IPAR

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Voltarol Emulgel Extra Strength 2% w/w Gel

DICLOFENAC SODIUM (as DICLOFENAC DIETHYLAMMONIUM)

PA0030/045/003

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Voltarol Emulgel Extra Strength 2% w/w Gel from Novartis Consumer Health UK Ltd on 14th February 2014 for local symptomatic relief of pain and inflammation in trauma of the tendons, ligaments, muscles and joints and localised forms of soft tissue rheumatism.

This application for a marketing authorisation was submitted in accordance with Article 8(3) of Directive 2001/83/EC, a line extension of the existing PAs 30/45/1 and 30/45/2,Voltarol Emulgel 1% w/w gel and Voltarol Emulgel P 1% w/w gel, respectively. It is a full national application relating to a known active substance.

This product will be available over the counter through pharmacy outlets only.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Voltarol Emulgel Extra Strength 2% w/w Gel
Name(s) of the active substance(s) (INN)	DICLOFENAC DIETHYLAMMONIUM
Pharmacotherapeutic classification (ATC code)	M02A A15
Pharmaceutical form and strength(s)	2% w/w Gel
Marketing Authorisation Number(s) in Ireland (PA)	PA0030/045/003
Marketing Authorisation Holder	Novartis Consumer Health UK Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Voltarol Emulgel Extra Strength 2% w/w Gel

II.2 Drug substance

The active substance is diclofenac diethylamine (diclofenac diethylammonium) an established active substance described in the British Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Voltarol Emulgel Extra Strength is a white, pleasantly perfumed, homogenous, non greasy emulsion in an aqueous gel which contains diclofenac diethylammonium 2.32% w/w corresponding to diclofenac sodium 2% w/w (20mg/g)

The other ingredients include butylhydroxytoluene (E321), carbomers, cocoyl caprylocaprate, diethylamine, isopropyl alcohol, liquid paraffin, macrogol cetostearyl ether, oleyl alcohol, propylene glycol (E1520), perfume eucalyptus sting and purified water.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for semi-solid preparations for cutaneous application, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as aluminium laminated tubes with a polypropylene screw cap in pack sizes of 20, 30 or 50g. Not all pack sizes may be marketed.

Evidence has been provided that the packaging type complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years. This medicinal product does not require any special storage conditions.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Voltarol Emulgel Extra Strenth 2% w/w gel.

III NON-CLINICAL ASPECTS

III.1 Introduction

Diclofenac 2.32% gel (corresponding to 20 mg of diclofenac sodium in 1 gram of gel, or diclofenac sodium 2%), has been developed as a higher-strength formulation of the well-known, globally marketed Voltarol Emulgel The pharmacological and toxicological properties of diclofenac are well known. For this reason the applicant complemented existing experience by additional investigations of the Diclofenac 2.32% gel on local tolerance including sensitizing and photosensitizing tests. In addition a series of toxicology studies were performed to qualify degradation products.

All studies were stated as being performed to GLP standards.

III.2 Pharmacology

Diclofenac is a potent, efficacious and well-established non-steroidal anti-inflammatory drug (NSAID) that has been in widespread therapeutic use for many years. It is well tolerated with a safety profile at least equal to that of any other commonly used NSAID.

Diclofenac has a marked effect on the arachidonic acid cascade. This is primarily a potent inhibition of cyclo-oxygenase (COX) but it also appears to inhibit the production of leukotrienes, probably by enhancing incorporation of arachidonic acid into triglycerides and thereby reducing its availability as a substrate. Consequent on these actions, diclofenac has profound anti-inflammatory, antinociceptive and antipyretic actions, which have been demonstrated by oral treatment in a variety of animal models. Similar anti-inflammatory and antinociceptive effects are apparent when diclofenac is administered topically. For example, topical application of diclofenac sodium showed significant suppression of the inflammatory response in the adjuvant arthritis model and edemas in the paw, skin and ear induced by different chemicals.

Studies with topically applied Voltarol Emulgel, which contains 1.16% diclofenac diethylamine, have also shown anti-inflammatory properties.

As the pharmacological properties of the active substance are well-known, no additional animal pharmacology studies have been performed using the proposed clinical formulation. This is considered to be acceptable from a nonclinical viewpoint.

III.3 Pharmacokinetics

An *in vitro* study was used to compare the skin permeation of diclofenac from the Diclofenac 2.32% gel formulation to that from the marketed Voltarol Emulgel 1%. Diclofenac 2.32% gel contained twice the concentration of the active in Voltarol Emulgel and oleyl alcohol, a permeation enhancer. Diclofenac 2.32% gel delivered 3 times more diclofenac in comparison to Voltarol Emulgel.

