CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Voltaren Emulgel 1.16% gel, gel 11.6 mg/g
Novartis Consumer Health B.V., the Netherlands

diclofenac (as diethylamine)

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 31377

15 January 2009

Pharmacotherapeutic group:	anti-inflammatory preparations, non-steroids for topical use
ATC code:	M02AA15
Route of administration:	cutaneous
Therapeutic indication:	local alleviation of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and the fingers.
Prescription status:	non-prescription
Date of authorisation in NL:	6 June 2007
Application type/legal basis:	Directive 2001/83/EEC, Article 8(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 Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Voltaren Emulgel 1.16 % gel, gel 11.6 mg/g, from Novartis Consumer Health B.V. The date of authorisation was on 6 June 2007.

The product is indicated for the local alleviation of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and the fingers. The effect of Voltaren Emulgel is built up gradually during the first week of the treatment.

A comprehensive description of the indication and posology is given in the SPC. An extensive discussion regarding the initially claimed indications, and the adoption of the currently approved indication is described in paragraph *II.3 Clinical aspects*.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). It is a prostaglandin synthetase inhibiting substance with antiphlogistic, antipyretic, and analgesic properties.

This national application for marketing authorisation concerns Voltaren Emulgel 1.16% gel, gel 11.6 mg/g, containing the active ingredient diclofenac diethylamine 11.6 mg/g. This application is an update of two previous applications which were withdrawn in May 1988 and June 1992 by Ciba-Geigy. The first submission for registration (1985) was rejected; the proposed indication was '*artrose*'. The second submission for registration (1992) was also rejected; the proposed indication then was '*as an aid in the treatment of sports injuries and injuries due to accidental contusions and distortions*'.

This application is made according to article 8(3) of Directive 2001/83/EEC. Voltaren Emulgel 1.16% gel, gel 11.6 mg/g is a line extension, a different pharmaceutical form, to the already existing Voltaren K 12.5 mg film-coated tablets (RVG 20982). The Voltaren film-coated tablets have been registered in the Netherlands (Novartis Consumer Health B.V.) since 8 September 1998 by a national procedure.

At the time of application no topical formulations containing a NSAID were registered in the Netherlands for the claimed indications. In the past, several applications for topical NSAIDS have been declined due to reasons of lack of demonstration of efficacy and insufficient pharmacokinetic data.

New clinical data were provided to support the indications, which were claimed by the MAH at the start of the procedure. In support of the claim '*pain of non-serious arthritis of the knee or fingers*' two new pivotal efficacy studies, VOSG-PE-303 and VE-OA-1 respectively, were submitted. Moreover, in support of the second applied indication '*pain and inflammation due to muscle and joint injuries*' clinical documentation including two new pivotal efficacy studies, NF 113 and D458 L7/D141, were submitted. See paragraph *II.3 Clinical aspects* for an elaborate discussion of these studies.

Steps taken for the assessment of the product:

- The application was submitted on 26 May 2004.
- On 8 October 2004 a letter with comments from the MEB was sent to the MAH.
- The MAH responded to these comments in a letter sent on 17 May 2005.
- A second letter with comments from the MEB was sent to the MAH on 26 July 2005.
- The MAH sent its response to these comments on 28 July 2005. In addition, the MAH requested a hearing.
- A hearing took place on 10 November 2005.
- The MAH sent a letter with their comments on the outcome of the hearing to the MEB on 14 February 2006.
- The MEB sent a third letter with its decision to refuse the registration application together with the grounds for refusal to the MAH on 29 June 2006.
- On 8 August a letter was sent to the MEB by the MAH, in which an appeal was announced.
- The actual appeal was sent to the MEB by fax on 12 October 2006.

- Subsequently, a hearing took place on 1 February 2007, after which the MEB revised its initial opinion provided that the indication is restricted.
- The product was authorized in the Netherlands on 6 June 2007.

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 diethylamine, an established active substance described in the BP*, but not in the Ph.Eur.*. The active substance is sparingly soluble in water and freely in ethanol 96%. Diclofenac diethylamine is a white to almost beige crystalline powder, which is not hygroscopic.

Manufacture
Diclofenac diethylamine is synthesized in two reaction steps followed by purification. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH based on the BP* monograph. Additional specifications for particle size are laid down. 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 9 full scaled batches from the production sites.

Stability
Stability data on the active substance have been provided for 3 full scaled batches stored at 25°C/60RH for 36 months and at 40°C/75%RH for 6 months. The batches were adequately stored. A retest period of 36 months, without special storage conditions in the proposed packaging material has been granted.

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

Medicinal Product

Composition
The product is a gel for cutaneous use. One gram of Voltaren Emulgel contains 11.6 mg of the active substance diclofenac diethylamine.
The gel is packaged in a membrane-sealed lacquered aluminium tube (30, 50 and 100 g) with inner coating of a phenoxy-epoxy based lacquer closed with polypropylene screw cap or an aluminium laminated tube (20, 30, 50, 60, 100, 120 and 150 g) closed by a moulded seal, with a polypropylene screw cap. The packaging is usual for this type of dosage form.

The excipients are: carbomer, macrogolcetostearylether, cocoylcaprylocaprate, diethylamine, isopropyl alcohol, propylene glycol, liquid paraffin, perfume cream 45, purified water.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The product contains isopropanol, which serves also as preservative. It has an adequate antimicrobial activity. The preservative efficacy of the gel has been investigated by a challenge test according to the Ph.Eur. The product satisfies criteria A of the Ph.Eur. Herewith, the antimicrobial preservation has been adequately demonstrated.

