CBG MEB

Public Assessment Report

Scientific discussion

Diclofenac HTP 1%, gel

(diclofenac sodium)

NL License RVG: 116368

Date: 1 November 2018

This module reflects the scientific discussion for the approval of Diclofenac HTP 1%, gel. The marketing authorisation was granted on 9 July 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

A list of literature references is given on page 23-24.

List of abbreviations

AESGP	Association of the European Self-Medication Industry
ASMF	Active Substance Master File
AUSCAN	Australian/Canadian Osteoarthritis Hand Index
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMS	Concerned Member State
DMSO	Dimethyl Sulfoxide
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
GVP	Guideline on Good Pharmacovigilance Practices
HDPE	High-density Polyethylene
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
NNT	Number Needed to Treat
NSAID	Non-steroidal Anti-inflammatory Drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
OTC	Over-the-counter
PAR	Public Assessment Report
PGA	Patient Global Assessment
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PP	Per Protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RH	Relative Humidity
RMP	Risk Management Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Diclofenac HTP 1%, gel from Healthypharm B.V.

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 Diclofenac HTP 1% is built up gradually during the first week of the treatment.
A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a bibliographic application based on the well-established medicinal use of diclofenac. The active substance is a phenylacetic acid derivative and an NSAID. It has been registered in the Netherlands for decades in various pharmaceutical forms (tablet, injection, suppository, suspension, gel) for the treatment of pain and inflammation in various conditions.

No new (pre)clinical studies were conducted. The MAH submitted non-clinical and clinical overviews based on scientific literature. This is accepted as this type of application does not require submission of the results of pre-clinical or clinical trials. It should be demonstrated that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. 'Well-established use' refers to the use for a specific therapeutic use.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Diclofenac HTP 1% is a white, smooth, homogeneous gel, with a slight characteristic odour and pH between 6.0 and 8.0.

The gel contains 10 mg of diclofenac sodium per 1 g of gel, which corresponds with 9.3 mg/g diclofenac.

The excipients are sodium hydroxide, hydroxyethylcellulose, carbomere, propylene glycol, triglycerides, methyl parahydroxybenzoate (E218), propyl parahydroxy-benzoate (E216), and purified water.

The product is packed in a 100 g aluminium (Alu) tube with a HDPE cap.

II.2 Drug Substance

The active substance is diclofenac sodium, an established active substance described in European Pharmacopoeia (Ph.Eur.). The active substance is sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), and slightly soluble in acetone. No different polymorphic forms have been observed for diclofenac sodium. Several diclofenac salts are available.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEP with additional requirements for particle size, ethylenediaminetetraacetic acid and some additional residual solvents. The specifications and test methods are acceptable. Batch analytical data demonstrating compliance with this specification have been provided by the CEP holder and finished product manufacturer.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 25°C/60%RH (66 months) and 40°C/75% RH (6 months). The results of the stability studies show little to no variation in impurities and assay at both storage conditions. Based on the provided data, the proposed re-test period of 5 years is acceptable.

II.3 Medicinal Product

Pharmaceutical development
The development and characterisation of the product has been described in sufficient detail. Over the course of the development, the MAH has adjusted the target pH of the drug product slightly. The microstructure of the gel has been adequately characterized in the pharmaceutical development. Aspects as indicated in the Ph.Eur. monograph on semi-solid preparations for cutaneous application (i.e. Rheological properties and Particle size distribution) are sufficiently discussed. The choice of the excipients, including the preservative, is justified, their function suitably explained. The choice for the container closure system (aluminium (Alu) tube) is adequate.

Manufacturing process
The process consists of weight, mixing of all ingredients and filling in the tubes. As the active substance is dissolved in the drug product, the manufacturing process can be considered a standard process. Validation data have been provided. The limits for in-process controls for viscosity and pH will be re-evaluated and further tightened post approval.

Control of excipients
The excipients comply with their respective Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests description, average fill, pH, identification and assay of preservatives and active substance, related substances, viscosity, density and microbiological purity. The methods are adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches.
The limit for viscosity should be re-evaluated when stability results of batches manufactured with adjusted pH are available. As the dynamic of the active substance is located below the dermis, a routine in-vitro release test is expected (see commitments listed in section II.4 Discussion on chemical, pharmaceutical and biological aspects).

Stability of drug product
Stability data on the product has been provided on three batches of pilot scale and three batches of full scale stored at 25°C/60%RH (12-36 months), 20°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in aluminium tubes. Variation was noted for the assay of preservatives and the active substance. Consequently the tests method has been adjusted. Validation data confirmed that the improved method is suitable. As the product is packed in an aluminium tube, photostability is not addressed, which is acceptable.
Based on the submitted stability data a shelf-life of 24 months is justified. Stability data has been provided to demonstrate that the product remains stable after first opening of the container. An in-use shelf life of 3 months has been granted. The product should be stored below 30°C.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Diclofenac HTP 1% gel has a proven chemical-pharmaceutical quality. Controls have been laid down for the active substance and finished product.

Concerning safety, the proposed product contains preservatives methylparaben and propylparaben. There concentrations are usual and have been accepted for this formulation. According to the Guideline 'Excipients in the label and package leaflet of medicinal products for human use' the labelling of a medicinal product for oral, topical, and parenteral use should always include the warning 'May cause allergic reactions (possibly delayed)'. On the other hand, different to Voltaren emulgel, the proposed product does not contain a fragrance (perfume).

The following post-approval commitments were made:
- In view of the observed impact of a slight change in pH on viscosity, the range of the in-process control for pH should be tightened.
- Further tightening of the specification for viscosity should be re-evaluated when stability results of batches manufactured with adjusted pH are available.
- As the dynamic of the active substance is located below the dermis, a routine *in-vitro* release test should be laid down and appropriately substantiated.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

Diclofenac is a non-steroidal agent with marked analgesic, antipyretic and anti-inflammatory properties. It is an inhibitor of prostaglandin synthesis (cyclo-oxygenase). In the EU, the sodium salt of diclofenac is a well-known active substance in registered medicinal gel products for cutaneous use to reduce inflammation and as an analgesic reducing pain in certain conditions.

The MAH has not provided additional studies. Further studies are not required, since a non-clinical overview based on literature review is appropriate for this application. The pharmacodynamics, pharmacokinetics and toxicology of diclofenac sodium for topical cutaneous use are well-known. Animal experiments with sodium or diethylammonium salts of diclofenac formulated in an emulsion cream or gel, respectively showed that diclofenac sodium is absorbed through the skin into in the tissue underlying the site of application and is only gradually released into the systemic circulation.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since other, comparable formulations are registered in the Netherlands, approval of the marketing authorisation application for Diclofenac HTP 1%, gel is not expected to lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

The active substance in Diclofenac HTP 1% is diclofenac sodium, a phenylacetic acid derivative and a non-steroidal anti-inflammatory drug (NSAID). Diclofenac is a well-known active substance with established efficacy and tolerability. Various pharmaceutical forms have been registered in the Netherlands for decades for the treatment of pain and inflammation in various conditions.

The following indication was initially applied for:
'Diclofenac HTP 1% is indicated as anti-inflammatory and analgesic agent in the treatment of mild to moderate muscle pain, bruises and post-traumatic pain.'

The last two indications were dropped in the second round of assessment, leaving only the mild to moderate pain indication.

However, this indication was not approvable and the Board intended to reject the application, as:
- well-established used of diclofenac was not adequately demonstrated.
- bridging of the product to the literature was lacking.
- the provided literature overview did not sufficiently demonstrate the efficacy of topical diclofenac in the sought indications.

