CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Eminocs 50 mg/ml oral solution
MarvecsPharma services Srl, Italy

diclofenac potassium

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/800/01/MR
Registration number in the Netherlands: RVG 31532

18 September 2009

Pharmacotherapeutic group:	anti-inflammatory and anti-rheumatic products, non-steroids
ATC code:	M01AB05
Route of administration:	oral
Therapeutic indication:	short-term treatment of painful post-traumatic inflammations, e.g. after sprains; postoperative inflammations and pain, e.g. after dental and orthopaedic operations; primary dysmenorrhoea.
Prescription status:	prescription only
Date of first authorisation in NL:	5 October 2004
Concerned Member States:	Mutual recognition procedure with IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Eminocs 50 mg/ml oral solution, from MarvecsPharma services Srl. The date of authorisation was on 5 October 2004 in the Netherlands.

The product is indicated for the short-term treatment of the following acute disorders:

- painful post-traumatic inflammations, e.g. after sprains
- postoperative inflammations and pain, e.g. after dental and orthopaedic operations
- primary dysmenorrhoea

A comprehensive description of the indications and posology is given in the SPC.

In addition to these indications, the MAH also applied for the indication "*Diseases associated with fever, especially for brief use as an adjuvant in the case of chemotherapy for infectious diseases. Fever as such is not an indication*". Italy however objected against this indication, because the reference product in the bioavailability study was not approved for this indication in Italy. It was therefore decided to withdraw this indication.

Eminocs oral solution contains the potassium salt of diclofenac, a prostaglandin synthetase inhibiting substance with antiphlogistic, antipyretic and analgesic properties. Eminocs oral solution is suitable for the treatment of acute pain and inflammation. An important part of the mode of action is subscribed to the (experimentally proven) inhibition of the biosynthesis of prostaglandins. Prostaglandins play an important role in the development of inflammation, pain and fever.

This mutual recognition procedure concerns a hybrid application claiming essential similarity with the innovator product Cataflam 50 mg, coated tablets (NL license RVG 13245), which has been registered in the Netherlands by Novartis Pharma B.V. since 1989. In addition, reference is made to Cataflam authorisations in the individual member states. No other oral solutions are registered in the Netherlands.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC, because the reference product is of a different pharmaceutical form.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Cataflam 50 mg tablets registered in the Netherlands. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This hybrid product can be used instead of its reference product.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is diclofenac potassium, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is sparingly soluble in water, freely soluble in methanol, soluble in ethanol and slightly soluble in acetone. There is no indication that polymorphism or isomerism exists.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
Diclofenac potassium is synthesized in a two step process, one of which is a purification step to change the counter salt. Solvents and reagents have been adequately described. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for residual solvents and particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability
Stability data on the active substance have been provided for three small production scaled batches, one medium production scaled batch and eight full scaled batches stored at 25 °C/60% RH (up to 60 months) and 40 °C/75% RH (6 months). The batches were adequately stored. Several out of specifications (water) were observed when the material was packed in drums. No out of specifications occurred when the material was packed in the proposed commercial packaging. The re-test period of 5 years is acceptable, if stored in the original packaging (closed container and protected from light).

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
The product at issue is an oral solution containing 5.0 g diclofenac potassium per 100 ml, and the following excipients: ethyl alcohol, glycerol, potassium hydrogen carbonate, saccharin sodium, caramel (E150a) and purified water. The solution is packaged in brown glass type III bottles with polypropylene screw-cap closure, holding 20, 25, 50 or 100 ml solution. The product is accompanied with a colourless transparent glass (graduated) dosing pipette with black butyl sucker and polypropylene screw cap (CE approved). The dosing device is to be attached on the bottle instead of the original screw cap after first opening of the container. The excipients and packaging are usual for this type of dosage form, although the ethyl alcohol content is rather high.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation contains a colourant, preservative and sweetening agent. The batch used in the bioequivalence study was of the same composition as commercial batches and manufactured with the same process. The pharmaceutical development of the product has been adequately performed.
In studies using brown and clear bottles it appears that diclofenac is vulnerable to light (UV radiation). Caramel E10a is added to the solution in order to mask the presence of a low percentage on an impurity, which is yellow deep coloured itself. In subsequent studies the compatibility of this colourant to the formulation has been shown. Overage is not used.

Excipients
The excipients ethyl alcohol, glycerol, potassium hydrogen carbonate, saccharin sodium and purified water comply with Ph.Eur. requirements. The excipient caramel complies with an in-house specification. These specifications are acceptable.

Manufacturing process
One manufacturing site is used. The manufacturing process of the oral solution is simple and common and consists of the following steps: weighing, dissolving, stirring, filtration in order to render a particle fee solution, and filling/packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot scaled batches. Validation of three production scale batches will be performed post-approval. The product is manufactured using conventional manufacturing techniques.

Quality control of drug product
The product specification includes tests for appearance, identification, pH, relative density, evaporation, fill weight (minimum fill), ethanol content, assay, related substances and microbial quality. The shelf-life requirement for evaporation and assay differ from the release requirement, all other requirements are identical for release and shelf-life. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot scaled batches, demonstrating compliance with the release specification.