The excipients comply with Ph.Eur. requirements, except for the ingredients diethylamine and the flavour that are not described in any pharmacopoeia. The specifications for the excipients are acceptable.

Manufacturing process
The manufacturing process is a standard process and has been adequately validated according to relevant European guidelines. Retrospective validation data on the product have been presented for numerous full scaled batches.

Quality control of drug product
The product specification includes tests for appearance, viscosity, pH, identity, assay, degradation, and microbiological purity. The specification is in line with the BP-monograph. Based on the stability data, the shelf-life requirements are only different for appearance. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 full scaled batches, demonstrating compliance with the release specification.

Stability tests on the finished product
Stability data on the product have been provided for numerous full scaled batches stored at 25°C/60% RH (36 months). Also 5 full scale batches were studied at 40°C/75% RH (6 months), 3 full scaled batches at 30°C/60%RH and 3 full scaled batches at 30°C/70%RH. The conditions used in most of the stability studies are according to the ICH stability guideline. The batches were stored in both tube types. All parameters remained within specification for all conditions. Only a slight discoloration was observed. A 3 year shelf-life without special storage conditions is acceptable in view of the available stability data. However, the MAH applies a storage temperature restriction not to store above 30°C as a precaution measure. In-use stability data justify the in-use stability of 24 months after first opening.

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

The active substance has been available on the European market for over 10 years. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application

Environmental risk assessment
The approval of this product will not result in an increase in the total quantity of diclofenac diethylamine 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

Clinical aspects

The MEB has been assured that GCP standards were followed in an appropriate manner in the studies conducted. The formulation of the batches used in key clinical studies are identical to that proposed for marketing.

The indications as proposed by the MAH at the start of the procedure were:

A. relief of pain of non-serious arthritis of the knee or fingers
B. relief of pain and inflammation due to muscle and joint injuries, e.g. sprains, strains, bruises (sports injuries)

After elaborate discussion the approval was granted for the following indication:

'For the local alleviation of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and the fingers. The effect of Voltaren Emulgel is built up gradually during the first week of the treatment'.

The procedures of both proposed indications will be discussed separately.

Indication A. *'Relief of pain of non-serious arthritis of the knee or fingers'*

In support of the claim 'pain of non-serious arthritis of the knee or fingers' two new pivotal efficacy studies, VOSG-PE-303 and VE-OA-1, respectively were submitted. These studies are summarized in Table 1 and 2. In addition there were 7 studies submitted providing supportive evidence for safety.

Table 1. Summary of the pivotal studies supporting the first indication: relief of pain of non-serious arthritis of the knee or fingers.

Study	**VOSG-PE-303**	**VE-OA-1**
Indication	Relief of joint pain in non-serious knee arthritis	Relief of joint pain in non-serious finger arthritis
Design	Randomized double-blind, parallel group, placebo-controlled, 3-weeks study	Randomized double-dummy, active controlled, 3-week study
Subjects	238 patients suffering from osteoarthritis of the knee	321 patients suffering from osteoarthritis of the fingers
Treatment arms	Voltaren Emulgel 4g (117 subjects) or placebo (120 subjects), four times daily	Voltaren Emulgel 3 g (165 subjects) four times daily or oral ibuprofen 3 x 400 mg daily (156 subjects)
Primary efficacy parameters	Average over Day 1-14 of daily pain on active movement (POM) (VAS 0-100).	Response rate, which was defined as the number of patients who had a pain reduction from baseline to the end of the 21 days of at least 40% on a 100 mm VAS (global assessment of pain).
Secondary efficacy parameters	Several secondary outcome measures such as pain relief over day 1-7, and day 1-14, and day 1-21, spontaneous pain (VAS 0-100), and rescue medication, the WOMAC at week 1, 2, and 3 were measured at day 0, 1, 2, 7, 14, and 21.	Several other secondary outcome measures for pain and function such as grip strength were assessed.

Table 2. Outcome of the pivotal studies supporting the first indication: relief of pain of non-serious arthritis of the knee or fingers.

VOSG-PE-303			VE-OA-1			
Pain	Baseline	VAS score (% relief from baseline) Week 1 – week 2 – week 3	Pain (VAS score)	Day 1	Day 21	Responder rate % patients
Voltaren Emulgel	69 mm	50 mm (28%) – 41 mm (41%) – 34 mm (51%)	Voltaren Emulgel 4DD	58 mm	34 mm	42%
Placebo	66 mm	53 mm (20%) – 49 mm (26%) – 40 mm (40%)	Ibuprofen 3x400 mg daily	56 mm	36 mm	35%

Pivotal study VOSG-PE-303, (Published as **Niethard** *et al* 2005**)** A multi-centre, randomized, double blind, parallel group, placebo controlled study of 3 weeks duration in 238 patients with moderate to severe painful unilateral osteoarthritis (OA) of the knee for at least 6 months, was conducted to determine the efficacy and safety of Voltaren Emulgel 1.16% gel. Patients received either 4 g Voltaren Emulgel (117 subject, mean age 66 yrs) or placebo (120 subjects, mean age 66 yrs) 4 times daily for 3 weeks to the affected knee. Rescue medication (Paracetamol < 2 g/day) was permitted. The primary efficacy measure was the average over Day 1-14 of daily pain on active movement (POM) (VAS 0-100 mm). Several secondary outcome measures such as pain relief over day 1-7, and day 1-14, and day 1-21, spontaneous pain (VAS 0-100 mm), and rescue medication, the WOMAC at week 1, 2, and 3 were measured at day 0, 1, 2, 7, 14, and 21. The mean baseline POM and spontaneous pain were 72 mm and 69 mm in the Voltaren group and 71 mm and 66 mm in the Placebo group.