The above mentioned reasons for non-approval of the initially claimed indications were discussed in a hearing with the MAH on 4 April 2016. In this meeting, the company indicated that they would amend the indication in line with Voltaren Emulgel, the only topical NSAID on the market in the Netherlands. The indication was adapted to:
'Diclofenac HTP 1% is indicated for the local alleviation of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and the fingers.'

The MAH stated that they would provide the necessary documentation to demonstrate well-established use in this indication, an overview of efficacy, as well as further support for bridging between the literature and Diclofenac HTP.

The submitted documentation is discussed below.

IV.2 Justification for well-established use

The justification for well-established use focusses on the following points:
1) The time over which the substance has been used
2) Quantitative aspects of the use of the substance
3) The degree of scientific interest in the use of the substance
4) The coherence of scientific assessments
5) Documentation covering all aspects of the safety and/or efficacy assessment
6) Missing information
7) Relevance of the submitted data in view of differences between formulations, and relevance of post-marketing experience

The MAH's argumentation is presented below.

1) The time over which the substance has been used

According to European Union reference dates, 1977 is the date of the first marketing authorization of a medicine containing diclofenac as active substance. The Directive refers to the active substance in a specific medical use, independently of strength and dosage form. The use of diclofenac 1% gel for the therapeutic indication osteoarthritis is known since 1987.

The following reference dates are taken into account:

- 39 years since the active substance diclofenac started to be used in the specific medical use of the application (Voltaren tablets) – reference date for well-established use applications
- 29 years since the first diclofenac gel 1% (Voltaren gel, 1987)
- 18 years since approval of the first similar product (Veral gel, 1998, Czech Republic)
- 10 years since approval of a product which is identical to Diclofenac HTP (Dagesil, 2006, Portugal)

2) Quantitative aspects of the use of the substance

The MAH discussed the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods.

NSAIDs are among the most widely used medicines in the world because of their demonstrated efficacy in reducing pain and inflammation (Ong *et al.* 2007), with topical diclofenac as one of the most widely used NSAIDs (McPherson & Cimino 2013). In an examination of sales of NSAIDs in 15 countries performed in 2011, diclofenac and etoricoxib together account for approximately one-third of all sales of NSAIDs in these countries. There was no difference between high- and low-income countries. Diclofenac was by far the most popular NSAID (McGettigan & Henry 2013). Diclofenac is to a large extent used in arthritis. The quantitative aspects of the use of the substance for the proposed therapeutic indication can be observed not only by the extensive published literature, but also by the sales data of diclofenac gel 1% in the EU, demonstrating the level of exposition. The total exposition in 2015 is 177.413 thousand units.

Moreover, since 2013 EMA carries out single assessments of related PSURs for medicines containing the same active substances. According to the timelines defined in Guideline on Good Pharmacovigilance Practices (GVP), the last submission date for diclofenac topical formulations, was December 2015. The PSUR submission frequency is 3 years. In the Eudravigilance database 425 products are listed that are formulated as diclofenac gel (172 contain sodium, 228 diethylamine and 24 contain epolamine). The list of medicinal products containing diclofenac and respective designation of the active substance introduced in the Eudravigilance database has been presented.

Diclofenac HTP corresponds to the product Dagesil which has been marketed in Portugal since 2007. The last Periodic Safety Update Report covered the time period from 28 April 2011 to 30 September 2015. The available data confirmed that diclofenac remains an effective and well tolerated medication for the treatment of its indicated disorders when administered as recommended. The safety of this marketed product is monitored on a continuous basis by the on-going pharmacovigilance activities. For this reason, no additional risk-benefit analysis was planned.

3) The degree of scientific interest in the use of the substance

The MAH indicates that topical diclofenac has a high degree of interest in the scientific community confirmed by the number of publications retrieved from Pubmed in the last 5 years with the term “topical diclofenac”, which is 262. In 2015 there were 66 articles published and the MAH refers to 22 articles published in 2016:

- 4 clinical trials (diclofenac as active control for symptomatic pain in OA, efficacy in ocular surgery post-operative pain, treatment of cyclic mastalgia, pain associated with OA of the knee);
- 3 *in vitro* and *in vivo* studies regarding topical diclofenac delivery (new formulation, ocular delivery and active control as active ingredient);
- 3 pharmacodynamic studies;
- Studies in other therapeutic indications.

One of the publications from 2016 is a prospective, randomised, complete crossover study regarding safety aspects, where it was concluded that topical diclofenac does not significantly interfere with the antiplatelet effects of aspirin and may be a safer alternative to the oral formulation (Rowcliffe *et al*. 2016).

Additionally in 2016 a review study was published regarding the efficacy and safety of topical NSAIDs in the management of osteoarthritis that assesses evidence from real-life setting trials and surveys,

where it was concluded that topical NSAIDs have a moderate effect on pain relief, with efficacy similar to that of oral NSAIDs, with the advantage of a better risk/benefit ratio. In real-life studies, topical and oral NSAIDs demonstrate an equivalent effect on knee pain over 1 year of treatment, with fewer adverse events due to lower systemic absorption compared with oral NSAIDs. As a result, topical NSAIDs may be the preferred treatment option, especially in OA patients aged 75 years, and those with comorbidities or at an increased risk of cardiovascular, gastrointestinal or renal side effects. Furthermore, using topical NSAIDs in inflammatory rheumatic diseases leads to a 40% reduction in the need for concomitant oral NSAIDs (Rannou *et al.* 2016).

4) The coherence of scientific assessments

The MAH states that there is extensive clinical evidence demonstrating the clinical efficacy of topical NSAIDs in the management of osteoarthritis. Treatment with topical NSAIDs can help to improve the functional capacity of patients, resulting in improved mobility (Huskinsson 2010). Topical NSAID therapy has been recommended as the first line therapy before the use of systemic NSAIDs by all of guidelines of recognised health professional and scientific societies/committees involved in clinical research and practice in the field of pain and musculoskeletal diseases. According to these guidelines, evidence suggests that treatment with a topical NSAID is at least as effective as systemic NSAID therapy.

Table 1. Management of osteoarthritis and pain guidelines

GUIDELINE	RECOMMENDATION
NHG – Pain Standard 2015	*Acute and chronic nociceptive pain: Diclofenac gel 2-4 times daily 1-3% included as one of the proposed step 2 medications. Other step 2 medications include oral or rectal diclofenac, oral naproxen and oral, rectal or topical ibuprofen*
American Association of Orthopaedic Surgeons (AAOS) 2013	*Knee OA*: Strongly recommend oral or topical NSAIDs or tramadol for the pharmacologic management of patients with symptomatic OA of the knee.
American College of Rheumatology (ACR) 2012	*Hand OA*: Initial management of hand OA should include one or more of the following - topical capsaicin - topical NSAIDs, including trolamine salicylate - oral NSAIDs, including COX-2 inhibitors - tramadol *Knee OA*: Initial management of knee OA should include one of the following - acetaminophen - oral NSAIDs - topical NSAIDs - tramadol

	- intra-articular corticosteroid injections • Topical rather than oral NSAIDs should be used in patients with hand or knee OA aged ≥75 years
American Geriatric Society (AGS) 2009	• *Hand OA*: Topical treatments are recommended over systemic treatments, especially for mild to moderate pain and when only a few joints are affected
American Pain Society (APS) 2002	• *Hand or Knee OA*: Topical NSAIDs and capsaicin have clinical efficacy and are safe in the treatment of hand or knee OA
European League Against Rheumatism (EULAR) 2003, 2007	• *Hand OA*: Topical treatments are recommended over systemic treatments, especially for mild to moderate pain and when only a few joints are affected • *Hand or Knee OA*: Topical NSAIDs and capsaicin have clinical efficacy and are safe in the treatment of hand or knee OA
National Institute for Health and Clinical Excellence (NICE, United Kingdom) 2014	• Topical NSAIDs should be considered for pain relief in addition to nonpharmacologic treatment • o Topical NSAIDs and/or acetaminophen should be considered ahead of oral NSAIDs, COX-2 inhibitors, or opioids
Osteoarthritis Research Society International (OARSI) 2008	• *Knee OA*: Topical NSAIDs and capsaicin may be effective as adjunctives and alternatives to oral analgesics/anti-inflammatory agents in patients with knee OA

The analysis of available guidance justifies the position of Diclofenac HTP 1% gel in the therapeutic indication currently approved in the Netherlands, i.e. 'local alleviation of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and the fingers.'

