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Public Assessment Report

Scientific discussion

Diclofenac Renantos 10 mg/g gel

DICLOFENAC SODIUM

CZ/H/0792/001/DC

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This module reflects the scientific discussion for the approval of Diclofenac Renantos. The procedure was finalised on 10.12.2019. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Diclofenac Renantos 10 mg/g gel, from Renantos Pharmavertriebsgesellschaft mbH, Germany.

The product is indicated for the local symptomatic treatment of mild to moderate acute muscle pain, pain in acute sprains, strains and contusions following blunt trauma in adults and for local symptomatic short-term treatment of pain in acute sprains, strains and contusions following blunt trauma in adolescents aged 14 years and over.
A comprehensive description of the indications and posology is given in the SmPC.

The medicinal product contains diclofenac sodium as an active substance. Diclofenac is a non-steroidal anti-inflammatory drug that has been widely used for many years to treat mild to moderate pain and inflammation. As with all NSAIDs, diclofenac works by inhibiting the action of cyclooxygenase (COX), an enzyme that converts arachidonic acid into prostaglandins (PGs), thromboxanes (TX), and prostacyclins.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC. The concerned member states were BE, DE, IT, LU and PT.

To support the application based on literature review, the Applicant submitted *in vitro* release and permeation tests.

No Paediatric Investigation Plan (PIP) has been submitted.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for this product.

A break-out session has been held during the CMDh Plenary. For more details please refer to section VI of this assessment report.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as a gel, each gram of gel contains 10 mg of *Diclofenac sodium.*

The product is packaged in the aluminium tube with epoxy-phenolic coating and closed by aluminium membrane, with a high-density polyethylene screw cap as described in section 6.5 of the SmPC. The packed sizes are 60 g or 100 g of gel.

II.2 Drug Substance

The product contains an active substance called *Diclofenac sodium* {chemical name: Sodium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate}.

The active substance is described in Ph. Eur. A copy of the current Certificate of Suitability has been presented. Additional tests (residual solvents and particle size) are included in the specifications.

Manufacture
The active substance manufacturer holds a certificate of suitability of the Ph. Eur. Monograph. All aspects of the manufacture and control of the active ingredient are therefore covered by the certificate of suitability.

Stability
Diclofenac sodium is packed in a double polyethylene bag placed in either a polyethylene or a fibre drum.
According to the results of the stability tests, the re-test period is required 5 years from the date of manufacture and the storage condition for *Diclofenac sodium* is established as “Store in an air-tight container, protected from light.”

II.3 Medicinal Product

Pharmaceutical development
The formulation development has been adequately described. The finished product is presented as a white, smooth, homogeneous gel, with a slight characteristic odour.
The product contains conventional pharmaceutical ingredients. Excipients [sodium hydroxide (pH adjustment), hyetellose, carbomer, propylene glycol (E1520), triglycerides, medium chain, propyl parahydroxybenzoate (E218), methyl parahydroxybenzoate (E216), water, purified] are well known and widely used as pharmaceutical excipients and comply with the relevant pharmacopoeia monograph. The function of each excipient is explained.

Adventitious agents
No material of human or animal origin is contained or used in the manufacturing process of the drug product.

Manufacture of the product
A detailed description of manufacturing process is provided. Satisfactory validation has been provided for both pack sizes.

The batch formula, manufacturing process and in-process controls were described in adequate details. The production batch sizes have been stated.

Product specification
The product specification includes appropriate tests for this kind of dosage form (description, average fill, pH, density, viscosity, identification and assay of preservatives, identification and assay of *Diclofenac sodium*, related substances, microbiological quality test). Analytical methods have been satisfactorily described. Validation of the analytical methods has been presented.
Batch analysis has been performed on 5 batches (100 g packaging size) and on 3 batches (60 g packaging size) of the finished product. The batch analysis results comply with the specifications and demonstrate consistent manufacture.

Stability of the product
Stability studies of the finally packaged product have been conducted appropriately in accordance with relevant guidelines. The parameters tested included description, average fill,

pH, density, viscosity, identification and assay of preservatives, identification and assay of *Diclofenac sodium*, related substances, microbiological quality test. A shelf-life of 24 months for the product in a sealed tube and the special storage conditions “Store below 25 °C, do not refrigerate or freeze” were accepted. A shelf-life of 6 months for the product after first opening of the container and the special storage conditions “Store below 25 °C, do not refrigerate or freeze” were accepted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the drug substance and drug product has been satisfactorily presented. The results of tests indicate satisfactory consistency and uniformity of drug product characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinical setting.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of diclofenac sodium are well known. As diclofenac sodium is a widely used, well-known active substance, the Applicant did not provided additional studies and further studies were not required. Overview based on literature review was, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Justification for not providing the fully ERA was provided and based on the fact, that the application did not cover new route of administration or new indication or patient, it was not expected that environmental exposure to diclofenac would increase significantly.

