Mutual Recognition Procedure

Public Assessment Report

Diclofenac-ratiopharm Schmerzpflaster
Diclofenac-ratio Schmerzpflaster
Diclo-ratiopharm Schmerzpflaster

Diclofenac

DE/H/1479-81/001/MR

Applicant: ratiopharm GmbH

Date: 03.01.2018

This module reflects the scientific discussion for the approval of Diclofenac. The procedure was finalised on 09.07.2008.

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	DE/H/1479: Diclofenac-ratiopharm Schmerzpflaster DE/H/1480: Diclofenac-ratio Schmerzpflaster DE/H/1481: Diclo-ratiopharm Schmerzpflaster
Name of the drug substance (INN name):	Diclofenac sodium
Pharmaco-therapeutic group (ATC Code):	M01AB05
Pharmaceutical form(s) and strength(s):	Medicated plaster; 140 mg
Reference Number(s) for the Decentralised Procedure	DE/H/1479-81/001/MR
Reference Member State:	DE
Concerned Member States:	DE/H/1479: AT, BE, CZ, DK, ES, HU, IT, PL, SE, SK and UK DE/H/1480: FR, PL and PT DE/H/1481: ES and IT
Applicant (name and address)	ratiopharm GmbH Graf-Arco-Str. 3 D-89079 Ulm Germany
Names and addresses of manufacturers responsible for batch release in the EEA:	Merckle GmbH Ludwig-Merckle-Str. 3 D-89143 Blaubeuren Germany

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the applications for *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster*, indicated for local symptomatic treatment of pain in acute strains, sprains or bruises of the extremities following blunt trauma, e.g. sport injuries, are approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

The products were granted national marketing authorisations in Germany on 27th August 2007. With Germany as the Reference Member State in this Mutual Recognition Procedure (MRP), the Marketing Authorisation Holder, ratiopharm GmbH, is applying for marketing authorisations for *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* in Austria, Belgium, Czech Republic, Denmark, France, Hungary, Italy, Poland, Portugal, Spain, Sweden, Slovak Republic and the United Kingdom.

II.2 About the product

Diclofenac is a phenylacetic acid derivative which belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs) which also exhibits analgesic and antipyretic properties. NSAIDs are inhibitors of the enzyme cyclo-oxygenase, and therefore inhibit the biosynthesis of prostaglandins and thromboxanes from arachidonic acid.

Topical administration of non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, offers the advantage of local, enhanced drug delivery to affected tissues with a reduced incidence of systemic adverse effects due to reduced serum concentrations. Moreover, topical application also lessens the risk of drug-drug interactions (e.g., NSAID-mediated protein binding displacement of warfarin). The benefit of topical NSAID treatment has been proven in the past.

Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster contain 140 mg diclofenac-sodium on a 140 cm² plaster. The product is intended for 'Local symptomatic treatment of pain in acute strains, sprains or bruises of the extremities following blunt trauma, e.g. sport injuries'.

II.3 The development programme

The objective of the development programme was to formulate a robust, stable, acceptable formulation of *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* for topical use. Therefore the applicant submitted two placebo controlled clinical trials and one bioavailability study in order to prove efficacy and safety as full application.

II.4 General comments on the submitted dossier

In preparation of this MR procedure, the applicant has submitted one bioavailability study and two placebo-controlled clinical studies to prove efficacy and safety of *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster*:

STUDY CRO-PK-01-47. Multiple dose comparative bioavailability study of *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* in patients with traumatic blunt soft tissue injury.

II.5 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its National authorisation.

For the manufacturing site outside the Community, the RMS has accepted copies of current Certificate issued by the inspection services of the Ministry of Health, Labour and Welfare, Government of Japan as certification that acceptable standards of GMP are in place at this non-Community site.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The active substance diclofenac sodium is described in the European Pharmacopoeia. The quality of the drug substance, sourced from two manufacturers, is controlled in compliance with the corresponding monograph of the European Pharmacopoeia (Ph Eur). The suitability of the monograph to test the drug substance of both manufacturers has been verified and Certificates of Suitability have been granted by EDQM.
Both Certificates are valid.

Drug product

The ingredients and the manufacturing process of the drug product are considered to be suitable to produce a pharmaceutical product of the proposed quality.
Relevant quality characteristics of the drug substance and the drug product (release and shelf-life) are specified. The proposed limits are accepted.
The description of the analytical methods used to analyse the drug substance and drug product are adequate, the validation results are plausible.
The stability data presently available are sufficient to justify the whole claimed shelf-life of 3 years for the package proposed for marketing.