According to information provided by the Association of the European Self-Medication Industry (AESGP), topical diclofenac has been accepted as a non-prescription medicinal product in multiple EU countries.

5) Documentation covering all aspects of the safety and/or efficacy assessment

The MAH submitted a review of the relevant literature and included several evidences, not only data related to tests and trials. It concerns information about the medical use of approved products in the EU, not only for the indication proposed but for all the approved therapeutic indications in several member states. It includes information about the recognized OTC use and a PRAC review. It is declared that the product is currently on the Portuguese market with a proven safety profile (PSUR submitted in the application) and that there are similar products on the market in Portugal, Spain and Czech Republic. Estimated sales for all similar products are 454 thousand units in the period of 2015.

6) Missing information

No specific studies were carried out with Diclofenac HTP. The MAH emphasises that there is consistent evidence that diclofenac is safe and effective for topical application for management of mild to moderate pain related to osteoarthritis in several pharmaceutical forms (ointment, gel, solution, patches). Dagesil - identical to Diclofenac HTP - has proven efficacy and safety and has been on the market in Portugal since 2007.

Several well-established use applications have been approved in the EU for diclofenac gel 1%, based on the following attributes:

- Different diclofenac salts (sodium, epolamine, diethylamine)
- Different formulations
- Indications "local symptomatic local relief of pain in acute strains, sprains or contusions following blunt trauma, Adults: local symptomatic relief of pain and inflammation in: - trauma of the tendons, ligaments, muscles and joints, e.g. due to sprains, strains and bruises -

localised forms of soft tissue rheumatism - the relief of pain of non-serious arthritic conditions."
- No clinical studies or *in vitro* studies to support similarity performance to existing formulations (information available from PARs).
- No safety or efficacy concern and thus no serious concern for public health.

Moreover, the MAH argues that its *in vitro* studies bridge the skin permeation performance of their product to other products on the market.

7) Relevance of the submitted data in view of differences between formulations, and relevance of post-marketing experience

The MAH indicated that:
- o Regardless of the salt, topical diclofenac is safe and effective
- o Regardless of the formulation in excipients, topical diclofenac is safe and effective
- o Regardless of the type of dosage form, topical diclofenac is safe and effective

Data related to the level of exposure of diclofenac gel 1% in the therapeutic indication osteoarthritis is only available in the Netherlands since this is the only member state where this medicinal product is exclusively used in osteoarthritis. Therefore, with the exception of Netherlands, the exposure data presented concerns all therapeutic indications of topical diclofenac.

The MAH estimates that the exposition for the specific indication approved in the Netherlands represents approximately 50% of all European diclofenac gel 1% sales. This would mean an estimated exposition of close to 90.000 thousand units in the year 2015.

IV.3 Discussion on well-established use

Well-established use of topical diclofenac in the treatment of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and of the fingers is considered demonstrated. The active substance has been used in OA for decades, and it has an established position in therapeutic guidelines, also as a topical formulation. The quantitative aspects of well-stablished use have also been fulfilled as diclofenac as an active substance is widely used in osteoarthritis and in the Netherlands, the sales of Voltaren Emulgel which has the sought indication were 45 thousand units in 2015.

IV.4 Justification for bridging

For this well-established use application there is no legal requirement to show 'clinical equivalence' to literature data. This is mentioned in Annex I to Directive 2001/83/EC:
With respect to the provisions on 'well-established medicinal use' it is in particular necessary to clarify that 'bibliographic reference' to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.

The MAH argued that millions of units of diclofenac medicinal products have been sold in the EU in different formulations with high levels of pharmacovigilance monitoring and with recognised safety and efficacy obtained from real use experience. This can be considered valid proof that the global literature data from reviews and therapeutic guidelines applies to this particular product in the same extent that it applies to any diclofenac gel 1% that fulfils the scientific and quality criteria to be placed on the market. This is in accordance with the concept of well-established use.

The MAH further argued that the critical quality attributes are similar to currently marketed products and provided an *in vitro* skin permeation test that showed a comparable permeation performance of Diclofenac HTP to Sandoz Schmerzgel, Dolotren Gel and Voltaren Emulgel. The MAH also argued that there is good *in vitro-in vivo* correlation for diclofenac. The MAH conducted additional tests, in comparison to Voltaren Emulgel, to answer to questions raised by the MEB regarding pharmaceutical attributes, and states that:

1) Results for physical-chemical specifications are similar
2) Differential Scanning Calorimetry shows that diclofenac is completely dissolved in the gel, like Voltaren Emulgel.
3) Gel microstructure is very similar confirmed by microscopic view.
4) The difference in the mean size of droplets from test product and Voltaren Emulgel was very small.
5) Physical stability prediction by Zeta Potential determination revealed that both products have systems physically with good and comparable stability.
6) The content of diclofenac in both phases showed that the partition of the active substance between aqueous phase and lipophilic phase was equivalent, which means that diclofenac base (independent of the salt) is readily available from the aqueous phase in the same proportion as Voltaren Emulgel (60-70%).

The MAH concluded that the *in vitro* test together with the pharmaceutical results are robust data that show that the test formulation has the same performance as products already on the market and in literature references. From a chemical-pharmaceutical point of view bridging between the literature and Diclofenac HTP is sufficiently justified.

IV.5 Discussion on bridging

Several suitable products for bridging in this case were identified from literature, including Voltaren Emulgel (1.16% diethylamine salt), on which the applicant focuses in the pharmaceutical development. Differences in the proposed product and the product(s) from literature were noted among others with respect to the active substance (salt), gelling agent, solvents/preservatives, liphilic vehicle, lipophilic vehicle/emulgator, alkalizing agent. All these aspects were adequately discussed. An in-vitro release study was performed to support the application, however, this is not considered a validated clinical method.

The *in-vitro* comparison provided by the MAH focuses on the proposed product compared to Voltaren Emulgel 1.16%. No data on comparison with the other relevant formulations from literature have been provided.

Although the pH and viscosity do not differ much from the pH and viscosity of Voltaren Emulgel, other differences still exist between the proposed product and Voltaren Emulgel which include difference in salt form (sodium versus diethylamine), globule sizes, different gelling agent, differences in solvent/excipients/preservatives, and difference in alkalizing agents

An in-vitro release study (via a Modified Franz Diffusion Cell system) was performed. The *in-vitro* release (artificial membrane) is found to be different to Voltaren Emulgel. There was no significant difference in *in-vitro* skin permeation (excised human skin). However, the *in-vitro* release method used is not a generally accepted method to demonstrate therapeutic equivalence of topical products with a site of action below the dermis.