Systemic levels following repeated application of 2g Diclofenac 2.32% gel bid for 7 days was similar to systemic exposure after repeated application of 2g Voltarol Emulgel qid for 7 days in humans and was generally below 10 ng/ml.

As the pharmacokinetic properties of the active substance are well-known, no further animal pharmacokinetic studies have been performed using the proposed clinical formulation. This is considered to be acceptable from a nonclinical viewpoint.

III.4 Toxicology

A series of preclinical local safety studies was performed with Diclofenac 2.32% gel to determine its local tolerability which included sensitizing and photosensitising tests. In brief, the topical formulation Diclofenac 2.32% gel was well tolerated in a variety of local toxicity studies, including a 28-day and 90-day dermal irritation and a photoirritation study. Diclofenac 2.32% gel was also not observed to exhibit sensitisation or photosensitisation potential.

Diclofenac related compounds whose specifications (0.5%) at the end of shelf life were above ICH guidelines levels for qualification (CPMP/ICH/2738/99) were qualified.

The studies indicated that the degradation products, at their specified levels were shown to be less toxic than that of the parent compound in acute and/or chronic oral toxicity studies and were not found to be genotoxic in bacterial reversion assays and in *in vitro* chromosomal aberration tests.

As the toxicological properties of the active substance are well-known, no further animal toxicology studies have been performed using the proposed clinical formulation. This is considered to be acceptable from a nonclinical viewpoint.

III.5 Ecotoxicity/environmental risk assessment

The PEC surface water of diclofenac resulting from use of Diclofenac 2.32% gel is 0.93 µg/l. An assessment factor of 10 and NOEC from the most sensitive of the species tested in chronic toxicity tests are used to compute the PNEC. The PEC/PNEC ratio obtained for the active ingredient, diclofenac is less than 1 and show that usage of Diclofenac 2.32% gel is unlikely to represent a risk to the aquatic environment. Diclofenac has no significant bioaccumulation potential and is degraded slowly in the environment. Exposure to sunlight was observed to increase its degradation. The use of Diclofenac 2.32% gel as a human medicinal product is not likely to represent a significant environmental safety risk.

III.6 Discussion on the non-clinical aspects

Overal, Diclofenac 2.32% gel was well tolerated in the local toxicity studies and was not observed to exhibit sensitization potential or photosensitization potential. Based on the non-clinical data and its similarity to the approved and marketed Voltarol Emulgel 1%, the use Diclofenac 2.32% gel for the relief of pain, inflammation and swelling in soft tissue injuries, soft tissue rheumatism and for the relief of pain due to osteoarthritis is supported from a non-clinical perspective.

IV CLINICAL ASPECTS

IV.1 Introduction

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

Pharmacovigilance System

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.2 Pharmacokinetics

The quantity of diclofenac absorbed through the skin is proportional to the size of the treated area, and depends on both the total dose applied and the degree of skin hydration. Studies show that the amount of diclofenac absorbed is quite low relative to tablets. Diclofenac is metabolised mainly in the liver and mainly excreted in the urine.

IV.3 Pharmacodynamics

Pharmacodynamics

Diclofenac 2.32% gel is an anti-inflammatory and analgesic preparation designed for topical application. Inhibition of prostaglandin synthesis is the primary mechanism of action of diclofenac. Prostaglandins are substances which mediate pain and inflammation in the body. In inflammation and pain of traumatic or rheumatic origin, Diclofenac 2.32% gel relieves pain and decreases swelling.

Local tolerability studies in the skin did not suggest that phototoxic (toxicity from exposure to light), sensitisation, or irritation are likely with Diclofenac 2.32% gel when used as directed.

IV.4 Clinical Efficacy

This application referred to the many studies that have shown that diclofenac reduces pain and inflammation. Studies were provided showing how Diclofenac 2.32% twice a day compared to diclofenac 1.16% (which is already licensed) four times a day. Another study compared twice a day with three times a day administration.

The application is to licence this gel for

For the 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.

Efficacy data were derived from a well-controlled pivotal study, in conjunction with the bridging study looking at blood levels and in conjunction with supportive published clinical studies with diclofenac 1.16% gel. One study demonstrated equivalent systemic (blood) exposure to diclofenac from diclofenac 2.32% gel applied twice a day, whether under non-occlusive or semi-occlusive conditions, and equivalence to diclofenac 1.16% gel applied four times a day. Diclofenac 2.32% gel is therefore intended for the same indications as diclofenac 1.16% gel, i.e. for the relief of pain, inflammation and swelling in soft tissue injuries, and localised forms of soft tissue rheumatism.
The same maximal daily dose and treatment duration as diclofenac 1.16% gel is also recommended for Diclofenac 2.32% gel.