Stability tests on the finished product
Stability data on the product have been provided on three pilot scaled batches stored at 25 °C/60% RH (24 months), 30 °C/65% RH (24 months) and 40 °C/75% RH (6 months). Data of batches produced at a former production site have also been provided (up to 36 months long-term, 18 months intermediate and 6 months accelerated). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in brown type III glass bottles. No changes were observed. The proposed shelf-life of 36 months is acceptable. The specific storage condition ‘do not freeze or store in the refrigerator, do not store above 25 °C’ is required. In-use stability studies have been performed for preservative efficacy according to Ph. Eur. with the brown glass bottles and the colourless transparent glass dosing pipette with black butyl sucker and polypropylene screw cap.. After 28 days no increase of the inoculated microorganisms has been observed. The test has also been performed at the end-of-shelf-life of 20 ml and 100 ml bottles. An in-use period of 1 month has been granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This active substance has been available on the European market for more then 10 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of diclofenac released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

The MAH claims essential similarity to the original product Cataflam tablets, which is a different pharmaceutical form. Therefore a bioavailability study is submitted in which the bioavailability of test product Eminocs 50 mg/ml oral solution (MarvecsPharma services Srl, Italy) is compared with that of reference product Cataflam 50 mg (Novartis Pharma, The Netherlands)

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
An open, randomised, single-dose, two-way cross-over comparative bioavailability study was carried out under fasted conditions in 24 (12 males, 12 females) healthy volunteers, aged 20-44 years. Each subject received a single dose (50 mg, 1 ml drops 5% w/v or one tablet) of one of the 2 diclofenac formulations. The reference tablet was administered with 240 ml water after a 10 hour fasting period. For the test, 1 ml of diclofenac 5% w/v solution for drops, corresponding to 50 mg of diclofenac was dispensed into a sufficient large vial in order to allow a first filling from the 240 ml glass of water and then rinsed twice. The subjects were asked to drink the rest of the water. For each subject there were 2 dosing periods, separated by a washout period of 7 days. Blood samples were collected predose and at 5, 10, 15, 20, 30, 45 min and at 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, and 12 hours after administration of the products.
All 24 subjects were eligible for pharmacokinetic analysis.

The method was validated and the validation report provided. The statistical evaluation was according standards.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of diclofenac under fasted conditions.

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1383 ± 423	1392 ± 423	1679 ± 669	0.21 (0.08 – 0.75)	2.4 ± 0.5
Reference	1187 ± 356	1198 ± 355	1155 ± 754	0.50 (0.25 – 3.00)	2.4 ± 0.9
***Ratio (90% CI)**	---	1.17 (1.08 - 1.25)	1.67 (1.32 - 2.09)	---	---
CV (%)	---	13.8	48.7	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life

**ln-transformed values*

$AUC_{0-\infty}$
After administration of 50 mg Diclofenac drops 5% w/v, the AUC is statistically significant higher (ca. 17%) compared with the AUC after administration of Cataflam 50 mg tablet. However the calculated 90% confidence intervals ranged between 1.08 – 1.25, which is within the acceptance range normally used for prove of bioequivalence. Therefore, the small increase in AUC after administration of the drops (compared to the tablet formulation) is considered not clinically relevant and acceptable.

C_{max}
The C_{max} was statistically significantly higher after administration of diclofenac drops (ca. 67%). In addition, the individual C_{max} values ranged from 186 – 3160 ng/ml for the tablet formulation and ranged from 806 – 3330 ng/ml for the drops. T_{max} was shorter after administration of the drops compared with the tablet. The results indicate that the rate of absorption is markedly increased after administration of the solution (drops) compared with the tablet formulation. In the table below, reported data with regard to C_{max} levels from registered diclofenac containing products are listed. In addition, also the C_{max} levels observed for the drops and Cataflam in the submitted bioavailability study are included.

C_{max} reported in SPC of diclofenac containing products registered in the Netherlands and study data submitted

Product	Dose	C_{max} (ng/ml)
Reported in SPC of diclofenac containing products		
Prolonged release tablet containing diclofenac	75 mg 100 mg	400 ng/ml 500 ng/ml
Enteric coated tablet containing diclofenac	50 mg	1500 ng/ml
I.m. injection containing diclofenac	75 mg	2500 ng/ml
Cataflam tablet (normal)	50 mg	1200 ng/ml
Study data submitted		
Diclofenac drops 5% w/v	50 mg	1679 ng/ml
Cataflam tablet (normal)	50 mg	1155 ng/ml

These data indicate that the C_{max} levels observed after administration of Cataflam 50 mg in the submitted study are in line with those reported in the SPC. The C_{max} levels observed after administration of the drops (50 mg) are in the order of those reported in the SPC of Enteric coated tablets containing diclofenac 50 mg, and well below the reported value in the SPC of i.m. injection containing diclofenac.

Discussion

Efficacy
The efficacy of diclofenac potassium with respect to posttraumatic inflammation, post-surgical pain and primary dysmenorrhoea are sufficiently discussed in the expert report in contrast to conditions accompanied by fever.