Both the proposed product and Voltaren emulgel are o/w emulsion gel and permeation through the skin occurs from this aqueous phase. It has been demonstrated (via phase partition determination) that the fraction diclofenac (%) in the aqueous phase is similar in both products (%). As the pH is similar in both products, diclofenac will be present in this aqueous phase fully as anion, so the difference between sodium salt and diethylamine salt is not relevant in this respect. The gradient between the aqueous phase and skin, which is the driving force for the permeation, will therefore also be comparable. Diclofenac transported from the aqueous phase through the skin will be replenished with diclofenac present in the lipophilic globules as depot until exhaustion of that depot. In this respect, the difference of size of the globules will not limit this replenishing.
Although there is a difference in gelling agents, there is only a small difference in viscosity and density.

However the available efficacy data across different topical diclofenac gel and solution formulations is considered supportive for bridging between literature and Diclofenac HTP 1%, as irrespective of formulation, efficacy has been demonstrated as described in section IV.6.. In this respect, the in-vitro

release study (artificial membrane) is over-discriminating. Much larger differences in in-vitro release profile compared to the proposed product can be assumed for the other formulation.

In conclusion, the bibliographic data can be bridged to the proposed product as efficacy of topical gel and solution containing diclofenac as active substance has been demonstrated, irrespective of product formulation.

IV.6 Justification for efficacy of topical diclofenac in the sought indication

Efficacy of topical diclofenac sodium in patients with osteoarthritis of the knee or hand has been demonstrated in a number of controlled studies. The majority of these studies were placebo controlled studies. In addition, three active controlled studies have been conducted.
The MAH presented a summary of the data gathered in double-blind, controlled studies demonstrating the efficacy of topical diclofenac to support the indication.

Published clinical double-blind studies
Results of individual placebo controlled studies
Study designs and results of double blind, placebo controlled studies using either diclofenac gel or solution conducted in patients with osteoarthritis of the knee or fingers are included in the dossier. All studies demonstrated superior efficacy of topical diclofenac over placebo. No safety concerns were noted.

Derry *et al*. (2012) provided a comprehensive overview of individual double-blind, placebo controlled studies using the clinical success rate following a Cochrane review on topical NSAID in treatment of chronic musculoskeletal pain. They defined clinical success as a 50% reduction in pain, or an equivalent measure such as a “very good” or “excellent” global assessment of treatment, or “none” or “slight” pain on rest movement, measured on a categorical scale.

Ten studies comparing a topical diclofenac formulation with placebo were included in their overview of success rates obtained in individual clinical studies (Altman 2009, 1% diclofenac sodium gel; Baer 2005, 1.5% diclofenac sodium solution; Baraf 2011, 1% diclofenac sodium gel; Bookman 2004, 1.5% diclofenac sodium solution; Brühlmann 2003, patch; Dreiser 1993, patch; Grace 1999, 2% diclofenac sodium gel; Niethard 2005, 1.16% diclofenac diethylamine gel; Roth 2004, 1.5% diclofenac sodium solution) and one comparing a topical diclofenac with both placebo and an oral NSAID (Simon 2009, 1.5% diclofenac sodium solution).

Results of the clinical success rates were reported by treatment duration, 2-3 weeks, 4-6 weeks and 8-12 weeks. The clinical success rate was higher in all studies. The effect appeared to be most pronounced in the studies up to 6 weeks of treatment although it was still statistically significant in studies up to 12 weeks of treatment.

Placebo controlled studies meta-analysis
The 2012 Cochrane review ‘Topical NSAID in treatment of chronic musculoskeletal pain’ (Derry *et al.* 2012) also included a meta-analysis on clinical success rates. In addition, two studies using a plaster and two studies with unpublished data were included. In total, twelve studies comparing a topical diclofenac with placebo (102- 93-1 [unpublished data; 108-97 [unpublished data]; Altman 2009; Baer 2005; Baraf 2011; Bookman 2004; Brühlmann 2003 (patch); Dreiser 1993 (patch); Galeazzi 1993 (plaster); Grace 1999; Niethard 2005; Roth 2004), one comparing a topical diclofenac with both placebo and an oral NSAID (Simon 2009), and two comparing topical diclofenac with only an oral NSAID (Tugwell 2004; Zacher 2011) were included.
The clinical success rates, relative benefit (RR) and number needed to treat (NNT) by treatment duration are presented in the table below.
Clinical success was defined as a 50% reduction in pain, or an equivalent measure such as a “very good” or “excellent” global assessment of treatment, or “none” or “slight” pain on rest or movement, measured on a categorical scale. Studies of short duration (2 to 3 weeks) reported patient global evaluations, while studies of longer duration (4 to 12 weeks) used more strictly defined criteria (≥ 50% pain relief or OARSI).

Table 2. Topical diclofenac versus placebo

Study duration	Number of studies	Number of participants	Success with topical NSAID (%)	Success with placebo (%)	RR (95% CI)	NNT (95% CI)
Topical diclofenac						
2 to 3 weeks	4	569	40	20	2.0 (1.5 to 2.6)	5.0 (3.6 to 7.8)
4 to 6 weeks	2	375	48	28	1.7 (1.3 to 2.2)	5.2 (3.5 to 11)
8 to 12 weeks	4	2440	60	50	1.2 (1.1 to 1.3)	10 (7.3 to 17)

Notes:
Efficacy at 2 to 3 weeks: topical diclofenac (patch or gel); Brühlmann 2003; Dreiser 1993; Grace 1999; Niethard 2005; 284 participants were treated with diclofenac and 285 with placebo.
Efficacy at 4 to 6 weeks: topical diclofenac (solution - Pennsaid); Baer 2005; Bookman 2004; 189 participants were treated with diclofenac and 186 with placebo.
Efficacy at 8 to 12 weeks: topical diclofenac (gel or solution); Altman 2009; Baraf 2011; Simon 2009; 1234 participants were treated with diclofenac and 1206 with placebo.

In addition an analysis of efficacy between topical diclofenac gel (n=4 studies) and solution (n=4 studies) was conducted. Although the authors concluded that formulation can influence efficacy, the difference in effect did not reach statistical significance.
No direct comparison was made between the gel and solution diclofenac formulations. Moreover, no studies with short term duration were conducted with diclofenac solution. The interpretation of the observed numerical differences between formulations is therefore seriously hampered.

A pooled analysis was performed by Baraf *et al.* in 2011 in which the data from three 12-weeks studies were pooled to evaluate the efficacy of diclofenac sodium gel 1%, both in patients below 65 years and above 65 years. This analysis included both patients with knee osteoarthritis aged 25–64 (n=602) and ≥ 65 (n=374) years. Patients in each age group applied > 90% of scheduled doses. Among patients aged 25–64 years, the improvement from baseline to week 12 (least squares mean [standard error]) was greater for diclofenac sodium gel versus vehicle for WOMAC (Western Ontario and McMaster Universities) pain (-5.8 [0.3] vs -4.7 [0.3], p=0.007), WOMAC physical function (-17.9 [0.9] vs -14.2 [0.9], p=0.002), global rating of disease ((-29.5 [1.6] vs -23.8 [1.6], p=0.01) and pain on movement (-37.3 [1.8] vs -29.0 [1.8], p < 0.001). Among patients aged ≥ 65 years, the improvements from baseline for most efficacy outcome scores were significantly greater with diclofenac sodium gel versus vehicle: WOMAC pain (-5.3 [0.3] vs -4.1 [0.4], p=0.02), WOMAC physical function (-15.5 [1.1] vs -11.0 [1.1], p=0.004) and pain on movement (-33.7 [2.2] vs -26.4 [2.2], p=0.02).
The authors concluded that diclofenac sodium gel 1% was effective across age groups for treatment of knee osteoarthritis. Furthermore, the authors concluded that efficacy of diclofenac sodium gel did not differ significantly between patients aged 25–64 years and 65 years.

