Public Assessment Report

UK PAR

Diclodent 0.74 mg/ml Mouthwash (Oromucosal Solution)

(diclofenac acid)

UK Licence No: PL 20117/0112

Morningside Healthcare Limited
Lay Summary

Diclodent 0.74 mg/ml Mouthwash (Oromucosal Solution)
(diclofenac acid)

The product may be referred to as ‘Diclodent Mouthwash’ in this report.

This is a summary of the Public Assessment Report (PAR) for Diclodent Mouthwash (Oromucosal Solution; PL 20117/0112). It explains how the application for Diclodent Mouthwash was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Diclodent Mouthwash. For practical information about using Diclodent Mouthwash, patients should read the package leaflet or contact their doctor or pharmacist.

What is Diclodent Mouthwash and what is it used for?
Diclodent Mouthwash is a ‘generic medicine’. This means that Diclodent Mouthwash is similar to a ‘reference medicine’ already authorised in Italy called Dicloral 0.74 mg/ml Mouthwash (Athena Pharma Italia s.r.l., Italy), which has been authorised since 2001.

Diclodent Mouthwash is used to reduce pain, redness, heat and swelling in the mouth and throat that may be associated with gum disease, or inflammation of the mouth, lips, tongue, or throat, sore throat, or following dental treatment. A mouthwash is also known as an oromucosal solution.

How does Diclodent Mouthwash work?
Diclodent Mouthwash contains the active substance, diclofenac (as diclofenac acid). Diclofenac acid is one of a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).

How is Diclodent Mouthwash used?
Diclodent Mouthwash is available as an oromucosal solution, containing 0.74 mg/ml diclofenac acid for use in the mouth.

The patient should always use Diclodent Mouthwash exactly as the doctor or dentist has advised. The patient should check with the doctor or dentist, if unsure.

This medicine should be gargled or used to rinse (the mouth). Diclodent Mouthwash should not be swallowed.

The usual dose is 15 ml, as a single rinse or gargle, either two, or three times a day.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

This medicine can only be obtained with a prescription.

What benefits of Diclodent Mouthwash have been shown in studies?
No additional clinical studies were needed as Diclodent Mouthwash is a generic medicine that is an aqueous solution and contains the same active substance as the reference medicine, Dicloral 0.74 mg/ml Mouthwash (Athena Pharma Italia s.r.l., Italy).
What are the possible side effects of Diclodent Mouthwash?
Like all medicines, Diclodent Mouthwash can cause side effects although not everybody gets them.

For the full list of all side effects reported with Diclodent Mouthwash, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Diclodent Mouthwash.

Why is Diclodent Mouthwash approved?
It was concluded that, in accordance with EU requirements, Diclodent Mouthwash has been shown to have comparable quality and is considered to be bioequivalent to Dicloral 0.74 mg/ml Mouthwash (Athena Pharma Italia s.r.l., Italy). Therefore, the MHRA decided that, as for Dicloral 0.74 mg/ml Mouthwash (Athena Pharma Italia s.r.l., Italy), the benefits outweigh the identified risks and recommended that Diclodent Mouthwash can be approved for use.

What measures are being taken to ensure the safe and effective use of Diclodent Mouthwash?
A Risk Management Plan has been developed to ensure that Diclodent Mouthwash is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Diclodent Mouthwash, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Diclodent Mouthwash
A Marketing Authorisation was granted in the UK to Morningside Healthcare Limited on 03 March 2016.

The full PAR for Diclodent Mouthwash follows this summary.

For more information about treatment with Diclodent Mouthwash, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2016.
Scientific discussion

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Limited a Marketing Authorisation for the medicinal product Diclodent 0.74 mg/ml Mouthwash (Oromucosal Solution) on 03 March 2016. The product may be referred to as ‘Diclodent Mouthwash’ in this report.

Diclodent Mouthwash is a Prescription Only Medicine (POM), which can be used for the symptomatic treatment of local painful inflammatory diseases of the oral cavity and the throat and/or following dental treatment or dental extraction.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application cross-referring to the reference product Dicloral 0.74 mg/ml Mouthwash (Athena Pharma Italia s.r.l., Italy), which has been authorised in Italy since 2001.

Diclodent Mouthwash contains diclofenac (as diclofenac acid), as the active substance. Diclofenac, a phenyl acetic acid derivative, is a well-known non-steroidal anti-inflammatory drug (NSAID). Diclofenac has a well-known and extremely favourable efficacy/tolerability ratio, however a mouthwash solution containing this substance has not previously been authorised in the UK.

No new non-clinical were submitted, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for this type of application. In accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), a bioequivalence study was not required to support this application for a locally-acting oromucosal aqueous product (mouthwash), containing the same active substance as the reference product. The applicant has submitted bibliographic data to support the application.

