COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Kruidvat diclofenac 1%, gel

(diclofenac sodium)

NL License RVG: 122124

Date: 8 June 2020

This module reflects the scientific discussion for the approval of Kruidvat diclofenac 1%, gel. The procedure was finalised at 25 October 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NSAID	Non-steroidal Anti-inflammatory Drug
OA	Osteoarthritis
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) has granted a marketing authorisation for Kruidvat diclofenac 1%, gel, from MAE Holding B.V.

The product is indicated for local alleviation of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and the fingers.

The effect of Kruidvat diclofenac 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 non-steroidal anti-inflammatory drug (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

Kruidvat diclofenac 1% is a white, smooth, homogeneous gel, with a slight characteristic odour. 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, hydroxyethyl cellulose, carbomer, 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 sealing membrane closed by 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 a white or slightly yellowish, slightly hygroscopic, crystalline powder and 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 Ph.Eur.

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 for one full-scale batch demonstrating compliance with the specification.

Stability of drug substance

Stability data on the active substance have been provided for three batches stored at 25°C/60%RH (66 months), 40°C/75% RH (6 months) and 25 °C/60% RH (3 months). Based on the provided data, the proposed re-test period of 5 years is acceptable. The storage restriction is store in air tight container, protected from light.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. A discussion has been provided on the selection of excipients and proposal for a formulation. Further testing was done on the test product and literature reference products, mainly Voltaren Emulgel 1%. Despite using different excipients

and the salt of active substance, the formulation used in Kruidvat diclofenac 1% has been shown to have similar pharmaceutical behaviour supporting a well-established use application. Parameters tested were optical microscopy, laser diffraction, zeta potential, penetrometry, viscosity, infrared spectroscopy, differential scanning calorimetry and high performance liquid chromatography. *In vitro* release and *in vitro* permeation studies were performed using Voltaren Emulgel 1% as well as other literature reference products. Overall, the pharmaceutical development has been adequately described.

Manufacturing process

The process consists of weighing, homogenizing, mixing, cooling and filling in the tubes. The description of the process is in sufficient detail. The manufacturing process is regarded a non-standard process and process validation data on the product has been provided for three full scale batches.

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, density, viscosity, identification and assay of preservatives and active substance, related substances, microbiological purity and *in vitro* release test. The methods are adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches demonstrating compliance with the proposed release specification.

Stability of drug product

Stability data on the product has been provided on several full-scale batches stored at 25°C/60%RH (up to 24 months), 30°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. 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 for 3 months after first opening of the container. The product should be stored below 30°C and not in a refrigerator or freezer.

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 Kruidvat diclofenac 1%, gel has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitments were made:

- The MAH agreed to re-evaluate the shelf-life limits for the viscosity test after completing the stability studies.
- The MAH agreed to present the results for preservative efficacy testing at 24 months and 36 months when available.

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 Kruidvat diclofenac 1% 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

Diclofenac is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why

there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.
The submitted dossier is based on already published scientific literature to substantiate the clinical efficacy and safety of the product for the proposed indication to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years.

IV.2 Pharmacokinetics

The provided literature references presented by the MAH demonstrate that transdermal penetration of diclofenac after topical administration is highly variable between subjects and formulations. Further, the dose of a topical formulation is difficult to standardise for comparison between products as little as 1 mg or 1 ml more or less applied product affects the administered dose. Therefore extrapolation of reported effects of one topical diclofenac product to another is difficult.
The possible differences in transdermal penetration between different diclofenac salts is unclear. The study by Galzigna *et al* (1989) investigated the pharmacokinetics of diclofenac following application of two formulations containing different diclofenac salts. However pharmacokinetic parameters could not be computed because of low number of measurements. Vincent *et al* (1999) studied percutaneous absorption of five NSAID-containing gels *in vitro*, including two different salts of diclofenac: epolamine and sodium. The difference between two diclofenac gels in diffusion efficacy however was not statistically significant. In addition, the provided pharmacokinetic data suggest that systemic absorption is rather low, and thus should not result in adverse events related to systemic exposure.

IV.3 Pharmacodynamics

Diclofenac primarily reduces pain and inflammation by inhibiting COX-2. This mechanism of action is considered established. The MAH has presented various studies in which the pharmacodynamics effects of topical diclofenac were assessed. These studies confirm that topical diclofenac's mechanism of action functions indeed by inhibiting COX-2 activity, thereby reducing inflammation. Furthermore the onset of action is fast, within the first few hours after application, thus providing fast relief to patients. This mechanism of action is considered to be well established, even though it is not yet fully understood.

IV.4 Clinical efficacy

The MAH has presented studies that provide evidence for the clinical efficacy of topical diclofenac sodium for various musculoskeletal (pain) conditions. Only the studies in support of the indication i.e. OA in the knee/hand are presented here. The following six studies were presented in detail in the clinical overview by the MAH.