Regarding the ITT population, the mean change from baseline for the average daily POM score over day 1-14 was 14 mm (20%) in the Voltaren group and 10 mm (14%) in the placebo group. The mean change from baseline for spontaneous pain at week 1, 2, and 3 was 19 mm (28%), 28 mm (41%), 35 mm (51%) in the Voltaren group and 13 mm (20%), 17 mm (26%), 26 mm (40%) in the placebo group. The use of rescue medication did not differ between the groups.

Study VOSG-PE-303 showed a difference for several clinical efficacy measures between Voltaren Emulgel and placebo in favour of Voltaren Emulgel. Regarding the primary outcome measure, the difference in the percentages of mean change for POM between Voltaren and placebo were 8, 15, and 11% at week 1, 2, and 3, respectively. According to the MEB, no clinically important differences were found in this study if the OsteoArthritis Research Society International/ Outcome Measures in Rheumatology (OMERACT) Responder criteria are applied. In these criteria, a 'Responder' is defined as a patient who has: a) 50% improvement in pain score OR physical function score, AND b) the magnitude of improvement must be 20% of the measurement of the scale in use (i.e. 20 mm on a 100 mm VAS or 1 point on a 5-point Likert scale). These criteria can be used for all sought indications due to the comparability in types of pain. Therefore, the MEB concludes that the obtained effect in comparison with placebo can not be considered clinically relevant. In addition, no acute pain relief was demonstrated because measurements between day 0 and 4 did not show clinically relevant difference between Voltaren Emulgel and placebo. Furthermore, a comparison with an active drug is lacking. To demonstrate the external validity of the observed results and to assess clinical relevance in relation to known standard therapy for this indication, a comparison with an oral NSAID or paracetamol should have been performed.

Pivotal study VE-OA-1, (Published as **Zacher** *et al* 2001) A multi-centre, randomized, double blind, active controlled, double dummy study of 3 weeks duration in 327 patients with activated painful OA of the fingers was conducted to compare the efficacy and safety of Voltaren Emulgel 1.16% gel (165 subjects, mean age 60.7 yrs) versus oral ibuprofen (3x400 mg/d) (156 subjects, mean age 63.2 yrs). The gel medication was applied 4 times at a mean interval of 4-5 hours. A dose of approximately 3 g was allowed for both hands. The study was designed to prove non-inferiority of Voltaren gel treatment with ibuprofen treatment. Rescue medication (Paracetamol < 3 g/day) was permitted.

The primary efficacy was the response rate, which was defined as the number of patients who had a pain reduction from baseline to the end of the 21 days of at least 40% on a 100 mm VAS scale. Non-relevant inferiority was defined as a difference of 20% in terms of the response rate in the original hypothesis. Several other secondary outcome measures for pain and function such as grip strength were assessed.
Baseline data showed that the mean of the number of painful and swollen joints was 7.7 and 5.5 in the Voltaren group and 7.9 and 6.0 in the Ibuprofen group. The pain intensity score at baseline was 5.95 cm (VAS 0-10 cm) in the Voltaren group and 6.01 cm in the ibuprofen group. In the PP population, a total of 116 patients (39%) were considered as responders to study medication, 44% treated with Voltaren compared to 34% treated with Ibuprofen, difference 10% CI -4%; 24%. The ITT analysis showed similar results. These data were supported by the results of the secondary parameters.

Study VE-OA-1 did not show differences in clinical efficacy between Voltaren Emulgel and oral ibuprofen. The interpretation of the observed results is hampered by the absence of a placebo arm, especially in this pain indication in which high placebo effects can be observed. Moreover, the non-inferiority margin is not substantiated. A three-arm placebo-controlled study should have been performed in correspondence with the current CPMP guidance documents regarding Points to Consider on Clinical Investigation of Medicinal Products used in the Treatment of Osteoarthritis (CPMP/EWP/784/97).

The company submitted 7 supportive studies to demonstrate efficacy and safety of Voltaren Emulgel 1.16%. In five single blind studies, Voltaren Emulgel was compared with another NSAID containing gel. Both products were equally effective, but the interpretation of the observed results was hampered by the absence of a placebo arm, the fact that the comparator was not approved in the Netherlands and in some studies the too low number of patients included. In another single blind study Voltaren Emulgel was compared with indomethacin gel and placebo. Slight improvements were found for all pain parameters with no difference between the three treatment groups. A comparison with an active oral drug approved for this indication is lacking. The last study to be mentioned was a double blind study in which Voltaren Emulgel was compared with placebo in 70 patients suffering from osteoarthritis of the knee receiving analgesics, NSAIDs or second line agents. There was a trend in favour of Voltaren Emulgel for improvement in pain parameters. However, no clinically relevant differences were observed between placebo and Voltaren Emulgel as adjunct therapy in patients with osteoarthritis of the knee who were receiving analgesics, NSAIDs or second line agents.