No new non-clinical were submitted, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Diclodent Mouthwash outweigh the risks and a Marketing Authorisation was granted.

II QUALITY ASPECTS
II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The medicinal product is available as an oromucosal solution (mouthwash). Each 100 ml of solution contains 0.074% w/v diclofenac free acid as the active substance. The product also contains pharmaceutical excipients namely, sorbitol liquid non crystallising (E420), choline, sodium benzoate (E211), disodium edetate, acesulfame potassium (E950), peppermint oil, peach flavour, Ponceau Red
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(E124) and purified water. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in 200 ml amber (Type III) glass bottles, each with a child resistant polypropylene closure.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Diclofenac acid

Chemical Name: 2-[(2,6-Dichlorophenylamino]benzeneacetic acid
Molecular Formula: C_{14}H_{11}Cl_{2}NO_{2}
Structure

Molecular mass: 296.13
Appearance: White to slightly yellowish hygroscopic, crystalline powder
Solubility: Soluble in methanol and slightly soluble in water
Polymorphism: Polymorphic forms have not been observed in diclofenac free acid and no polymorphic forms of diclofenac free acid has been reported in the literature.

Diclofenac free acid is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, stable, oromucosal solution (mouthwash) that was considered to be bioequivalent to the reference medicinal product,
Dicloral 0.74 mg/ml (Athena Pharma Italia s.r.l., Italy). Suitable pharmaceutical development data have been provided for this application.

With the exception of choline solution and peach flavour, all the excipients comply with their respective European Pharmacopoeia monographs. Choline solution and peach flavour are controlled to a suitable in-house specification. Peach flavour is also in compliance with the current European Directive (Directive 88/388/EC) concerning heavy metal content in flavours.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

**Control of Finished Product**
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with the special storage conditions ‘Store in the original package.’ has been accepted. There are no special temperature storage conditions for this product.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**
A bioequivalence study was not necessary to support this type of application for an aqueous solution for topical use.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for Diclodent Mouthwash.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:
Diclodent 0.74 mg/ml Mouthwash (Oromucosal Solution)

Each ml of the solution contains 0.74 mg diclofenac (free acid).

Contains sorbitol (E420), sodium benzoate (E211) and ponceau red (E124).

See leaflet for further information.

For oral use, not to be swallowed. Read the package leaflet before use.

Keep out of the sight and reach of children.

This medicinal product does not require any special storage conditions.
III  NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of diclofenac free acid are well known. As diclofenac is a well-known active substance, the applicant has not provided new non-clinical data for this application and none are required. An overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
The pharmacology of diclofenac is well known and adequately described in the applicant’s non-clinical overview.

III.3 Pharmacokinetics
The pharmacokinetic properties of diclofenac are well known and adequately described in the applicant’s non-clinical overview.

III.4 Toxicology
The pharmacokinetic properties of diclofenac are well known and adequately described in the applicant’s non-clinical overview.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, the risks to the environment are not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

It is recommended that a Marketing Authorisation is granted for Diclodent Mouthwash, from a non-clinical point of view.

IV.  CLINICAL ASPECTS

IV.1 Introduction.
The clinical pharmacology of diclofenac following oral administration is well established, however diclofenac has never been approved in the UK as a mouthwash and the clinical pharmacology of diclofenac following buccal administration is limited. Bibliographic clinical data on the use of diclofenac formulation as a mouthwash has been submitted to support the application; this is acceptable.

This is a topically acting product and although it is presented as an aqueous solution, it is not intended to act systemically but locally. Based on this, the guideline on The Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents applies. However, a biowaiver has been granted as Diclodent Mouthwash is an aqueous solution and identical to the reference product.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.
IV.2 Pharmacokinetics
The pharmacokinetic profile of the oral formulation of diclofenac is well known, however limited information is available on the pharmacokinetics of this topical locally-acting formulation of diclofenac. Taking into account that this is a locally acting product, this is not unexpected. Such information is not considered critical in the current case.

Bibliographic (published and unpublished) pharmacokinetic data, following diclofenac administration (mainly oral tablet formulation), have been provided.

However, in one bioavailability study (1993/1994), systemic absorption of diclofenac through the buccal mucosa after repeated buccal treatments of a proposed mouthwash formulation, “Diclofenac Mouthwash 0.074%”, was evaluated in healthy male volunteers. The subjects received 25 ml of mouthwash twice a day for 7 consecutive days, plus one last dose on the 8th day. Each subject was instructed to circulate the solution in the mouthwash, without swallowing it, for 4 minutes, then the solution was expelled and the subject rinsed his mouth 3 times for 1 min with 20 ml of distilled water.

After buccal circulation the dosing solution of the last administration was expelled into a container and stored until analysed.