Grace et al. (1999)

Grace D et al, in 1999 assessed the efficacy and safety of a topical formulation of 2% diclofenac in lecithin organogel in the treatment of pain associated with mild to moderate osteoarthritis (OA) of the knee in 70 patients. Patient responses to disease-specific (WOMAC VA3.0) and quality of life (Medical Outcome Survey SF-36) health status measures were assessed. Global assessments were made at baseline and post-treatment. The physician conducted a global assessment and range of motion of the knee at baseline and posttreatment. Patients received a 2 week supply of 500 mg paracetamol tablets with PHLO-JEL containing 2% diclofenac as the active gel or the gel alone as placebo. The medication was self-administered 3 times daily at about the same time intervals for 2 weeks.

The table below shows the patients' baseline scores and change scores on the full WOMAC index. It can be seen that on the WOMAC total score and individual subscale scores the treatment with Diclofenac Sodium produces a significant reduction in score when compared to the placebo gel.

Table 1 WOMAC total and subscale item mean scores by group (Grace *et al., 1999)*

	Active. n = 34 X ± SD	Placebo. n = 34 X ± SD
WOMAC total		
Pretreatment	46.25 ± 16.13	41.04 ± 16.47
Post-treatment	33.62 ± 17.8	37.74 ± 20.33
Pre-post change*,**	−12.63 ± 13.26*	−3.30 ± 17.11
Pain subscale		
Pretreatment	44.68 ± 17.50	39.77 ± 17.89
Post-treatment	28.19 ± 18.31	35.42 ± 19.86
Pre-post change**	−16.49 ± 15.16*	−4.35 ± 22.55
Stiffness subscale		
Pretreatment	49.06 ± 18.60	47.56 ± 20.72
Post-treatment	40.49 ± 22.10	46.09 ± 24.48
Pre-post change	−8.57 ± 20.11*	−1.47 ± 19.04
Physical function subscale		
Pretreatment	46.37 ± 16.51	40.61 ± 18.14
Post-treatment	34.41 ± 18.14	37.44 ± 21.16
Pre-post change**	−11.96 ± 13.37*	−3.17 ± 17.72

*p = 0.05 level within treatment.
**p = 0.05 level between treatments.

Niethard et al. (2005)

In 2005, Niethard et al., assessed the efficacy and safety of topical diclofenac diethylamine gel, 1.16%, (approximately 4 g of gel per dose) applied 4 times a day for 3 weeks to alleviate the symptoms of OA of the knee. 238 patients were randomised to apply either double-blind active or placebo gel for 3 weeks. Paracetamol (up to 2 g/day) was supplied as rescue medication.

Treatments differed significantly for daily pain on movement (POM) at Day 5, and continued on most days through the end of the study. Peak differences were achieved in the second

week. On the primary outcome, average pain on movement over Days 1–14, diclofenac gel was significantly superior to placebo gel. Scores for all 3 WOMAC indices for diclofenac gel treatment were significantly superior to placebo at Weeks 2 and 3. A significant difference was achieved on pain intensity "right now" at all 3 weeks. 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) compared to placebo.

Altman et al. (2009)
The efficacy and safety of diclofenac sodium gel in 385 patients with primary hand OA was measured in a study performed by Altman et al. In this trials patients were randomly assigned to self-apply topical 1% diclofenac sodium gel (Voltaren Gel) (n = 198) or vehicle (n = 187) to both hands 4 times daily for 8 weeks and the primary outcome included OA pain intensity (100-mm visual analogue scale), total Australian/Canadian Osteoarthritis Hand Index (AUSCAN) score, and global rating of disease activity at 4 and 6 weeks.
Diclofenac sodium gel decreased pain intensity scores by 42%–45%, total AUSCAN scores by 35%–40%, and global rating of disease by 36%–40%. Significant differences favouring diclofenac sodium gel over vehicle were observed at Week 4 for pain intensity and AUSCAN, with a trend for global rating of disease activity. At Week 6, diclofenac sodium gel treatment significantly improved each primary outcome measure compared with vehicle. Secondary outcomes (onset of efficacy in weeks 1 and 2, durability of efficacy at 8 weeks, measures of disease activity in the dominant hand, pain intensity in the non-dominant hand, AUSCAN sub indices, end of study rating of efficacy, and Osteoarthritis Research Society International response criteria.) generally supported the primary outcomes. In this trial, diclofenac sodium gel provided sustained symptom reduction in hands affected by OA. These results suggest that topical diclofenac sodium gel should be considered a safe and effective treatment option for patients with hand OA.

Barthel et al. (2009)
The study assessed the efficacy and safety of topical diclofenac sodium 1% gel in 492 patients with mild to moderate symptomatic knee osteoarthritis. Patients received 4 g of diclofenac sodium 1% gel or vehicle 4 times daily for 12 weeks. Primary efficacy outcomes at week 12 were the WOMAC pain subscale, WOMAC physical function subscale, and global rating of disease.
Diclofenac sodium 1% gel showed to be effective in the in alleviation of the symptoms of primary osteoarthritis of the knee and demonstrated that could be a good treatment option for mild to moderate osteoarthritis of the knee in patients who have an increased risk for gastrointestinal, renal, or cardiovascular adverse events, or who prefer not to take systemic therapy.