Conclusions of the MEB
The provided evidence of clinically relevant efficacy was considered insufficient to approve the sought indications as could be judged from the studies. The proposed indication of this local product was OA, therefore the MEB was of the opinion that the CPMP guideline PtC on clinical investigation of medicinal products used in the treatment of osteoarthritis (CPMP/EWP/784/97) was applicable. Hence, to show therapeutic equivalence, 3-arm studies comparing placebo, the new product, and the product already approved for this indication (in this case a simple oral NSAID or paracetamol) were considered necessary.
The company did not provide sufficient information regarding the primary efficacy measure, the average daily pain on active movement (POM) score focussed only on the secondary outcome measures: spontaneous pain (100 mm VAS), the WOMAC and daily global evaluation of pain relief and pain intensity. The conclusions of the company were based on figures (change in VAS score) of the active group but did not take into account the percentage of improvement in the placebo group. Furthermore, % of improvement was present on group level but not on the individual level, which was proposed by the OMERACT responder criteria. Based on % of improvement between the Voltaren Emulgel group and placebo no clinically relevant differences were observed

Regarding the first indication 'relief of pain of non-serious arthritis' the conclusions are based on the following considerations:

- In pivotal study VOSG-PE-303, the obtained effect in comparison with placebo is not clinically relevant. In principle, a response can be defined as clinically relevant if there is 50% improvement in pain score, where the magnitude of improvement must be at least 20% of the size of the scale. Furthermore, a comparison with a simple oral NSAID or paracetamol has not been made to test the external validity of the observed results and to assess clinical relevance in relation to known standard therapy.

- Efficacy has not been measured during the first days of the treatment period.
- In pivotal study VE-OA-1 the interpretation of the results is hampered by the absence of a placebo arm.
- The interpretation of the results of the remaining supportive studies in which Voltaren Emulgel 1.16% gel was compared with gel formulations of different NSAIDs is hampered by the absence of a placebo arm, the absence of an approved comparator or a too low number of included patients.

Therefore the MEB decided to refuse the registration application for this indication.

The company did not agree with this descision, and therefore filed an appeal. See page 12.

Indication B. '*Relief of pain and inflammation due to muscle and joint injuries, e.g. sprains, strains, bruises (sports injuries)*'

In support of the second indication '*pain and inflammation due to muscle and joint injuries*' two new efficacy studies, NF 113 and D458 L7/D141, were submitted. These studies are considered pivotal (see Table 3). Additional efficacy and safety elements are derived from 9 studies.

Table 3. Summary of the pivotal studies supporting the second indication: pain and inflammation due to muscle and joint injuries.

Study	NF113	D 458L7/D141
Indication	Pain and inflammation due to muscle and joint injuries	Pain and inflammation due to muscle and joint injuries
Design	Randomized double-blind, parallel group, placebo-controlled, 7-days study	Randomized double-blind, parallel group, placebo-controlled, 14-days study
Subjects	83 patients with soft tissue trauma resulting in a minor sprain, 35 patients with tear of muscle or tendon, 74 patients with pulled muscle/contusion with or without haematoma and 62 patients with other forms of traumatism.	80 patients suffering from acutely sprained ankles.
Treatment arms	Voltaren Emulgel (126 subjects) or placebo (128 subjects), four times daily. Rescue medication was permitted.	Voltaren Emulgel (40 subjects) or placebo (40 subjects) three times daily. Rescue medication was permitted.
Efficacy para-meters	General assessment of efficacy, assessment of pain, spontaneous pain on movement and pain on pressing, change in pain.	Efficacy measures were pain when lying, pain on movement, pain when standing, pain on pressure, functional restriction, circumference of joint.
Outcome	During the first 2 days the pain reduction in the Voltaren groups was 10.2 % and in the placebo group 11.6 %. At day 7 these percentages were 34% and 33.5%, respectively. Similar results were found for pain on pressing. No difference in 'change in oedema' was observed between the groups. The need for rescue medication was some lower in the active treatment group (34%) in comparison with placebo (45%).	Pain reduction when at rest in the morning and evening during the first 4 days was in the Voltaren group 83% and 84% , respectively and in the placebo group 71% and 65%, respectively. Pain reduction during movement in the morning and evening during the first 4 days was in the Voltaren group 60% and 59%, respectively and in the placebo group 44% and 44%, respectively. Pain reduction measured on a 5 point Likert scale decreased in the Voltaren group during day 1-14 from 3.68 to 1.68 (54%) and in the placebo group from 3.53 t0 1.72 (51%). Also no differences in circumference of joints, pain when standing, and pain on pressure were demonstrated

		between the two groups. Similar numbers of patients in each group required rescue analgesia. 60% of actively treated patients stopped using the gel before the 14th day as they were free of symptoms compared with 38% of the placebo group.
Comment	*A slight difference in favour of Voltaren compared to placebo was found for outcome measures for which unusual scales were used. However, for the more commonly used pain VAS score, no differences between the groups were observed from day 0 to 7. Furthermore, for this indication, a comparison with a simple oral NSAID should have been made to test the external validity of the observed results and to assess clinical relevance in relation to known standard therapy.*	*A slight difference in favour of Voltaren compared to placebo was found for VAS pain scores at rest and during movement, however regarding other outcome measures such as the circumference of joints, pain on pressure, and the use of rescue medication, no differences between the groups were observed. Furthermore, for this indication, a comparison with a simple oral NSAID should have been made to test the external validity of the observed results and to assess clinical relevance in relation to known standard therapy.*