Blood samples were collected for plasma levels before and up to and including 8 hours after the last administration (15th treatment, day 8).

Diclofenac appeared to be absorbed rather quickly, when considering the brief contact of the solution with the oral mucosa. Concentrations were detectable in all subjects within 10 minutes. The peak concentration was reached within 45 minutes, with an average C\text{max} of $21.8 \pm 5.4$ ng/ml. Although with different experimental conditions, it is evident that the diclofenac concentrations recorded in this trial are much lower than those reported in the literature for oral diclofenac. Values of C\text{max} ranging from 500 ng/ml (1979) to 720-1100 ng/ml (1980) have been reported for the single oral dose of 25 mg diclofenac, while AUC values of 490-510 h*ng/ml for repeated administration of 25 mg three times a day (t.i.d.) over 15 days have been described (1979).

Therefore it can be stated that the systemic bioavailability of diclofenac after 7 days of mouth rinsing twice a day (b.i.d.) with 25 ml of “Diclofenac Mouthwash 0.074%” is about 1/10th in terms of AUC and 1/20th to 1/50th in terms of C\text{max} of that obtained with the oral administration of 25 mg diclofenac tablets.

The amount of diclofenac recovered in the expelled solutions was 19.0±2.6 mg, these data suggesting that almost all the dose administered to the volunteers was recovered in the expelled solution, that is, volunteers did not swallow the solution.

No new clinical pharmacokinetic data have been submitted and none are required for an application of this type.

IV.3 Pharmacodynamics
The pharmacodynamic profile of diclofenac following oral administration is well established. Based on the approved indications for the reference product and the efficacy studies reviewed in the literature evaluation, it is considered that the pharmacodynamic profile of diclofenac following buccal administration is not likely to differ.

Given the low levels of absorption of diclofenac from the product when administered via the buccal route, it is highly likely that most of the effect occurs locally, as intended, and as demonstrated by the clinical studies in the clinical overview.
An adequate summary of the pharmacodynamic profile of diclofenac has been presented in the clinical overview. No new pharmacodynamic data are presented or are required for this type of application.

IV.4 Clinical Efficacy
No new efficacy data are presented or are required for this type of application as this is a generic application. The efficacy of diclofenac, following systemic administration and topical (mouth wash) use, is adequately reviewed in the clinical overview.

Initially, small studies conducted to demonstrate the efficacy of diclofenac mouthwash were presented in the clinical overview. Two of the studies demonstrate the efficacy of the mouthwash in reducing pain but in one study, diclofenac mouthwash was considered insufficient to reduce postoperative periodontal pain on its own, as the study was conducted with subjects receiving ibuprofen. In both studies however, efficacy in other proposed indications other than pain was not demonstrated. This was considered by the Applicant to be due to the fact that different concentrations or different dosages to that proposed were used in these studies.

The third study compared the reference product with another diclofenac mouthwash, also not approved in the UK. Both products were found to be equally as effective at alleviating pain and inflammation symptoms in patients with painful inflammatory conditions of the oral cavity. As there was no placebo arm in this study, it is possible, as seen with studies conducted in pain, that there was a high placebo effect and superiority to placebo should have been demonstrated.

Based on the initial review it was considered that further information on efficacy which supported the use of the proposed indications were required. In response, the applicant provided additional bibliographic data that adequately addressed the concerns raised following the initial review the application. This additional data were derived from 3 controlled ENT trials in pharyngitis and pharyngotonsillitis, two studies in oral or parodontal surgery, one multicentre trial in oral mucositis by radiotherapy, and one meta-analysis study on the three ENT trials.

IV.5 Clinical Safety
The safety profile of diclofenac is well-known and has been adequately summarised by the Applicant in the clinical overview. No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application.

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 Diclodent Mouthwash.

A summary of safety concerns is listed in the table below:

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<th>Summary of safety concerns</th>
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<td>Important identified risks</td>
<td>• Hypersensitivity</td>
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<td>Important potential risks</td>
<td>• Sensitization phenomenon</td>
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<td>• Use in patients with fructose intolerance</td>
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<td>Missing information</td>
<td>• Use in pregnancy and lactation</td>
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Routine pharmacovigilance and routine risk minimisation activities are acceptable to monitor the safety concerns described in the Risk Management Plan.
IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Diclodent Mouthwash.

V. USER CONSULTATION
A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
QUALITY
The important quality characteristics of Diclodent Mouthwash are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
No new efficacy data have been submitted and none are required for this type of application.

SAFETY
No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with diclofenac is considered to have demonstrated the therapeutic value of the compound in the proposed indication. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
Diclodent 0.74 mg/ml Mouthwash (Oromucosal Solution)

(diclofenac acid)

PL 20117/0112

**STEPS TAKEN AFTER AUTHORISATION-SUMMARY**

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