The 50% response rate for diclofenac sodium and placebo as well as number needed to treat at 2 and 4 weeks observed in Cochrane analysis are similar to those observed in trials conducted with oral NSAIDs and cox inhibitors as analysed by Moore *et al.* (2010).

Active comparative studies
Three active controlled studies were found in literature.

Tugwell *et al.* (2004) conducted a study in 622 patients with radiological evidence of primary knee OA and mild to severe symptoms comparing topical diclofenac solution (Pennsaid, 1.5% w/w diclofenac sodium in a vehicle solution containing 45.5% w/w dimethyl sulfoxide (DMSO) three times daily 50 drops) to oral diclofenac (50 mg three times daily) capsules in a double dummy, double blind design. Efficacy variables were pain and physical function, measured by the WOMAC OA Index, and patient global assessment (PGA). Equivalence in the per-protocol group was based on previously defined ranges of clinically significant difference.

Pain improved by 44% vs 49% (p=0.23), physical function improved by 39% vs 46% (p=0.06), stiffness by 39% vs. 45% (p=0.24) and PGA by 43% vs 49% (p=0.13), all topical vs oral diclofenac group, respectively.
The difference in mean (95% CI) change scores between treatments was 13.3 mm (-8.6 to 35.2) for pain (total scale 500 mm), 71.0 mm (-2.4 to 144.5) for physical function (total scale 1700 mm), and 4.3 mm (-1.2 to 9.8,) for PGA (total scale 100 mm). The difference between treatments for each efficacy variable fell within the predefined equivalence ranges (pain, ± 75 mm; physical function, ± 255 mm; PGA, ± 20 mm), indicating that no clinically relevant difference was found between the 2 treatment arms. Therefore, the authors concluded that application of this topical diclofenac solution produced relief of symptoms equivalent to oral diclofenac.

Simon *et al.* (2009) evaluated the safety and efficacy of topical diclofenac in 775 patients with knee osteoarthritis in a confirmatory 12-week, 5-arm randomised controlled study. The study included a topical diclofenac arm (Pennsaid, 1.5% w/w diclofenac sodium in a vehicle solution containing 45.5% w/w DMSO), a placebo arm, a DMSO vehicle arm, an oral diclofenac arm (100 mg slow release) and a combination arm of topical diclofenac plus oral diclofenac to assess combined treatment. Co-primary efficacy variables were WOMAC pain and physical function and a patient overall health assessment. Secondary variables were WOMAC stiffness and patient global assessment (PGA) of the knee osteoarthritis.

Results showed that topical diclofenac was superior to placebo for pain (6.0 vs. 4.7, p=0.015), physical function (15.8 vs. 12.3, p=0.034), overall health (0.95 vs. 0.37, p < 0.0001), and PGA (1.36 vs. 1.01, p=0.016), and was superior to DMSO vehicle for all efficacy variables. No significant difference was observed between DMSO vehicle and placebo or between topical diclofenac and oral diclofenac.
The authors concluded that topical diclofenac in DMSO vehicle is an effective treatment option for knee osteoarthritis with efficacy similar to, but tolerability better than oral diclofenac. DMSO vehicle was no more efficacious than placebo.

Zacher *et al. (*2011) reported the results of a multi-centre, randomised, double blind, active controlled double dummy study of 3 weeks duration in 327 patients with activated painful OA of the fingers. The study compared the efficacy and safety of Voltaren Emulgel 1.16% gel applied 4 times daily as a 10 cm ribbon of ointment (165 subjects, mean age 60.7 years) versus oral ibuprofen 400 mg taken three times daily (156 subjects, mean age 63.2 years). 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 Visual Analogue Scale (VAS). 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 reduction of pain in both groups was comparable. Measured on the VAS, the pain decreased by 24.5 mm (topical diclofenac group) and 21 mm (ibuprofen group) during treatment. In the case of the secondary outcome variables, a comparable improvement in symptoms was observed for all values in both treatment groups.
The authors concluded that a 21-day topical treatment for active osteoarthritis of the finger joints (Heberden's and/or Bouchard's nodes) with diclofenac is at least as efficacious as systemic treatment with ibuprofen.

Response rates were also calculated in the Cochrane review of Simon *et al.* and Tugwell *et al*.:

- Simon (2009) compared 40 drops of 1.5% topical diclofenac solution with DMSO (Pennsaid) administered four times daily with a slow release 100 mg oral diclofenac tablet taken once daily, for 12 weeks. The response rate was 47% (73/154) with diclofenac solution and 51% (77/151) with diclofenac tablets (response: ≥ 50% pain relief).

- Tugwell (2004) compared 50 drops of 1.5% topical diclofenac solution with DMSO (Pennsaid) with a 50 mg oral diclofenac tablet administered three times a day for 12 weeks. The response

rate was 66% (201/303) with diclofenac solution and 70% (210/301) with diclofenac tablets (response: OMERACT-OARSI).

IV.7 Clinical safety

The MAH presented an overview of adverse events observed in all the reviewed literature, including studies in osteoarthritis, actinic keratoses, thrombophlebitis and mastodynia.

Patients exposed
In all the reviewed trials there were altogether 1682 patients exposed to topical diclofenac. Their age ranged from 11 to 94 years and 47.7% were male.

Adverse events
The most frequently observed adverse events were pruritus, rashes, erythema and paresthesia, which resolved spontaneously upon discontinuation of the therapy. The overall incidence of possibly drug-related above-mentioned adverse events was 2.11% (32 patients). The treatment was discontinued for these adverse reactions in 6 patients from 1632 ones (0.37%). Systemic adverse events, mainly mild gastrointestinal ones, such as nausea or epigastric pain, occurred in 2 cases from 1632 patients (0.12%).

Although planned, the applicant could not perform a meta-analysis across placebo-controlled studies for differences in adverse events between diclofenac and placebo, as only one of the placebo-controlled studies reported adverse events. A fixed-effect meta-analysis was performed across four studies that compared diclofenac to piroxicam. The pooled relative risk for skin adverse reactions of diclofenac versus piroxicam was 1.44 (95% Ci 0.73 – 2.83) indicating that there was no difference between the treatments.

As topical diclofenac in the sought indications is intended for short-term use, long-term safety is not discussed in this report.

Adverse events of special interest

Gastrointestinal adverse events
The MAH briefly discusses the risk of gastrointestinal adverse events during treatment with topical diclofenac.

A case-control study of Evans et al (1995) in 1103 patients admitted to hospital for upper gastro-intestinal bleeding or perforation found no significant association between topical NSAIDs and these events. The study did not differentiate between NSAIDs.

The MAH has found four reports of gastro-intestinal haemorrhage after treatment with topical diclofenac (Zimmerman et al, 1995). However, in two of these cases diclofenac was used for the treatment of lower back pain which was retrospectively shown to be caused by peptic ulcer. In the other two cases the patients had a prior history of peptic ulcer. A review by Rosenstein et al (1999) report gastro-intestinal adverse events with several NSAIDs, however excluding diclofenac. An epidemiologic study by Figueras et al (1994) analyzing spontaneous ADRs reports in the database of the Spanish System of Pharmacovigilance identified one case of gastrointestinal bleeding from duodenal ulcer that may be attributed to topical piroxicam.