Pivotal study NF113

This pivotal parallel-group, randomised, double-blind, placebo-controlled study was designed to investigate the efficacy of Voltaren Emulgel 1.16% gel (126 subjects) compared with placebo gel (128 subjects) in patients with soft tissue trauma resulting in a minor sprain (83 patients), tear of muscle or tendon (35 patients), pulled muscle/contusion with or without haematoma (74 patients) or other forms of traumatism (62 patients). Patients received treatment 4 times daily, for 7 days. Rescue medication was permitted. 75% of the patients, treatment was started within 8 days of the injury, and within 9-31 days for the remainder. Voltaren Emulgel 1.16% gel was applied 4 times daily at a mean dose of 2.2g. Criteria for efficacy were 'general assessment of efficacy ('excellent', 'good', 'fair' or 'nil'), pain (VAS 0-100mm), spontaneous pain on movement and pain on pressing ('nil', 'moderate', 'marked', 'very marked'), change in pain '(improvement', 'no change', 'exacerbation'). Assessments were performed at day 0, 1, 2, 3, 4, 5, 6 and at day 7.

Global analysis of mean pain at each time is shown in the following table. During the first 2 days the pain reduction in the Voltaren groups was 10.2% and in the placebo group 11.6%. At day 7 these percentages were 34% and 33.5%, respectively. This was not statistically significantly different.

Table 4. Mean pain scores (VAS 0-100 mm) and change from baseline at day 1 to day 7.

Day	Voltaren	Placebo
0	58.3	62.4
1	53.2 (-8.7%)	56.8 (-9.0%)
2	48.1 (-17.4%)	50.8 (-18.6%)
3	41.8 (-28.3%)	45.2 (-27.6%)
4	35.5 (-39.1%)	39.1 (-37.3%)
5	31.2 (-46.5%)	35.1 (-43.8%)
6	27.1 (-53.5%)	30.5 (-51.1%)
7	24.3 (-58.3%)	28.9 (-53.7%)

Regarding the results of spontaneous pain on deliberate movement on day 7, 44% (51) of the active treatment group having no pain, 43% (50) having only moderate pain and 13% (15) marked pain compared with 35% (41), 38% (44) and 24% (28) of the subjects in the placebo group respectively. 3 subjects (3%) of the placebo group had very marked pain at 7 days. Similar results were found for pain on pressing. No difference in 'change in oedema' was observed between the groups. The need for rescue medication was some lower in the active treatment group (34%) in comparison with placebo (45%).

In this placebo-controlled study a slight difference in favour of Voltaren compared to placebo was found for outcome measures for which unusual scales were used. However, for the more commonly used pain

VAS score, no significant differences between the groups were observed from day 0 to 7. Furthermore, for this indication, a comparison with a simple oral NSAID should have been made to test the external validity of the observed results and to assess clinical relevance in relation to known standard therapy.

Pivotal study D458L7/D141
This double-blind, randomised, parallel-group, placebo-controlled study evaluated the efficacy and safety of Voltaren Emulgel 1.16% gel with placebo in 80 patients with acutely sprained ankles, 40 randomised to each group. The majority of the ankle injuries were sustained during sport. Voltaren Emulgel, or placebo, was applied three times daily for up to 14 days. Rescue medication was permitted. Efficacy measures were pain when lying, pain on movement, pain when standing, pain on pressure, functional restriction, circumference of joint assessed at day 1, 2, 3, 4, 7, 10, and 14.
The results of morning and evening pain at rest and movement were shown in the following table.

Table 5. Mean pain scores (VAS 0-100 mm).

Pain when at rest in the *morning*			**Pain when at rest in the *evening***		
Day	Voltaren	Placebo	Day	Voltaren	Placebo
1	27.2	27.3	1	31.3	25.1
2	16.7	18.0	2	16.4	18
3	7.3	11.6	3	7.3	12.6
4	4.5	7.8	4	4.8	8.8

Pain reduction when at rest in the morning and evening during the first 4 days was in the Voltaren group 83% and 84%, respectively and in the placebo group 71% and 65%, respectively.

Table 6. Mean pain scores (VAS 0-100 mm).

Pain during movement in the *morning*			**Pain during movement in the *evening***		
Day	Voltaren	Placebo	Day	Voltaren	Placebo
1	61.2	53.3	1	63.5	53.4
2	47.6	45.1	2	46.8	46.9
3	33.0	35.5	3	33.6	36.9
4	24.1	29.7	4	26.1	30.1

Pain reduction during movement in the morning and evening during the first 4 days was in the Voltaren group 60% and 59%, respectively and in the placebo group 44% and 44%, respectively. Pain reduction measured on a 5 point Likert scale decreased in the Voltaren group during day 1-14 from 3.68 to 1.68 (54%) and in the placebo group from 3.53 to 1.72 (51%). Also no differences in circumference of joints, pain when standing, and pain on pressure were demonstrated between the two groups. Similar numbers of patients in each group required rescue analgesia. 60% of actively treated patients stopped using the gel before the 14th day as they were free of symptoms compared with 38% of the placebo group.