III.2 Non-clinical aspects

Pharmacology, Pharmacokinetics, Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of diclofenac sodium are well known.

Local tolerance testing has been performed with the medicated plasters Flector EP Tissuegel and *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster*. *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* are identical to Diclofenac 140 mg medicated plaster regarding the qualitative and quantitative composition. The study was carried out according to requirements of the Note for Guidance on Non-clinical Local Tolerance Testing of Medicinal Products (CPMP/SWP/2145/00). Due to data obtained, *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* and consequently also Diclofenac 140 mg medicated plaster can be considered as non-skin-irritant.

According to the Note for Guidance on Non-clinical Local Tolerance Testing of Medicinal Products (CPMP/SWP/2145/00, a repeated dose dermal tolerance test would have been required in principle. However, since Phase III clinical data are meanwhile available, it is expected that such a repeated dose study would not provide additional relevant information.

As diclofenac sodium is a widely used, well-known active substance, no further studies are required.

The submitted nonclinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The report is based on literature review and refers 44 publications up to year 2002.

III.3 Clinical aspects

Pharmacokinetics

The clinical overview on the clinical pharmacology, efficacy and safety is adequate. The bioavailability study and a general comparison of serum concentrations after topical application indicates no increased systemic availability of diclofenac from *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* in comparison to other topically applied diclofenac formulations. In so far no specific increased risk for systemic AEs in relation to a treatment with *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* is identified.

Dose finding

No dose-finding study was performed. This was not considered necessary because Flector® EP Tissugel, a very similar diclofenac plaster is already licensed. Flector® EP Tissugel contains 180 mg

diclofenac epolaminum (equivalent to 140 mg diclofenac-sodium) on a 140 cm² plaster. *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* also contain 140 mg diclofenac-sodium on a 140 cm² plaster.

Clinical studies

Study SPC 45

The study was performed as a prospective, observer-blind, randomized, placebo- and verum-controlled three-arm parallel-group, multi-centre study. The primary efficacy variable was the global efficacy at Day 8 as assessed by the investigator.

A total of 188 patients entered the study, of which 186 were included in the ITT population for analysis (n = 60 placebo, n = 60 *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster*, n = 66 reference group).

This study delivered unexpected results with view of the failure to differentiate between placebo and verum treatments. Both plasters were effective; however, this was also the case for the placebo group (e.g. best possible anticipated response in 35% of the placebo patients, in 33% of the *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* patients and in 30% of the patients in the reference group).

Since ratings were done only at two visits (namely at baseline and at day 8), and the nature of the disease was prone to a rather swift healing and thus pain relief, there is the probability that real treatment effects were diluted. Especially the chosen time point (Day 8) may have been too late to detect a treatment effect because of swiftly diminishing symptoms. This assumption is supported by the results of the subsequent study ME-2001/01 that showed the highest pain reduction at day 2 whereas on day 5 - 7 only a very minor difference to placebo was apparent.

These findings led to the conclusion to plan and to conduct a new Efficacy and Safety Study in order to improve the study design by considering above-mentioned effects.

Study ME-2001/01

This was a randomised, placebo controlled, double blind, multicentre study in 120 patients with traumatic blunt soft tissue injury. Primary efficacy variable was the area under the curve of tenderness (AUC) over the first 3 days following initiation of therapy.

Patients were enrolled within three hours of sustaining a contusion and treated twice-daily with the trial plaster over a period of 7 days. Patients were randomised (1:1) to two parallel groups, either to the *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* (60 patients) or to placebo (60 patients).

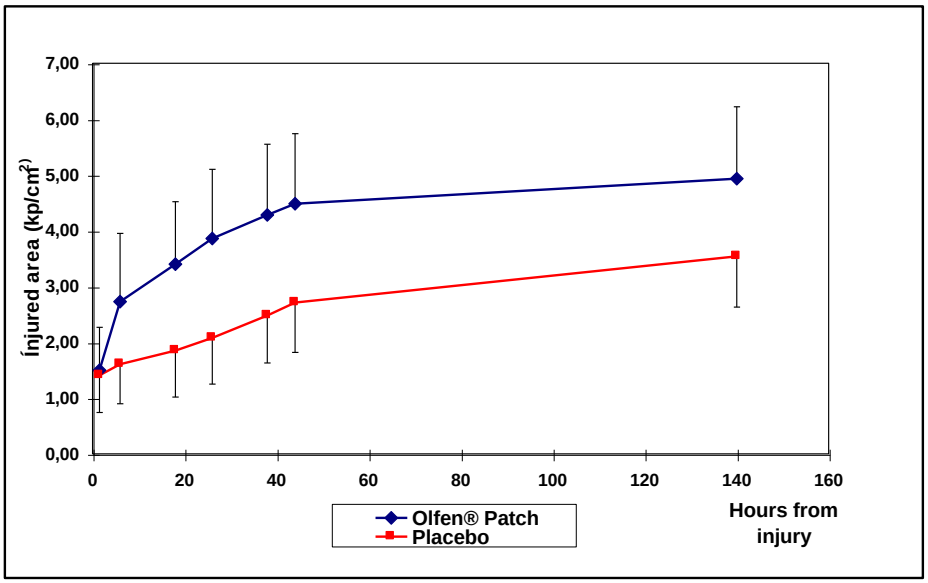
Tenderness was defined as the amount of pressure (measured by a calibrated calliper at the centre of the injury) that first produced a pain reaction as reported by the patient. Secondary parameters were pain at rest and pain on movement measured by VAS.