Baraf et al. (2010)
The study examined the efficacy and safety of topical diclofenac sodium 1% gel for symptomatic knee OA. 420 senior and younger patients were randomly assigned to diclofenac sodium 1% gel 4 g or vehicle 4 times daily to the symptomatic knee(s). Primary endpoints were WOMAC pain and physical function subscales, global rating of benefit at week 12 and pain on movement at week 4. Secondary endpoints included primary outcomes at weeks 1, 4, and 8;

WOMAC stiffness subscale; spontaneous pain; global rating of disease; and global evaluation of treatment.
At week 12, DSG provided significantly greater reductions in WOMAC pain (52.6% vs 43.1%; P = 0.008) and physical function (49.7% vs 39.4%; P = 0.004) versus vehicle and provided significant improvements in most secondary endpoints. This trial demonstrated that topical DSG provide good tolerability and efficacy as a monotherapy for unilateral or bilateral knee OA in senior and younger patients. Diclofenac sodium 1% gel showed that it could be an appropriate option for patients with knee OA consequent to sports injuries who desire effective local pain relief with minimal systemic NSAID exposure.

Baraf et al. (2011)
Later, in 2011, Baraf HS et al., evaluate the safety and efficacy of topical diclofenac sodium 1% gel versus vehicle in patients aged 25–64 or ≥ 65 years who have been diagnosed with knee OA based on pooled data from three 12-week, randomised, double-blind, parallel group, multicentre trials.
After a 1 week analgesic washout, patients applied 4 g of diclofenac sodium 1% gel or vehicle four times daily to one knee and were allowed to use rescue paracetamol up to 4 g/day. The MES included both patients aged 25–64 (n = 602) and ≥ 65 (n = 374) years. Among patients aged 25–64 years, the improvement from baseline to week 12 was greater for diclofenac sodium 1% gel versus vehicle for WOMAC pain, WOMAC physical function, global rating of disease and pain on movement. Among patients aged ≥ 65 years, the improvements from baseline for most efficacy outcome scores were significantly greater with diclofenac sodium 1% gel versus vehicle. Concluding, this study showed that diclofenac sodium 1% gel was effective and generally well tolerated in adults regardless of age. These data support the topical application of diclofenac sodium 1% gel for relief of OA knee pain in elderly and younger patients.

Analysis performed across trials (pooled analyses and meta-analysis)
The MAH has presented results from a few meta-analyses evaluating the efficacy of topical diclofenac against placebo or oral diclofenac. Most of the studies discussed in the meta-analyses are also presented in support for the OA indication in the clinical overview. The presented meta-analyses confirm the conclusions of the presented individual studies in such that topical diclofenac is efficient in reducing joint pain caused by OA of the knee or hand

<u>Conclusion</u>
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 (CPMP/EWP/784/97 Rev. 1) recommends 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. Furthermore, the most common used primary endpoints were the WOMAC scores on the pain and physical function subscales. Use of this endpoint is also in line with the EMA guidelines on Osteoarthritis (CPMP/EWP/784/97 Rev. 1) as it provides an assessment of pain and physical function.

Overall, the submitted literature is considered sufficient to support the efficacy of topical diclofenac gel and solution containing either sodium or diethylamine salt in the local treatment of pain in hand and knee osteoarthritis. The placebo controlled studies demonstrated efficacy of topical diclofenac gel and there is some supportive evidence for comparable effect to oral NSAID.

IV.5 Clinical safety

The MAH presented an overview of adverse events observed in all the reviewed literature, including studies in osteoarthritis, actinic keratosis, thrombophlebitis and mastodynia. Overall the most commonly reported adverse events with topical diclofenac are skin related adverse events such as pruritus and erythema. The incidence of systemic adverse events (mainly gastrointestinal) in the discussed studies is low. This is expected as the product is only applied for a short time, which is also reflected in the SmPC (< 3 weeks).
The safety profile of topical diclofenac in elderly and patient 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. This is also reflected in the SmPC as a contraindication. The overall safety profile of diclofenac 1% gel is considered acceptable.

IV.6 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 Kruidvat diclofenac 1%, gel.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis) - Use in pregnancy especially in the third trimester - Asthmatic patients
Important potential risks	None
Missing information	- Use in paediatric patients

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

IV.7 Discussion on the clinical aspects

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. Diclofenac as an active substance has been used in OA for decades, and it has an established position in therapeutic guidelines, also as a topical formulation.

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. The proposed product contains parabens, which can cause allergic reactions. This is mentioned in the SmPC. Long-term use of topical diclofenac on large areas may increase the risk of systemic adverse events. However this risk is considered small when used according to the proposed SPC. The overall benefit/risk of Kruidvat Diclofenac 1% gel is positive from the clinical perspective. The risk management plan is considered acceptable.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Diclofenac HTP 1%, gel (NL License RVG 116368). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Kruidvat diclofenac 1%, gel has a proven chemical-pharmaceutical quality. The efficacy has been demonstrated for alleviation of mild to moderate joint pain, caused by exacerbation of osteoarthritis of the knee and the fingers and that the safety issues that were identified are adequately addressed by SmPC warnings and the Risk Management Plan. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

The MEB on the basis of the data submitted, considered that well-established use has been demonstrated, and have therefore granted a marketing authorisation on 25 October 2018.

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

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.

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