In this placebo-controlled study a slight numerical difference in favour of Voltaren compared to placebo was found for VAS pain scores at rest and during movement, however regarding other outcome measures such as the circumference of joints, pain on pressure, and the use of rescue medication, no differences between the groups were observed. Furthermore, for this indication, a comparison with a simple oral NSAID should have been made to test the external validity of the observed results and to assess clinical relevance in relation to known standard therapy.

The company submitted 4 active-controlled studies that did not demonstrate differences in clinical efficacy between Voltaren Emulgel 1.16% and other NSAID gel formulations. The interpretation of the observed results is hampered by the absence of a placebo arm, especially in this pain indication in which high placebo effects can be observed. Other submitted studies were not relevant for the proposed indication or included too low number of patients to conclude. In one study a slight difference in favour of Voltaren compared to placebo was found, however, the number of subjects was very small. In 2 other placebo-controlled no differences in efficacy was demonstrated between Voltaren Emulgel, placebo or active control.

Regarding the indication **'pain and inflammation due to muscle and joint injuries'**, in pivotal study NF 113 a numerically slight but not statistically significant difference was found in advantage of Voltaren compared to placebo for outcome measures for which unusual scales were used, however, no difference for the more commonly used VAS pain score; a comparison with an active drug is lacking. Pivotal study D458 and L&/D141 showed a slight hardly relevant difference in favour of Voltaren compared to placebo; a comparison with an active drug is lacking. The interpretation of the results of the remaining 4 supportive active-controlled studies is hampered by the absence of a placebo arm.

Conclusion indication B: *'pain and inflammation due to muscle and joint injuries'*
The provided evidence of clinically relevant efficacy as can be judged from studies was insufficient to approve the sought indication. This was based on the following considerations:

- In pivotal studies NF 113 and D458L7/D141, no clinically relevant and statistically significant differences were observed between Voltaren Emulgel 1.16% and placebo. Furthermore, a comparison with a simple oral NSAID to test the external validity of the observed results and to assess clinical relevance in relation to known standard therapy has not been made.
- Efficacy has not been measured during the first days of the treatment period.
- The interpretation of the results of the remaining supportive studies in which Voltaren Emulgel 1.16% gel was compared with gel formulations of different NSAIDs is hampered by the absence of a placebo arm.

The company stated that further information was not available and it was decided that the application for the indication "pain due to muscular and joint injuries" will be withdrawn.

Safety

Data demonstrated that the use of Voltaren Emulgel 1.16% is safe.

A. *'Relief of pain of non-serious arthritis of the knee or fingers'.*
In pivotal study VOSG-PE-303, the safety profile demonstrated by Voltaren gel was similar to that of placebo with an incidence of adverse events of 9% in both active and vehicle placebo groups. A total of 2 patients, both in the Voltaren group, were withdrawn from the study due to adverse events, application site reaction and Quincke's oedema.
In pivotal study VE-OA-1, safety results showed that the total number of adverse events was higher in the Ibuprofen group. The number of adverse events with an intensity classified as severe was higher in the Ibuprofen group (14%) than in the Voltaren group (7%). The number of adverse events which led to a premature discontinuation of the study was higher in the Ibuprofen group (10%) than in the Voltaren group (3%).
In the supporting studies , the tolerability of the treatment was considered to be 'good' for the treatment groups. In several studies cutaneous adverse events were mentioned. They were in general mild to moderate , only one of these (reddening and burning of the skin) was considered severe.

B. *'Pain and inflammation due to muscle and joint injuries'.*
In pivotal Study NF113, 11 patients reported adverse events: 5/128- placebo and 6/126- Voltaren Emulgel 1.16% gel. One patient from the active treatment group reported an adverse gastrointestinal event and 5 patients from each treatment group reported local skin reactions. All adverse events were considered to be definitely or possibly related to treatment.
In pivotal Study D458L7/D141, cutaneous adverse effects were seen in 2 Voltaren Emulgel 1.16% gel treated patients and 6 placebo gel treated patients. All were 'probably' or 'definitely' related to treatment. There were no serious adverse events or deaths.
In the supporting studies , the tolerability of the treatment was considered to be 'good' for the treatment groups. No unwanted effects occurred and no pathological changes in the treated skin were observed.

Safety conclusion
The safety profile of Voltaren Emulgel 1.16%, gel 11.6 mg/g is more favourable than that of oral ibuprofen. No important differences in safety profiles were observed between Voltaren Emulgel 1.16%, other

NSAIDs-gel formulations or placebo. In general it can be concluded that the use of Voltaren Emulgel 1.16% gel seems to be relatively safe and that the product has a smaller risk than oral NSAID containing products (see page 5).

Appeal procedure by company

The company did not agree with the decision of the MEB to refuse the registration application for indication A, and therefore filed an appeal.