Renal and hepatic events
Acute renal failure has been reported for other topical NSAIDs but not for diclofenac. The applicant did not identify any reports of severe hepatic failure associated with the use of topical diclofenac.

Phototoxicity
It has been shown that the carbazole photodegradation product of diclofenac is a phototoxic agent (Moore 2002). However the product is quickly degradated further.
The MAH identified a case report where photoallergic contact dermatitis was associated with topical diclofenac use (Montoro et al, 2003). The adverse reaction was confirmed with a photopatch test.

Safety in special patient groups

Elderly and patients with comorbidities

In one randomized, double-blind, placebo-controlled trial including 1426 with mild to moderate osteoarthritis of the knee and 783 patients with mild to moderate osteoarthritis of the hand treated with topical diclofenac, no differences were found in the incidence of adverse events between patient aged <65 years and ≥65 years.

In patients with osteoarthritis of the knee, there were no differences in the incidence of adverse events between patients with and without comorbidities (hypertension, type 2 diabetes mellitus, cerebrovascular or cardiovascular disease). In patients with osteoarthritis of the hand, the incidence of adverse events was lower in patients with versus without type 2 diabetes mellitus and higher in patients with versus without cerebrovascular or cardiovascular disease.

Reference to this study was not given.

Patients with asthma

As it is known that up to 10% of asthmatic patients are intolerant to aspirin and other nonsteroidal anti-inflammatory drugs, reacting with bronchospastic and/or naso-ocular symptoms when these agents are administered (Swierczynska M et al, 2003), also topical diclofenac should be used with caution in patients with asthma.

Paediatric patients

The safety and efficacy in children has not been established.

Use in pregnancy and lactation

The use of topical diclofenac in early stages of pregnancy should be limited to cases where the potential benefit justifies the potential risk to the fetus.

Because prostaglanding-inhibiting drugs are known to have an effect on the fetal cardiovascular system and the kidneys the use of diclofenac should be avoided in late pregnancy (Jansen et al, 2000; Stone et al, 2002)

Because diclofenac can be found in mother's milk, use of topical diclofenac is not recommended in nursing mothers.

IV.8 Discussion on the clinical aspects

For this well-established use authorisation, reference is made to data from the literature.

The MEB considers studies performed with gel formulations, but also topical solutions relevant for the discussion on efficacy and bridging. Eight randomised, double-blind, placebo-controlled studies are discussed below, grouped by the product applied in the study:

- Voltaren gel (1% sodium salt), two studies
- Voltaren Emulgel (1.16% diethylalamine salt), one study
- Diclofenac sodium 2% gel, one study
- Diclofenac sodium 1% gel, one study
- Pennsaid (1.5% solution, sodium salt, with DSMO in the carrier), three studies

- Voltaren gel (1% sodium salt)

Altman et al. (2009)

The study by Altman et al. was a randomised, double-blind, placebo-controlled trial in patients diagnosed with primary OA in the dominant hand. Patients were randomised to self-apply topical 1% diclofenac sodium gel (Voltaren) (N=198) or vehicle (N=187) to both hands 4 times daily for 8 weeks. The primary outcome measures were OA pain intensity in 100-mm VAS. Total Australian/Canadian Osteoarthritis Hand Index (AUSCAN) score, and global rating of disease activity.

At week 8, change in OA pain intensity score from baseline (SD) was 35.5 (28.9) in the topical diclofenac group as compared to 29.6 (29.5) in the vehicle group (p=0.06). At week 4, change in OA pain intensity score from baseline (SD) was 31.1 (25.8) in the topical diclofenac group as compared to 23.9 (27.0) in the vehicle group (p=0.018). Already at week 1, topical diclofenac was statistically superior to vehicle in reduction of pain score and AUSCAN score. Global rating of disease was statistically significantly different between the study groups only at week 6. Use of rescue medication (paracetamol) was comparable between the treatment groups.

Baraf et al. (2011)
This was a randomised, double-blind, placebo-controlled trial in patients diagnosed with OA in one or both knees. Patients were randomised to self-apply 4 g of topical 1% diclofenac sodium gel (Voltaren) (N=208) or vehicle (N=212) to symptomatic knee(s) 4 times daily for 12 weeks. The primary outcome measures were WOMAC pain and physical function subscales and global rating of benefit at week 12. Pain on movement at week 4 (VAS) was an additional primary endpoint for European regulatory purposes.
At week 12, change in WOMAC pain score from baseline (SD) was 6.8 (4.5) in the topical diclofenac group as compared to 5.4 (4.5) in the vehicle group (p=0.008). Change in WOMAC physical function score from baseline (SD) was 21.5 (15.3) in the topical diclofenac group as compared to 16.8 (15.7) in the vehicle group (p=0.004). At week 4, change in pain intensity score on movement from baseline (SD) was 36.3 (24.3) in the topical diclofenac group as compared to 30.8 (24.1) in the vehicle group (p=0.03). Already at week 1, topical diclofenac was statistically superior to vehicle in reduction of WOMAC subscale scores and pain on movement. Global rating of benefit was not statistically significant between the treatment groups at any assessment point.

- Voltaren Emulgel (1.16% diclofenac diethylalamine)

Niethard et al (2005)
This was a randomised, double-blind, placebo-controlled trial in patients diagnosed with OA of the knees. Patients were randomised to sell-apply 4 g of topical 1.16% diclofenac diethylalamine gel (Voltaren Emulgel) (N=117) or vehicle (N=121) to symptomatic knee(s) 4 times daily for 3 weeks. Patients recorded daily pain on movement, spontaneous pain and pain relief, and every week efficacy was assessed at the study centre by pain intensity in the target knee, WOMAC pain score and in the end of the study as global evaluation of treatment.
At week 3, change in pain intensity score from baseline (SD) was 34 (26) in the topical diclofenac group as compared to 25 (24) in the vehicle group (p=0.006). Change in WOMAC pain score from baseline (SD) was 22 (21) in the topical diclofenac group as compared to 14 (23) in the vehicle group (p=0.0002). Already at week 1, topical diclofenac was statistically superior to vehicle in reduction of pain intensity score but not in WOMAC pain score. At the end of the study, patients rated diclofenac gel as significantly more effective in treating the pain of OA of the knee (p = 0.03) with 69% rating it as “good”, “very good” or “excellent” compared to only 58% for placebo. Use of rescue medication (paracetamol) was comparable between the treatment groups.

- Diclofenac sodium gel, 2%

Grace et al (1999)
This was a randomised, double-blind, placebo-controlled trial in patients diagnosed with OA of the knee. Patients were randomised to self-apply 2.5 g of topical 2% diclofenac sodium gel (N=38) or vehicle (N=36 to symptomatic knee 3 times daily for 2 weeks. The primary outcome measures were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score and subscale scores.
At week 2, change in WOMAC total score from baseline (SD) was -12.6 (13.3) in the topical diclofenac group as compared to -3.3 (17.1) in the vehicle group (p=0.05). Change in WOMAC pain score from baseline (SD) was -16.5 (15.2) in the topical diclofenac group as compared to -4.4 (22.6) in the vehicle group (p=0.05). Change in WOMAC physical function score from baseline (SD) was -12.0 (13.4) in the topical diclofenac group as compared to -3.2 (17.7) in the vehicle group (p=0.05). Global rating of benefit was not statistically significant between the treatment groups.

