Public Assessment Report

Decentralised Procedure

Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets

(Diclofenac sodium and misoprostol)

UK/H/4657/001-2/DC

UK licence no: PL 18909/0417-18

Arrow Generics Limited
LAY SUMMARY

On 31st May 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) to Arrow Generics Limited for the medicinal products Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets (PL 18909/0417-18, UK/H/4657/001-2/DC). These are prescription-only medicines (POM).

Diclofenac sodium and misoprostol 50 mg/200 microgram and 75 mg/200 micrograms modified release tablets help to relieve the pain and swelling of rheumatoid arthritis and osteoarthritis, and may help to protect patients at risk of irritation or ulceration of the stomach or intestines.

Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets contain diclofenac sodium and misoprostol. Diclofenac belongs to a group of medicinal products called Non-Steroidal Anti-Inflammatory drugs (NSAIDs).

Although NSAIDs relieve the pain, they can reduce the amount of natural protective substances called prostaglandins in the stomach lining.

This means that NSAIDs can lead to stomach upsets or stomach ulcers.

Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets also contain misoprostol which is very similar to these prostaglandins and may help protect your stomach.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets outweigh the risks and Marketing Authorisations were granted.
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## Module 1
### Information about initial procedure

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Diclofenac sodium and misoprostol</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>modified release tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>50 mg/200 micrograms and 75 mg/200 micrograms</td>
</tr>
</tbody>
</table>
| **MA Holder** | Arrow Generics Limited  
Unit 2 Eastman Way  
Stevenage  
Herts  
SG1 4SZ |
| **RMS** | UK                                                                 |
| **CMS** | Denmark, Germany, Norway and Sweden                                                                |
| **Procedure Numbers** | UK/H/4657/001-2/DC                                                                                 |
| **Timetable** | Day 210 – 23rd April 2013                                                                          |
Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3

PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Diclofenac sodium / Misoprostol 50 mg/200 micrograms modified-release tablets
(diclofenac sodium / misoprostol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 milligrams of diclofenac sodium and 200 micrograms of misoprostol

3. LIST OF EXCIPIENTS

These tablets also contain lactose monohydrate. Refer to leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

6 x 1 tablets
7 x 1 tablets
10 x 1 tablets
20 x 1 tablets
30 x 1 tablets
40 x 1 tablets
50 x 1 tablets
56 x 1 tablets
60 x 1 tablets
84 x 1 tablets
90 x 1 tablets
100 x 1 tablets
120 x 1 tablets
140 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use. Use as directed by a doctor
Tablets should be swallowed whole with a drink of water, not chewed.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

Warning: Not for use in pre-menopausal women unless using effective contraception

8. EXPIRY DATE

EXP: (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Arrow Generics Limited
Unit 2 Eastman Way
Stevenage
Herts
SG1 4SZ

12. MARKETING AUTHORISATION NUMBER(S)

PL 18999/0417

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Not applicable.

16. INFORMATION IN BRAILLE

diclofenac sodium / misoprostol 50 mg/200 micrograms modified-release tablets
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTERS

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac sodium / Misoprostol 50 mg/200 micrograms modified-release tablets</td>
</tr>
<tr>
<td>(diclofenac sodium/ misoprostol)</td>
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</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
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<tbody>
<tr>
<td>Arrow Generics Limited</td>
</tr>
<tr>
<td>Unit 2 Eastman Way</td>
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</tr>
<tr>
<td>Herts</td>
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</table>

<table>
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<tr>
<th>4. BATCH NUMBER</th>
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</thead>
<tbody>
<tr>
<td>BN:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warning: Not for use in pre-menopausal women unless using effective contraception</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Diclofenac sodium / Misoprostol 75 mg/200 micrograms modified-release tablets
(diclofenac sodium / misoprostol)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 75 milligrams of diclofenac sodium and 200 micrograms of misoprostol

3. LIST OF EXCIPIENTS

These tablets also contain lactose monohydrate. Refer to leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

| 6 x 1 tablets |
| 7 x 1 tablets |
| 10 x 1 tablets |
| 20 x 1 tablets |
| 30 x 1 tablets |
| 50 x 1 tablets |
| 60 x 1 tablets |
| 84 x 1 tablets |
| 90 x 1 tablets |
| 100 x 1 tablets |
| 120 x 1 tablets |
| 140 x 1 tablets |

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use. Use as directed by a doctor
Tablets should be swallowed whole with a drink of water, not chewed.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

Warning: Not for use in pre-menopausal women unless using effective contraception

8. EXPIRY DATE

EXP: (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Arrow Generics Limited
Unit 2 Eastman Way
Stevenage
Herts
SG1 4SZ

12. MARKETING AUTHORISATION NUMBER(S)

PL 18909/0418

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

[Not applicable.