IV. CLINICAL ASPECTS

IV.1 Introduction

As this was an application for a well-established medicine containing a well-known and widely used active substance, the Applicant did not provide any additional clinical studies.

The described literature search strategy was acceptable, the references were submitted as full-texts.

IV.2 Pharmacokinetics

The Applicant provided literature review and two *in vitro* tests to support this section.

During the procedure the Applicant submitted *in vitro* release and permeation tests. These tests were conducted on GLP site and the methods were validated. Based on the results of these tests PK profile of the diclofenac was considered well described. Each study contributes to the conclusion that bridge between Diclofenac sodium gel 10 mg/g and submitted literature references is sufficiently described.

IV.3 Pharmacodynamics

Diclofenac is a non-steroidal anti-inflammatory drug that has been widely used for many years to treat mild to moderate pain and inflammation. As with all NSAIDs, diclofenac works by inhibiting the action of cyclooxygenase (COX), an enzyme that converts arachidonic acid into prostaglandins (PGs), thromboxanes (TX), and prostacyclins.
Diclofenac reduces pain and inflammation by directionally inhibiting COX-2 in the arachidonic cascade, the mechanism of action of topical diclofenac is still not fully understood. Although the concentrations of diclofenac that are observed in the target tissues seem to be sufficient to exert a therapeutic response, it is unclear whether other mechanisms than COX-2 inhibition are also playing a role. For example, the method of application of topical diclofenac (e.g., cream or gel vs. a patch) may be important, as the act of rubbing may have its own beneficial effect (e.g., by activating gating mechanisms and desensitizing local nerve endings).

Pharmacodynamic properties in SmPC reflect information in submitted literature.

IV.4 Clinical efficacy

Musculoskeletal pain

Musculoskeletal pain comprises a wide array of patient disorders, ranging from acute, simple ligament injuries (e.g., ankle sprains), soft-tissue injuries (e.g., sprains, strains and contusions) and tendinopathies, to chronic conditions, including intra-articular disorders (e.g., rheumatoid arthritis and osteoarthritis), muscle pain syndromes (e.g., myofascial pain and fibromyalgia), and various spine-related neck and lower back conditions (e.g., disc degeneration, disc herniation, facet arthropathies, and spondylosis). These disorders are highly prevalent and exact a huge toll in terms of individual quality.

Studies provided by the Applicant as literature references sufficiently support proposed indication of musculoskeletal pain.

IV.5 Clinical safety

The safety profile of diclofenac is well known and adequately described in submitted literature. The Applicant provided comparison of safety profile of topical diclofenac with oral diclofenac or NSAID in general.

IV.6 Risk Management Plan

The Applicant 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 Renantos 10 mg/g gel.

Summary table of safety concerns as approved in the RMP:

Important identified risks	Hypersensitivity reactions Congenital malformations

	Skin reactions due to photosensitivity
Important potential risks	None
Missing information	Use in paediatric population under 14 years of age

Routine pharmacovigilance was suggested and no additional pharmacovigilance activities were proposed by the Applicant, which was endorsed.

Routine risk minimisation measures were considered satisfactory to minimise the risks of this medicinal product.

IV.7 Discussion on the clinical aspects

Efficacy and safety of diclofenac was adequately discussed and supported in approved therapeutic indications by relevant literature references. Based on scientific discussion and *in vitro* tests, the bridge between the product under assessment and literature references was established. The benefit risk of this product was therefore deemed positive.

V. USER CONSULTATION

Full User Testing was not provided by the MAH. However, justification for absence of User Testing was acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the risk-benefit ratio for Diclofenac Renantos 10 mg/g gel was considered positive.

The SmPC, PL and Labelling are satisfactory.

On the grounds of potential serious risk to public health raised during the procedure, a break-out session has been held on the CMDh level. Agreement among the CMSs has been reached that the benefit-risk ratio is favourable for Diclofenac Renantos 10 mg/g gel and that the objection raised should not prevent the granting of a Marketing Authorisation. The decentralised procedure was finalised with a positive outcome on 10.12.2019.

No conditions pursuant to Article 21a or 22 of Directive 2001/83/EC have been made during the procedure.

The commitment regarding the evaluation of the risk of the presence of nitrosamine impurities in the finished product has been submitted during procedure.