- Diclofenac sodium gel, 1%

Barthel et al (2009)
This was a randomised, double-blind, placebo-controlled trial in patients diagnosed with OA of the knee. Patients were randomised to self-apply 4 g of topical 1% diclofenac sodium gel (N=254) or vehicle (N=238) to symptomatic knee 4 times daily for 12 weeks. The primary outcome measures were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscales and global rating of disease at week 12.
At week 12, change in WOMAC pain score from baseline was -5.0 in the topical diclofenac group as compared to -4.0 in the vehicle group (p=0.01). Change in WOMAC physical function score from baseline was -15.0 in the topical diclofenac group as compared to -10.9 in the vehicle group (p=0.001). Change in global rating of disease from baseline was -27.0 in the topical diclofenac group as compared to -18.2 in the vehicle group (p<0.001). Statistically significant differences between the treatment groups in each endpoint were demonstrated starting from week 1.

- Pennsaid solution, 1.5% diclofenac sodium with DSMO

Bookman et al (2004)
This was a randomised, double-blind, placebo-controlled trial in patients diagnosed with OA of the knee. Patients were randomised to self-apply 40 drops (1.3 ml) of topical 1.5% diclofenac sodium solution (Pennsaid, containing DSMO) (N=84), vehicle (containing DSMO) (N=80) or placebo (N=84) to symptomatic knee 4 times daily for 28 days. The primary outcome measures was Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale.
At day 28, change in WOMAC pain score from baseline was -3.9 (95% CI -4.8,-2.9) in the topical diclofenac group, -2.5 (95% CI -3.3,-1.7) in the vehicle group and -2.5 (95% CI -3.3,-1.7) in the placebo group as compared to -4.0 in the vehicle group ($p<0.05$ compared to vehicle and placebo). Secondary endpoints WOMAC physical function and stiffness score, as well as pain on waling and patient global assessment supported the primary analysis. Data from earlier assessments than week 4 were not presented in the article.

Roth et al (2004)
This was a randomised, double-blind, placebo-controlled trial in patients diagnosed with OA of the knee. Patients were randomised to self-apply 40 drops (1.3 ml) of topical 1.5% diclofenac sodium solution (Pennsaid, containing DSMO) (N=164) or vehicle (containing DSMO) (N=162) to symptomatic knee 4 times daily for 12 weeks. The primary outcome measures were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscales and patient global assessment.
At week 12, change in WOMAC pain score from baseline (SD) was -5.9 (4.7) in the topical diclofenac group and -4.3 (4.4) in the vehicle group ($p<0.005$). Change in WOMAC physical function score from baseline (SD) was -15.4 (15.3) in the topical diclofenac group and -10.1 (13.9) in the vehicle group ($p<0.005$). Change in patient global assessment from baseline was (SD) was -1.3 (1.2) in the topical diclofenac group and –0.9 (1.2) in the vehicle group ($p<0.005$). Data from earlier assessments than week 12 were not presented in the article.

Baer et al (2005)
This was a randomised, double-blind, placebo-controlled trial in patients diagnosed with OA of the knee. Patients were randomised to self-apply 40 drops (1.3 ml) of topical 1.5% diclofenac sodium solution (Pennsaid, containing DSMO) (N=107) or vehicle (containing DSMO) (N=109) to symptomatic knee 4 times daily for 6 weeks. The primary outcome measures were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and physical function subscales and patient global assessment.
At week 6, change in WOMAC pain score from baseline (SD) was -5.2 (5.0) in the topical diclofenac group and -3.3 (4.3) in the vehicle group ($p=0.003$). Change in WOMAC physical function score from baseline (SD) was -13.4 (16.3) in the topical diclofenac group and -6.9 (13.2) in the vehicle group ($p=0.001$). Change in patient global assessment from baseline was (SD) was -1.3 (1.3) in the topical diclofenac group and –0.7 (1.1) in the vehicle group ($p=0.0001$). Data from earlier assessments than week 6 were not presented in the article.

Conclusion
The efficacy of topical diclofenac gel and solution in reduction in pain in OA of the hand and knee was demonstrated across these studies. The most recent EMA guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis recommends a 3 week assessment point for topical NSAIDs as this is considered maximum efficacy point over placebo. The presented studies using diclofenac gels demonstrated efficacy in pain reduction starting from week 1 which continued at least up to 3 weeks.
The use of rescue medication in many studies was comparable between the study groups, however paracetamol could be taken to any pain and it was not further specified in the studies to what extent rescue medication was used for the OA pain.

No data from a three-arm study including diclofenac gel, placebo and an oral NSAID is available. A study by Simon *et al* (2009) investigated the efficacy of topical diclofenac solution (Pennsaid) compared to vehicle, placebo and oral diclofenac in knee OA. In this study, change from baseline in WOMAC pain score at week 12 was comparable in the topical and oral diclofenac group, both separated from the placebo and vehicle arm. This study suggests that topical diclofenac is as effective as oral diclofenac in the treatment of pain associated with OA. However, the publication does not

present results from earlier assessment points at week 4 and 8, thus it is not clear whether there are differences in onset of efficacy and during the SmPC proposed treatment duration of 3 weeks.

No conclusion can be drawn from the active-controlled study by Zacher et al, in which Voltaren Emulgel was compared to oral 400 mg ibuprofen in hand OA, due to lack of placebo arm.

Overall the efficacy was shown in placebo controlled studies of topical diclofenac gel and there is some supportive evidence for comparable effect to oral NSAIDs. The available efficacy data support bridging between literature and Diclofenac HTP 1%, irrespective of the existing differences between the formulations.

The overall safety profile of diclofenac 1% gel is considered acceptable. The safety profile of (topical) diclofenac is well known. Most common adverse events after topical administration of diclofenac are local skin reactions including rash, eczema and pruritus. Diclofenac HTP gel contains parabens, which can cause an allergic reaction. This is mentioned in SmPC section 4.4. On the other hand, unlike Voltaren Emulgel, the product does not contain perfume, which can be considered a benefit. Moreover, the product has been marketed in Portugal since 2007 without safety problems.

As expected after topical administration for a short period of time, the incidence of systemic adverse events (mainly involving the gastrointestinal tract) in the reviewed studies is low. However it is possible that after topical administration of diclofenac to large surface areas, the systemic absorption increases and the risk of gastrointestinal adverse events increases, which is mentioned in the SmPC section 4.4.

Diclofenac has a potential for phototoxic reactions. This is reflected in SmPC section 4.4..

The safety profile of topical diclofenac in elderly and patients with comorbidities seems to be comparable to the overall patient population, excluding patients with asthma. NSAIDs as a class should be administered with caution to patients with asthma, this includes also topical NSAIDs. These are mentioned in the SmPC section 4.4.

IV.9 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Diclofenac HTP 1%, gel.

Table 3. Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Serious skin reactions including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis	Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects	NA
Use during pregnancy	Included in SPC section(s) • 4.3 Contraindications • 4.6 Fertility, pregnancy and lactation	NA
Important potential risks		
None	None	NA
Missing information		
Use in children and adolescents	Included in SPC section(s) • 4.2 Posology and method of administration	NA

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. A bridging report has been submitted, referring to the successfully user tested PL for Diclofenac Phagecon gel 10 mg/g. Bridging regarding layout is justified, as the MAH's in-house style has been user tested and approved in previous procedures.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Diclofenac HTP 1%, gel has a proven chemical-pharmaceutical quality. Well-established use of topical diclofenac in the treatment of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and of the fingers is considered demonstrated. The active substance has been used in OA for decades, and it has an established position in therapeutic guidelines, also as a topical formulation. The quantitative aspects of well-stablished use have also been fulfilled as diclofenac as an active substance is widely used in osteoarthritis and in the Netherlands, the sales of Voltaren Emulgel which has the sought indication were 45 thousand units in 2015.