Rescue medication (anti-inflammatory drugs, analgesics, psychotropic agents) was not permitted to use.

Results

The treatment groups were well balanced with regard to the demographic data. On average, the AUC for the primary outcome measure was 162.4 (median: 153.1) h*kp/cm² in the *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* treatment group. The corresponding value for the placebo group was 93.7 (median: 86.8) h*kp/cm². The treatment effect was statistically highly significant ($p<0.0001$) (see figure 1). However, the outcome tenderness measured with a tonometric instrument seems not sufficiently validated.

Figure 1. Tenderness reaction (kp/cm^2) at injured site over time. Values are means (standard deviations). Intention to treat analysis



But these results were also robust in all secondary efficacy variables. The absolute changes from baseline for pain at rest and on movement (based on VAS scores) were significantly and clinically relevantly more pronounced with *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* compared to placebo (see results for pain on movement table 43, figure 2). If the pain difference in mm on VAS over placebo is calculated, values for minimal perceptible difference and clinically important improvement were exceeded[1]. These results were still stable judging efficacy independent of the site of treatment (separately for legs, arms).

[1] Ehrich E.W., et al.; 'Minimal Perceptible Clinical Improvement with the Western Ontario and Mc Master Universities Osteoarthritis Index Questionnaire and Global Assessments in Patients with Osteoarthritis.' Journal Rheumatol 2000; 27: 1635-41

Todd K H, Funk J P (1996) The minimum clinically important difference in physician-assigned visual analog pain scores, Acad. Emerg. Med., 3:142 – 146

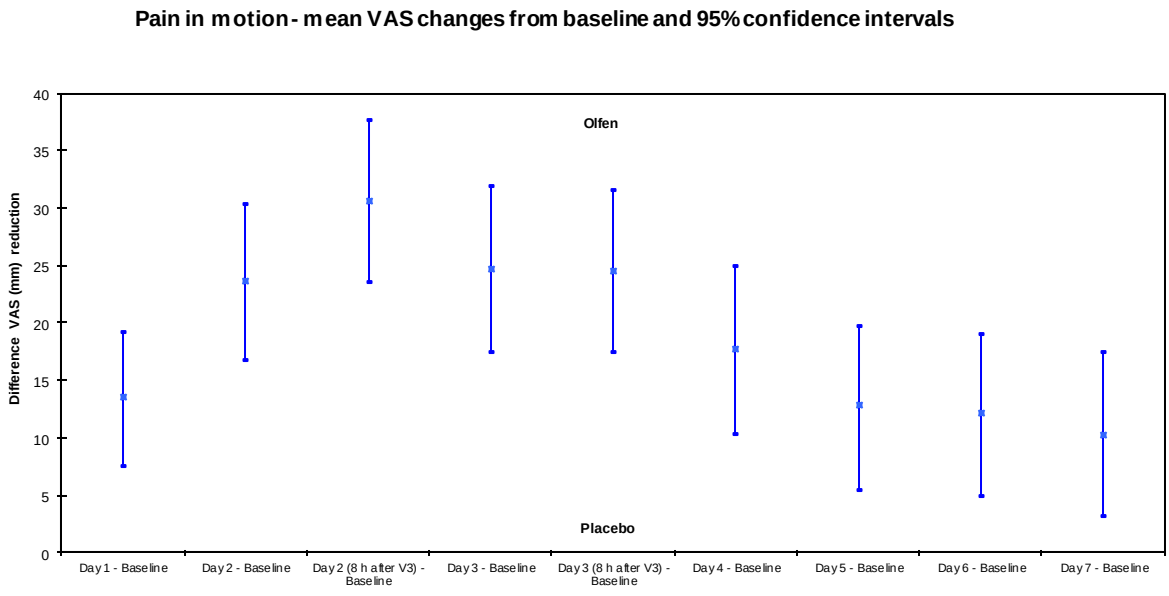
Tubach F, Ravaud P, Baron G et al: Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005; 64:29 - 33

