable also for the new subcutaneous route of administration in cattle.

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

Environmental risk assessment

The new administration route of Metacam 40 mg/ml solution for injection 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 Metacam 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, Metacam 40 mg/ml for injection is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The available data and evaluations concerning the safety for Metacam 5 and 20 mg/ml solution for injection for the approved intravenous and subcutaneous route of administration and Metacam 40 mg/ml

solution for injection for the intravenous route of administration approved for cattle are considered to be valid also for the new subcutaneous route of administration for Metacam 40 mg/ml solution for injection. A conclusion on local tolerance is available under Part 4.

Residues documentation

Pharmacokinetics

As Metacam 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, Metacam 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, of which 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, was submitted. This is acceptable.

The results of the pivotal bioequivalence study indicate that the pharmacokinetics of subcutaneously administered meloxicam, 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 Metacam 20 mg/ml solution for injection and subcutaneous administration to cattle for milk (5 day) and meat (except for the injection site) and offal (15 days) to Metacam 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 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 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 20 mg/ml solution for injection to cattle. The same withdrawal period in meat (including injection site) for subcutaneous administration of Metacam 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).

MRLs

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

The active substance in Metacam 40 mg/ml solution for injection for cattle and horses 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, <i>Equidae</i>	20 µg/kg	Muscle	NO ENTRY	Anti-inflammatory agents/Nonsteroidal anti-inflammatory agents
			65 µg/kg	Liver		
			65 µg/kg	Kidney		
		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 is already approved for intravenous use in cattle and horses, no further consideration of the analytical methods is required in relation to this application for the addition of a new route of administration (subcutaneous) for the target species cattle.

Withdrawal periods

The proposal to extrapolate the withdrawal periods established for subcutaneous injection of Metacam 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 Metacam 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 residues documentation

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.

In conclusion, the withdrawal periods established for Metacam 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 Metacam 40 mg/ml solution for injection to cattle at the same dose level.

Part 4 – Efficacy

Pharmacodynamics

The pharmacodynamic characteristics of meloxicam have been described in connection to the previous application for marketing authorisation. 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 $\pm$ 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 $\pm$ 19172.26	2494.39 $\pm$ 393.05	4.00 (2.00-8.00)
Reference	65385.86 $\pm$ 15712.82	2321.10 $\pm$ 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 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 $\pm$ 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 $\pm$ 13949.26	2422.06 $\pm$ 317.95	3.50 (3.00-5.00)
Reference	66753.70 $\pm$ 11995.56	2409.88 $\pm$ 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

For the current application, local tolerance of subcutaneous administration of Metacam 40 mg/ml was evaluated in the two bioequivalence studies and the local tolerance 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 hours after treatment and thereafter on daily basis to 7 days after treatment.

Swelling was found at the injection site between 1 and 4 hours after treatment with both the reference and test article. At 8 hours 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 hour 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 hours 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 hours 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 the new route of administration (subcutaneous injection) 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 Metacam 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 the new route of 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

This application concerns the extension of administration route for Metacam (meloxicam) 40 mg/ml solution for injection from intravenous injection to subcutaneous administration in cattle. Support has been provided through bioequivalence, local tolerance and residue depletion data.

Benefit assessment

Direct therapeutic benefit

Metacam 40 mg/ml solution for injection is authorised with the following indication in 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.

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

Additional benefits

When subcutaneous administration is applied, the use of Metacam 40 mg/ml solution for injection instead of Metacam 20 mg/ml solution for injection will result in a reduced volume needed for administration.

Risk assessment

Quality:

The current application refers to an already authorised product, Metacam 40 mg/ml solution for injection. There are no changes with regard to the quality of the product within the scope of this application and reference is made to the already approved quality documentation. This approach is considered acceptable.

Main potential risks have been identified as follows:

For the target animal:

The local tolerance for Metacam 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 Metacam 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 Metacam 40 mg/ml solution for injection can be stopped in Phase I. The use of Metacam 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 Metacam 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 Metacam 40 mg/ml solution for injection to cattle at the same dose level.

Evaluation of the benefit-risk balance

Metacam 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.

The current application concerns the extension of administration route for Metacam (meloxicam) 40 mg/ml solution for injection from intravenous injection to subcutaneous administration cattle only.

The new administration route (subcutaneous) is well tolerated by the target animals. The product presents an acceptable risk for users, consumers and the environment when used as recommended. A sufficient withdrawal period has been set.

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

Conclusion on benefit-risk balance

The overall benefit-risk evaluation is considered positive.

Conclusion

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Metacam 40 mg/ml solution for injection 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 marketing authorisation for the above mentioned medicinal product.