The following indication was initially applied for:
'Diclofenac HTP 1% is indicated as anti-inflammatory and analgesic agent in the treatment of mild to moderate muscle pain, bruises and post-traumatic pain.'

However it was considered that well-established use in the proposed indication was not demonstrated, and that bridging between the formulations referred to in the literature and Diclofenac HTP was not

sufficiently justified. Moreover, the provided literature overview did not sufficiently demonstrate the efficacy of topical diclofenac in the sought indications.

The MAH subsequently dropped the last two indications in the second round of assessment, leaving only the mild to moderate pain indication.

The application was discussed in the Board meeting of 26 November 2015. The Board considered that well-established use in the proposed indication was not demonstrated, and that bridging between the formulations referred to in the literature and Diclofenac HTP was not sufficiently justified.

Following a hearing on 4 April 2016, the company agreed to narrow the indication in line with Voltaren Emulgen, i.e. to the treatment of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and of the fingers. Documentation was submitted to demonstrate well-established use in this indication. The efficacy was substantiated, and further support for bridging between the literature and Diclofenac HTP was provided.

The submitted literature is considered sufficient to support the efficacy of topical diclofenac gel and solution containing either sodium or diethylalamine salt in the local treatment of pain in hand and knee osteoarthritis. Eight randomised, double-blind placebo-controlled trials in patients with hand or knee OA demonstrated a statistically significant and clinically relevant reduction in pain starting from week 1 and lasting at least up to 3 weeks.

The duration of effect of topical diclofenac gel in the treatment of pain in hand and knee OA is uncertain. Some of the provided studies demonstrated efficacy up to 12 weeks while in others the efficacy wore out during the treatment phase. Long-term use of topical diclofenac on large areas may increase the risk of systemic adverse events. The SmPC limits the use of Diclofenac HTP gel up to three weeks, which is acceptable.

Most common adverse events after topical administration of diclofenac are local skin reactions. The overall safety profile of diclofenac 1% gel is considered acceptable.

None of the formulations used in the presented literature are identical to Diclofenac HTP 1% gel. The MAH has presented comparative quality data for Voltaren Emulgel and the proposed product, which demonstrate differences in some characteristics as discussed in section II.4. However the available efficacy data across different topical diclofenac gel and solution formulations is considered supportive for bridging between literature and Diclofenac HTP 1%, as irrespective of formulation, efficacy has been demonstrated.

In the Board meeting of 2 June 2016 the responses of the MAH were discussed. Based on the totality of data provided in the dossier, the MEB considers the overall benefit/risk balance of Diclofenac HTP 1% gel positive.
Bridging between the literature and Diclofenac HTP has been sufficiently justified, and well-established use of diclofenac gel in the revised indication has been demonstrated. The MEB has therefore granted a marketing authorisation. Diclofenac HTP was authorised in the Netherlands on 9 June 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
- Type IB: B.II.b.5.a; - Type II: B.II.d.1.e	- Change to in-process tests or limits applied during the manufacture of the finished product; tightening of in-process limits - Change in the specification parameters and/or limits of the finished product; change outside the approved specifications limits range	No	23-05-2018	Approved	-
Type IB: B.II.e.5.d	Change in pack size of the finished product; change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products	Yes	02-01-2018	Approved	-

List of literature references

Altman RD, Dreiser RL, Fisher CL, Chase WF, Dreher DS, Zacher J. Diclofenac sodium gel in patients with primary hand osteoarthritis: a randomised, double-blind, placebocontrolled trial. J Rheumatol. 2009;36(9):1991-9.

Baer PA, Thomas LM, Shainhouse Z. Treatment of osteoarthritis of the knee with a topical diclofenac solution: a randomised controlled, 6-week trial [ISRCTN53366886]. BMC Musculoskelet Disord. 2005;6:44

Baraf HS, Gloth FM, Barthel HR, Gold MS, Altman RD. Safety and efficacy of topical diclofenac sodium gel for knee osteoarthritis in elderly and younger patients: pooled data from three randomised, double-blind, parallelgroup, placebo-controlled, multicentre trials. Drugs Aging. 2011 Jan 1;28(1):27-40.

Barthel HR, Haselwood D, Longley S 3rd, et al. Randomised controlled trial of diclofenac sodium gel in knee osteoarthritis. Semin Arthritis Rheum 2009;39(3): 203–12.

Bookman AA, Williams KS, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomised controlled trial. CMAJ. 2004;171(4):333-8

Brühlmann P, Michel BA.: Topical diclofenac patch in patients with knee osteoarthritis: a randomised, double-blind, controlled clinical trial. Clin Exp Rheumatol 2003; 21: 193 – 198.

Topical diclofenac patch in patients. Clinical and Experimental Rheumatology. 2003; 21:193–8. [PubMed: 12747273]

Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2012 Sep 12;9:CD007400

Dreiser 1993, Dreiser RL, Tisne-Camus M: DHEP plasters as a topical treatment of knee osteoarthritis – a double-blind placebo-controlled study. *Drugs Exp Clin Res* 1993; 19: 117 – 123.

Grace D, Rogers J, Skeith K, Anderson K. Topical diclofenac versus placebo: a double blind, randomised clinical trial in patients with osteoarthritis of the knee. *J Rheumatol*. 1999;26(12):2659–2663

Huskisson EC. Modern management of mild-to-moderate joint pain due to osteoarthritis: a holistic approach. J Int Med Res. 2010 Jul-Aug;38(4):1175-212.

McGettigan P, Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. PLoS Med. 2013;10(2):e1001388.

McPherson ML, Cimino NM. Topical NSAID formulations. Pain Med. 2013 Dec;14(1):S35-9.

Moore RA, Moore OA, Derry S Peloso PM, Gammaitoni AR, Wang H. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. Ann Rheum Dis 2010;69:374–379

Niethard FU, Gold MS, Solomon GS, Liu JM, Unkauf M, Albrecht HH, *et al*. Efficacy of Topical Diclofenac Diethylamine Gel in Osteoarthritis of the Knee. J Rheumatol. 2005 Dec;32(12):2384-92.

Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clin Med Res. 2007 Mar;5(1):19-34.

Rannou F, Pelletier JP, Martel-Pelletier J. Efficacy and safety of topical NSAIDs in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Semin Arthritis Rheum. 2016 Feb;45(4 Suppl):S18-21. Epub 2015 Dec 2.

Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution (Pennsaid) in the treatment of primary osteoarthritis of the
knee: a randomised, double-blind, vehicle-controlled clinical trial [see comment]. Arch Intern Med 2004 Oct 11; 164 (18): 2017-23

Rowcliffe M, Nezami B, Westphal ES, Rainka M, Janda M, Bates V, Gengo F. Topical diclofenac does not affect the antiplatelet properties of aspirin as compared to the intermediate effects of oral diclofenac: A prospective, randomised, complete crossover study. J Clin Pharmacol. 2016 Apr;56(4):422-8.

Simon LS, Grierson LM, Naseer Z, Bookman AA, Zev Shainhouse J. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared with those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. Pain. 2009 Jun;143(3):238-45.

Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (pennsaid) compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomised controlled trial. J Rheumatol. 2004 Oct;31(10):2002-12.

Zacher J, Burger KJ, Farber L, Grave M, Abberger H, Bertsch K. Topical Diclofenac Emulgel Versus Oral Ibuprofen in the Treatment of Active Osteoarthritis of the Finger Joints (Heberden's and/or Bouchard's Nodes): A Double-Blind, Controlled, Randomised Study. Postgraduate Medicine. 2011 Sep 123(5):1941-9260.