Bjordal JM et al, short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: a metaanalysis of randimised placebo-controlled trials, Eur J Pain (2006)

Table 43: Pain in motion – absolute changes from baseline

Pain in motion (mm VAS)		Change								
		V2-V1	V3-V1	V4-V1	V5-V1	V6-V1	V7-V1	V8-V1	V9-V1	V10-V1
Treatment										
Olfen	n	60	60	60	60	60	60	60	60	60
	Mean	-24.22	-46.62	-57.10	-65.88	-69.07	-71.50	-72.49	-73.25	-73.43
	SD	20.43	22.13	21.57	20.47	20.05	19.87	19.70	19.44	19.34
	Min	-86.00	-87.00	-98.00	-98.00	-100.00	-100.00	-100.00	-100.00	-100.00
	Q1	-39.00	-63.00	-73.50	-84.00	-85.00	-86.00	-88.00	-89.00	-89.00
	Median	-22.00	-50.00	-57.50	-66.50	-68.00	-72.00	-73.50	-74.00	-74.00
	Q3	-5.00	-30.00	-39.50	-48.50	-59.50	-62.50	-63.00	-65.00	-64.50
	Max	7.00	6.00	-17.00	-22.00	-22.00	-22.00	-22.00	-22.00	-22.00
Placebo	n	60	60	60	60	60	60	60	60	60
	Mean	-10.78	-23.02	-26.48	-41.25	-44.57	-53.83	-59.83	-61.27	-63.18
	SD	9.92	14.47	16.88	19.55	19.33	20.68	19.76	19.54	19.97
	Min	-38.00	-50.00	-61.00	-76.00	-82.00	-89.00	-91.00	-90.00	-95.00
	Q1	-19.00	-31.00	-40.00	-54.00	-59.50	-70.00	-77.00	-77.00	-78.00
	Median	-10.00	-24.00	-24.50	-44.50	-47.50	-53.50	-60.50	-64.00	-67.00
	Q3	-3.00	-12.50	-13.00	-27.50	-31.50	-38.00	-44.50	-47.00	-47.00
	Max	6.00	13.00	7.00	7.00	0.00	-3.00	-8.00	-6.00	-3.00

Figure 2. Effect over placebo for pain on movement (difference between active and placebo in absolute changes from baseline) by visit



Study ME-2001/01 was adequately powered and the statistical evaluation has been properly performed according to ITT. No patient was lost to follow up and only one patient discontinued study

medication. No major protocol violations were observed. Therefore, no PP analysis became necessary as proactively defined. This clearly speaks for the quality of the study.
Concerning the secondary endpoints all analyses were prospectively defined in the Statistical Analysis Plan. For both primary and secondary efficacy endpoints, clear two-sided hypotheses were defined and tested in an a priori ordering, which controlled the multiple alpha level of 5%. This procedure avoided multiple testing and minimised the risk of by chance findings. Thus, it can be concluded that the statistical analysis of efficacy results (for both primary and secondary endpoints) from study ME-2001/01 was robust.

In summary, the results documented in this confirmative placebo-controlled clinical study justify clinically relevant and statistically significant the efficacy in the claimed indication. Therefore efficacy is considered sufficiently proven.

Clinical safety
The risk profile shown in both clinical studies is congruent with that described in published studies with diclofenac and other topical NSAIDs.

Conclusion
In study SPC 45 no meaningful result was detectable because apparently the self-healing effect at day 8 diminished differences between test, active comparator and placebo.

Study ME-2001/01 shows statistically significant and clinically relevant superiority of *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* versus placebo. For the primary efficacy endpoint a tonometric measurement was used which is not clinically validated. However, the results for pain on movement and pain at rest measured by VAS (secondary endpoints, validated endpoints) can be accepted because all analyses were prospectively defined in the Statistical Analysis Plan. For both primary and secondary efficacy endpoints, clear two-sided hypotheses were defined and tested in an a priori ordering, which controlled the multiple alpha level of 5%. The difference versus placebo on VAS at day 2 and 3 reached >10 mm. The statically significance and the clinical relevance of the results is therefore considered adequately proven.

The risk profile shown in both clinical studies is acceptable and in consistence with that described in published studies with other topically applied NSAIDs.