In inflammation and pain of traumatic or rheumatic origin, Diclofenac 2.32% gel in a study of ankle sprain demonstrated that it relieved pain, decreased swelling, and shortened the time to return to normal function.

IV.5 Clinical Safety

The safety profile of Diclofenac 2.32% gel as determined by the clinical development program does not show any new safety issues. In the local tolerability studies, Diclofenac 2.32% gel was shown to have minimal or no irritation, sensitisation or phototoxic potential. Systemic absorption of diclofenac following topical administration of Diclofenac 2.32% gel to healthy volunteers was extremely low and so it is not expected to cause systemic adverse events.

In the major safety population, adverse events were limited to headache, nasopharyngitis, and pain in extremity. No serious or severe reactions occurred. The patients enrolled in the two trials were representative of the population likely to use the drug when it is licensed. This is further supported by the review of safety data for the marketed formulationVoltarol Emulgel 1%, 1.16% gel and other topical diclofenac products.

Periodic Safety Update Reports (PSUR): next PSUR 29/12/2015.

IV.6 Discussion on the clinical aspects

The studies performed for the new formulation, as well as the studies looking at the lower strength of diclofenac gel, provide appropriate assurances that the new formulation works in the conditions proposed and also suggest that no new or additional safety issues arise.

V OVERALL CONCLUSIONS

Diclofenac is a well known nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory and analgesic activities. Applying Diclofenac 2.32% gel topically allows diclofenac to penetrate the skin while maintaining low levels in the blood of the medicine and its breakdown products and so reducing the chance of systemic adverse events. This has been shown in the information and clinical trials results provided for Diclofenac 2.32% gel. Studies looking at blood levels suggest systemic absorption with topically applied NSAIDs is only 3-8% of the total systemic absorption achieved with oral administration.

Further advantages of topical delivery include avoiding the stomach and intestine and avoiding early breakdown of the medicine in the liver.

The use of topical NSAIDs in preference to systemic medications is a valid approach for treating localised lesions with an inflammatory component, a “patient-friendly” alternative since reduced doses and low systemic absorption make them safer for use, especially in the elderly. Ease of administration and patient acceptability may also increase compliance.

The benefits of Diclofenac 2.32 % gel have been established in a clinical program. Diclofenac 2.32% gel is intended for the relief of pain, inflammation and swelling in soft tissue injuries, soft tissue rheumatism and for the treatment of pain due to non-serious arthritis. Efficacy in these indications has already been established for the lower-strength product, and Diclofenac 2.32% gel has been shown to be effective in reducing the symptoms (pain on movement, pain at rest, etc.) of soft tissue injury (ankle sprain).

In inflammation and pain of traumatic or rheumatic origin, Diclofenac 2.32% gel relieves pain, decreases swelling, and shortens the time to return to normal function. In one ankle sprain study, Diclofenac 2.32% gel effectively relieved pain quickly. Due to an aqueous-alcoholic, base the gel also exerts a soothing and cooling effect.

7.1.2 Summary of risks and unanswered

Diclofenac 2.32% gel was well-tolerated in five clinical trials in this development programme. Adverse events were typical background medical issues that arise in any population observed for one or a few weeks and not specific to patients treated with Diclofenac 2.32% gel.
There were no unexpected adverse events relative to the known adverse event profile of diclofenac 1.16% gel. There was no evidence of toxicity to any particular body system with Diclofenac 2.32% gel. Local tolerability was good, with little evidence of any irritation, sensitisation or phototoxic potential.

The overall safety profile of the topical Diclofenac 2.32% gel is favourable.

7.2 Recommended use and overall

The benefit risk assessment for this new formulation of topical diclofenac is considered positive for the local symptomatic relief of pain and inflammation in adults and adolescents over 14 years in:

-trauma of the tendons, ligaments, muscles and joints,
e.g. due to sprains, strains and bruises.
-localised forms of soft tissue rheumatism.

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

The HPRA, on the basis of the data submitted, considered that Voltarol Emulgel Extra Strength 2% w/w gel demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

From a quality perspective the overall assessment outcome of Voltarol Emulgel Extra Strength 2% w/w gel is positive. Voltarol Emulgel 2% w/w is a line extension of Voltarol Emulgel and Voltarol Emulgel P 1% w/w gel, a well known medicinal product with a proven chemical-pharmaceutical quality.

VII UPDATES

VI. Update

This section reflects the significant changes following finalisation of the initial procedure.

Scope	Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/ non approval
Change in legal status form prescription to over the counter through pharmacy outlets only.	2152813 This was linked to crn 2149800	Section 4.2	2/10/2014	7/1/2015	Approved