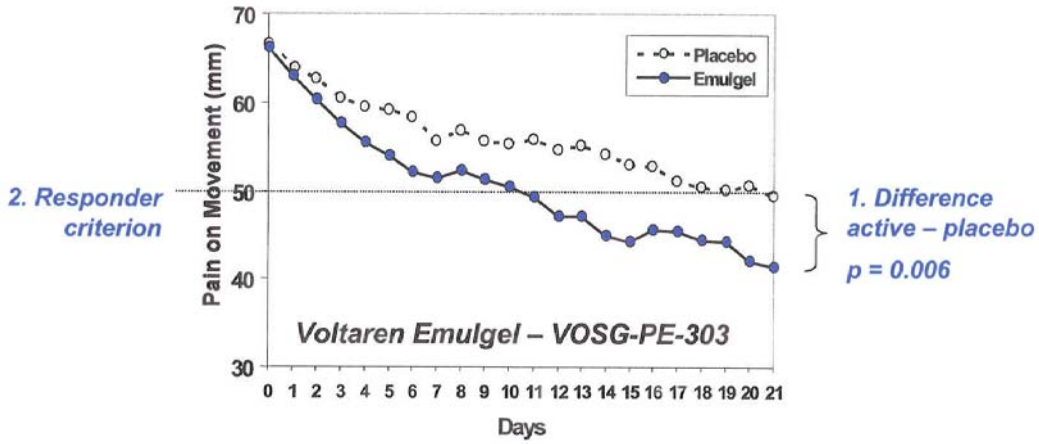
Argumentation of the company during the appeal procedure

In response to the objection the company stated that with respect to the OMERACT criteria 2002 these criteria were revised by the same group (**Pham** *et al*, 2004). The OMERACT-OARSI set of responder criteria (yes or no) defines a positive response either high improvement in pain or function ≥ 50% and absolute change ≥ 20 mm *or* improvement in at least 2 of the 3 following parameters; pain ≥ 20% and absolute ≥ 10 mm, function ≥ 20% and absolute ≥ 10 mm, or patient's global assessment ≥ 20% and absolute change ≥ 10 mm. Applying the latter (second part of the criteria) to study VOSG-PE-303, the company concluded that the obtained effects reach clinical relevance.

Regarding the **comparison with a simple oral NSAID or paracetamol**, the company was of the opinion that the CPMP guideline PtC on clinical investigation of medicinal products used in the treatment of osteoarthritis (CPMP/EWP/784/97) were not applicable because Voltaren Emulgel concerns a local product.

The company submitted efficacy data during the first days of treatment but no quantitative data were presented only a figure (Fig. 1). However, on the basis of this figure, it appeared that there were also no relevant differences in efficacy between Voltaren Emulgel and placebo during the first days of treatment.

Fig. 1 Relevance of treatment effect vs. placebo



Regarding the absence of a placebo arm in study VE-OA-1, the company argued that the efficacy of low dose ibuprofen was known from previous studies. However, the company did not discuss the recommendation of the use of a placebo arm in OA studies which were mentioned in the Guidelines; an important reason for this recommendation was the high and variable placebo effect in pain conditions such as OA.

The company presented the following points in the Documentation of Efficacy in Osteoarthritis; these were subsequently discussed.

1. The treatment effect of Voltaren Emulgel in patients with knee OA is comparable to that observed in recent, placebo-controlled oral NSAID and COXIB studies after 2 weeks of treatment.

2. In terms of responder rates (50% improvement, at least 20% of scale), significant separation between Voltaren Emulgel and placebo is achieved at 2 weeks both for OA pain and OA functional score.
3. The effect of Voltaren Emulgel builds up gradually since the first days of treatment and statistically significant separation of OA pain between active and placebo groups was demonstrated already after 1 week of treatment.
4. The treatment effect of Voltaren Emulgel in knee OA does not wane over 3 weeks of treatment; treatment effects with Voltaren Emulgel at 3 weeks and with oral NSAIDs and COXIBs at end-of-study are similar to those observed at 2 weeks.
5. In direct comparison, Voltaren Emulgel is as effective as oral ibuprofen 1200 mg/day (maximum OTC dose) over 3 weeks of treatment in OA of the hand. The incidence of AEs was clearly lower with Voltaren Emulgel as compared to the oral NSAID.
6. In conclusion, Voltaren Emulgel is an effective and safe medicine for the relief of pain in osteoarthritis of the knee and fingers, also in comparison to oral NSAIDs and COXIBs.

The company proposed an adapted indication, i.e. “Short-term treatment of joint pain caused by exacerbations of osteoarthritis of the knee or fingers for duration of maximal 3 weeks” and withdrew the indication “pain due to muscular and joint injuries”.

Conclusion MEB on indication A: ‘relief of pain of non-serious arthritis’ in the appeal procedure

The evidence of efficacy provided by the company specified above was insufficient to approve the proposed reworded indication namely “Short-term treatment of joint pain caused by exacerbations of osteoarthritis of the knee or fingers”. The company did not give additional information regarding the primary efficacy measure, the average daily pain on active movement (POM) score but only focussed on the secondary outcome measures: spontaneous pain (100 mm VAS), the WOMAC and daily global evaluation of pain relief and pain intensity. But the company demonstrated that the responder rates (active vs. placebo) with Voltaren Emulgel were statistically significantly different versus placebo, both in Pain Intensity and the WOMAC Pain score in study VOSG-PE-303. The results were in accordance with the definition for efficacy (at least 50% improvement, at least 20% of scale) according to the revised OMERACT criteria 2002. However, the durability of the effect of Voltaren Emulgel in OA had to be shown for the intended duration of use.