Therefore the benefit risk relation of *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* is considered acceptable.

Addendum after MRP:
Pharmacokinetic differences
The compared diclofenac serum concentrations of *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* and Flector plaster derived from different studies. However, for a valid comparison the conditions should be standardised and comparable as in a direct comparison.

Several issues may influence the bioavailability after topical application. Both the different areas of the skin[2] and the mode of application have an impact.
As such after application of 2x5g of a topical diclofenac containing product (Voltaren Emulgel) serum concentrations were determined between 3-15ng/ml whereas after occlusive condition the concentration was documented with 41ng/ml[3] [4]. The same results can be found in publications of topical ibuprofen where the serum concentration two hours after application of 300 mg ibuprofen was 0.64 ng/ml whereas under occlusion it was 7.1ng/ml[5].

[2] Vaile J H, Davis P (1998) Topical NSAIDs for musculoskeletal conditions, Drugs Nov; 56 (5) 793 – 799
[3] Radermacher J, Jentsch D (1991) Diclofenac concentrations in synovial fluid and plasma after cutaneous application in inflammatory and degenerative diease, Br J Clin Pharmacol, 31: 537 – 541
[4] Fowler PD, Dawes PT et al (1983) Plasma and synovialfluid concentrations of diclofenac sodium and its major hydroxylated metabolites during long-term treatment in rheumatoid arthritis, Eur J clin Pharmacol, 25: 389 - 394
[5] Dominkus M (1996) Comparison of tissue and plasma levels of ibuprofen after oral and topical administration', Arzneim.-Forsch./Drug Res. 46 (II), 1138 – 1143

In this regard it should be noted that in the eighties and nineties it was accepted that kinetic studies were conducted under occlusive conditions or as done in the Flector study (Assandri et al. 1993) under hyperaemic condition (irritation of the skin prior to patch application) because the detection limit at that time was much higher than today. The lower limit for diclofenac is documented with 10ng/ml in 1991[3].

This issue should be considered when the different serum concentrations of *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* and Flector Plaster are discussed.

In general, lower serum concentration levels may indicate that more active substance is located at the site of needed therapeutical action. This was originally the concept of topical application.
Therefore we are of the opinion that the submitted pharmacokinetic data may be included into the decision as supportive data but mainly to characterise the safety profile of the product.

Blinding
The traces of menthol (0.5%) in the verum plaster of study ME-2001/01 may be perceptible by its slight smell within the moment of application. Afterwards the plaster remained covered also when 8-12 hours later pain was measured. The patient also could not come in contact with his hands to the plaster because the application was done by an independent nurse.

In general, the cooling sensation of menthol lasts only a few minutes. The sensitivity for menthol at legs and arms which were treated in the study is shown to be least compared to all other areas of the body[6]. But there is a very market kind of additional cooling effect contained in both verum and placebo plaster because *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* is a 'self-adhesive tissue with gel'.
Additionally it should be considered that the plaster itself may have slight irritative effects.

Thus, both verum and placebo plaster are related with diverse sensational effects, a specific cooling effect of menthol is therefrom not discriminable by the patient. This is as well documented by 8 patients in each group reporting a cooling effect.

Therefore, we are of the opinion that the results of study ME-2001/01 are obtained under sufficiently blinded conditions and efficacy of *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* is shown.

III.4 Summary of Product Characteristics (SPC)

The proposed SPC adequately reflects the actual scientific knowledge on topical diclofenac for the relevant indication, additionally the relevant results documented in the studies are implemented therefore the SPC is considered acceptable.

III.5 Package Leaflet (PL) and User Testing

The PL proposal conforms to the current QRD-template and with the SPC proposal.
In general it is concluded that the PIL can be rated as readable and comprehensible according to the guideline of the European Commission. The results of the user test for *Diclofenac-ratiopharm / Diclofenac-ratio / Diclo-ratiopharm Schmerzpflaster* met the criteria of >80% correct answers after a few modifications. The subsequent two rounds of testing on groups of 10 participants showed markedly improvement.

III.6 Risk Minimisation Plan

Summary Pharmacovigilance system

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

[6] Eccles R, Menthol and related compounds. J Pharm Pharmacol, 1994, 46:618-630

Risk Minimisation Plan

The proposed pharmacovigilance activities and proposed risk minimisation activities are acceptable. As there are no specific safety concerns as identified with the reference medicinal product no additional risk minimisation activities are required.

IV. BENEFIT RISK ASSESSMENT

The overall risk/benefit of the product is favourable for the proposed indication. The application is approved. For intermediate amendments see current product information.