Safety
The tolerability profile of the registered formulations of diclofenac are well established. However, during the national procedure in the Netherlands some questions were posed if the higher C_{max} levels of diclofenac potassium solution may lead to a safety issue. The MAH concluded that peak plasma levels are in range with those reported in the literature with other diclofenac oral solution formulations and below the peak plasma levels that are obtained after intramuscular or intravenous doses of diclofenac (see table above). However, the data that needed to substantiate these conclusions were not present in the dossier. Side-effects can be dose-related and, therefore, the MAH had to substantiate that higher peak plasma levels of Eminocs 50 mg/ml drops do not have influence on safety. Furthermore, also short-term use may result in e.g. CNS or renal effects. Finally, the relatively high number of drops (20 drops to administer 50 mg) can lead to mistakes in the total count made by the patient.

Following assessment of the MAH's response to the questions as stated above, it was concluded that the high mean C_{max} levels observed for the drops compared to the tablet formulation are more related to low C_{max} levels observed in some subjects after administration of the tablet, and less attributed to high C_{max} levels after administration of the drops. In addition, the levels observed after administration of the drops are in the range of those observed after administration of the Cataflam tablet, and within the range of levels already known for diclofenac in published studies. Therefore, the higher C_{max} values of the drops formulation when compared to Cataflam are not a safety issue.

Conclusion
The calculated 90% confidence interval for the $AUC_{0-\infty}$ was within the bioequivalence acceptance range of 0.80-1.25. The C_{max} was statistically significantly higher after administration of Eminocs 50 mg/ml oral solution (ca. 67%). The calculated 90% confidence interval for the C_{max} (1.32-2.09) was outside the bioequivalence acceptance range of 0.80-1.25. However, the higher C_{max} values of Eminocs 50 mg/ml oral solution when compared to Cataflam 50 mg tablets are not a safety issue.

Risk management plan

Diclofenac was first approved in 1977, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of diclofenac can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Cataflam marketed in the Netherlands by Novartis Pharma, except for the indication "*Diseases associated with fever, especially for brief use as an adjuvant in the case of chemotherapy for infectious diseases. Fever as such is not an indication",* for which Eminocs is not indicated.

Readability test

A readability test has been performed in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. A first pilot test was performed with 5 participants and some changes were made to the lay-out, (sub) headings and some wording of the text.

Two further test rounds of 10 test persons were performed (diagnostic and scoring), which resulted in 97.8% correct answers and 99.3% correct answers respectively. The PIL was not changed between the first and second test round. One test person was excluded from the first round. The leaflet was thus found readable and understandable according to the European and MHRH requirements (>90% of the ten subjects could find the information asked for and >90% there of was able to understand it once found).

There were some recommendations for minor changes from the two test rounds: included into a final version. The MAH adapted the PIL in accordance with the above recommendations.

There were sufficient questions (15) about the critical sections. The conclusions were clear, concise and clearly presented. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The patient information leaflet has been adapted sufficiently taking into account the results of the test.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Eminocs 50 mg/ml oral solution has a proven chemical-pharmaceutical quality and is a hybrid form of Cataflam 50 mg tablets. Cataflam is a well-known medicinal product with an established favourable efficacy and safety profile.

Although the calculated 90% confidence intervals of the $AUC_{0-\infty}$ ranged between 1.08 – 1.25, which is within the acceptance range normally used for prove of bioequivalence, the C_{max} was statistically significantly higher after administration of Eminocs 50 mg/ml (ca. 67%). In addition, the individual C_{max} values ranged from 186 – 3160 ng/ml for the reference product Cataflam 50 mg and ranged from 806 – 3330 ng/ml for Eminocs 50 mg/ml, so the rate of absorption is markedly increased after administration of the solution (drops) compared with the tablet formulation. This, together with the notion that short-term use may result in e.g. CNS or renal effects, and the relatively high number of drops (20 drops to administer 50 mg) which can lead to mistakes in the total count made by the patient, led to several objections during the procedure. However, these objections were adequately resolved by the MAH's response. The higher C_{max} values of Eminocs 50 mg/ml oral solution when compared to Cataflam 50 mg tablets were not considered a safety issue by the member states. Moreover, no special claim was made.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product, except for the indication "*Diseases associated with fever, especially for brief use as an adjuvant in the case of chemotherapy for infectious diseases. Fever as such is not an indication"*, which is not an indication for Eminocs. The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Eminocs 50 mg/ml oral solution was authorised in the Netherlands on 5 October 2004.

There was no discussion in the CMD(h). Agreement with the member state was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Eminocs 50 mg/ml oral solution with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finished on 22 December 2006.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from December 2006 to December 2009.

The date for the first renewal will be: 22 December 2011.

The following post-approval commitments have been made during the procedure:

<u>Quality – medicinal product</u>
- The MAH has committed to validate three production scale batches post-approval.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
SPC and PIL changes concerning NSAIDs with regard to cardiovascular safety data.	NL/H/0800/ 001/II/001	II	---	14-6-2007	Approval	N
Change in the name of the medicinal product in the Netherlands, from Itami to Eminocs.	NL/H/0800/ 001/IB/002	IB	23-7-2008	25-8-2008	Approval	N