After an elaborate discussion the MEB revised its initial opinion provided that the indication is restricted, i.e. “For the local alleviation of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and the fingers. The effect of Voltaren Emulgel is built up gradually during the first week of the treatment”. Moreover, it should be communicated in the SPC (section 4.2 and 5.1) that the gel should not be used longer than 3 weeks due to lack of longer term efficacy data and that Voltaren Emulgel is not suitable for the treatment of acute pain.

Within these conditions the MEB considered that

- the efficacy of Voltaren Emulgel had been demonstrated for the treatment of mild to moderate pain;
- the product has a smaller risk than oral NSAID containing products (see page 11);
- the therapeutic effect was built up gradually during the first week and;
- the effect was clinically relevant in a revised indication and a revised advice for usage.

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

Readability test
A readability test has not been performed, which is acceptable since at the time of the application readability tests were not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Voltaren Emulgel 1.16%, gel 11.6 mg/g has a proven chemical-pharmaceutical quality.

The SPC, package leaflet and labelling are in the agreed templates.

Clinical efficacy
During several board meetings held in 2004 and 2006, an elaborate discussion has taken place on clinical relevance and efficacy for this product.
At the start of the procedure, the indications as claimed by the MAH were '*Relief of pain of non-serious arthritis of the knee or fingers'* and '*Relief of pain and inflammation due to muscle and joint injuries, e.g. sprains, strains, bruises (sports injuries)*'. In paragraph "*II.3 Clinical aspects*" the clinical studies submitted by the MAH in support of these indications have been discussed separately for each indication.

For the indication '*Relief of pain of non-serious arthritis of the knee or fingers'* the Board decided in an appeal procedure, after an initial refusal, that this indication is approvable, provided that it is restricted to *"For the local alleviation of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and the fingers. The effect of Voltaren Emulgel is built up gradually during the first week of the treatment"*. In addition, the gel should not be used longer than 3 weeks due to lack of longer term efficacy data.

The Board decided that the second indication *"Relief of pain and inflammation due to muscle and joint injuries, e.g. sprains,strains, bruises (sports injuries)"*, was not approvable based upon the submitted clinical documentation with Voltaren Emulgel 1.16% and placebo. A comparison with a simple oral NSAID to test the external validity of the observed results and to assess clinical relevance in relation to known standard therapy was not made. In addition, efficacy has not been demonstrated during the first days of the treatment period. Also, the interpretation of the results of the remaining supportive studies in which Voltaren Emulgel 1.16% gel was compared with gel formulations of different NSAIDs is hampered by the absence of a placebo arm.

Clinical safety
The active substance has been available on the European market for over 10 years, and therefore no new preclinical data have been submitted. This is acceptable for this type of application.
The safety profile of Voltaren Emulgel 1.16% is more favourable than that of oral ibuprofen. No important differences in safety profiles were observed between Voltaren Emulgel 1.16%, other NSAIDs-gel formulations or placebo. In general it can be concluded that the use of Voltaren Emulgel 1.16% gel seems to be relatively safe and that the product has a smaller risk than oral NSAID containing products

Voltaren Emulgel 1.16%, gel 11.6 mg/g was authorised in the Netherlands on 6 June 2007.

The last PSUR on diclofenac topical forms covered the period from 01November 2008 to 30 September 2009 and has been submitted under the EU PSUR synchronization scheme (September 2009). The next PSUR will cover the period from 01 October 2009 to 30 September 2012. The PSUR should be submitted within 60 days after data lock point.

There were no post-approval commitments made during the procedure.

References

Niethard FU, Gold MS, Solomon GS *et al* 2005. Efficacy of topical diclofenac diethylamine gel in osteoarthritis of the knee. *J Rheumatol*; 32:2384-92.

Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, Simon L, Strand V, Woodworth T, Doudagos M. 2004. Osteoarthritis Research Society International set of respinder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004; 12(5):389-399.

Zacher J, Burger KJ, Farber L *et al.* 2001. Topisches Diclofenac Emulgel versus orales Ibuprofen in der Therapie der aktivierten Arthrose der Fingergelenke (Heberden-und/oder Bouchard-Arthrose). *Akt Rheumatol*; 26:7-14.

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
NSAID	Non-Steroidal Anti Inflammatory Drug
OA	Osteoarthritis
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
POM	Pain on Active Movement
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
VAS	Visual Analogue Scale
WOMAC	A set of standardized questionnaires used by doctors to evaluate the condition of osteoarthritis patients

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the specification of the finished product. Tightening of specification limits.	IA	27-6-2007	8-8-2007	Approval	N
Addition of an aluminium laminated tube as immediate packaging for Voltaren Emulgel.	II	27-6-2007	8-8-2007	Approval	N
Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance, from a new manufacturer (replacement or addition).	IA	23-7-2008	14-10-2008	Approval	N
Change in the qualitative and/or quantitative composition of the immediate packaging material. Semi-solid and liquid pharmaceutical forms.	IB	3-9-2008	14-11-2008	Approval	N
Introduction of an additional, registered, packaging size on the market (120 g): evaluation of the mock-ups	II	29-4-2009	8-7-2009	Approval	N
Change in test procedure of the finished product.	IA	9-6-2009	5-9-2009	Approval	N
Addition of a pack size of 150 g.	IB	7-7-2009	11-9-2009	Approval	N
Update product information. Addition of already registered pack size of 60 g to the market.	II	6-10-2009	9-10-2009	Approval	N