16. INFORMATION IN BRAILLE

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### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

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Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the applications for Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets for the symptomatic treatment of osteoarthritis and rheumatoid arthritis and for patients with a special need for the prophylaxis of NSAID-induced gastric and duodenal ulceration, could be approved.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended for Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets. The originator product is Arthrotec 75 mg modified release tablets (PL 00032/0397), which was first licensed to Pharmacia, UK, on 13th May 1996.

With UK as the RMS in these Decentralised Procedures (UK/H/4657/001-02/DC), Arrow Generics Limited applied for the Marketing Authorisations for Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets in Denmark, Germany, Norway and Sweden.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). It inhibits COX₁ and COX₂, and has anti-inflammatory, analgesic and antipyretic properties. However the levels of prostaglandins in the GI tract are reduced, contributing to GI adverse events such as ulceration, bleeding and perforation. Diclofenac is widely used in the treatment of osteoarthritis and rheumatoid arthritis.

Misoprostol is a synthetic prostaglandin E₁ analogue which is widely used as a gastroprotective agent. Co-administration of misoprostol with a NSAID reduces the incidence of NSAID-induced gastric and duodenal ulceration and their complications.

No new non-clinical or clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator product that has been licensed for over 10 years.

Bioequivalence studies were submitted to support these applications, comparing the applicant’s test product diclofenac sodium 75 mg/misoprostol 200 micrograms tablets (Watson Laboratories Inc, USA) with the reference product Arthotec® Forte 75 mg modified-release tablets (Pfizer Pharma, Germany). These studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification for non-submission of a Risk Management Plan has been provided.

All Member States agreed to grant respective licences for the above products at the end of procedure (Day 210 – 23rd April 2013). After a subsequent national phase, the UK granted licences for these products on 31st May 2013 (PL 18909/0417-18).
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets |
| Name(s) of the active substance(s) (INN)          | Diclofenac sodium and misoprostol |
| Pharmacotherapeutic classification (ATC code)    | diclofenac, combinations, ATC code: M01AB55 |
| Pharmaceutical form and strength(s)              | modified release tablets |
| Reference numbers for the Decentralised Procedures | UK/H/4657/001-02/DC |
| Reference Member State                           | United Kingdom |
| Concerned Member States                          | Denmark, Germany, Norway and Sweden |
| Marketing Authorisation Number(s)                | PL 18909/0417-18 |
| Name and address of the authorisation holder     | Arrow Generics Limited  
Unit 2 Eastman Way  
Stevenage  
Herts  
SG1 4SZ |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Diclofenac sodium

Chemical Names: 2-[(2, 6-dichlorophenyl)amino] benzeneacetic acid monosodium salt
Sodium [o-(2, 6-dichloroanilino) phenyl] acetate

Structure:

\[
\text{\begin{center}
\includegraphics[width=0.3\textwidth]{diclofenac_structure.png}
\end{center}}
\]

Molecular Formula: C\textsubscript{14}H\textsubscript{10}Cl\textsubscript{2}NNaO\textsubscript{2}
Molecular Weight: 318.1 g/mol

Appearance: white or slightly yellowish, slightly hygroscopic crystalline powder
Solubility: sparingly soluble in water, freely soluble in methanol, soluble in ethanol and slightly soluble in acetone.

Diclofenac sodium is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance diclofenac sodium are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

INN: Misoprostol

Chemical Names: Mixture of methyl 7-[(1RS,2RS,3RS)-3-hydroxy-2-[(1E,4RS)-4-hydroxyl-4 methyloct-1-enyl]-5-oxocyclopentyl]heptanoate and methyl 7-[(1RS,2RS,3RS)-3-hydroxy-2-[(1E,4SR)-4 hydroxyl-4-methyloct-1-enyl]-5-oxocyclopentyl] heptanoate (Ph. Eur.)

Structure:

\[
\text{\begin{center}
\includegraphics[width=0.3\textwidth]{misoprostol_structure.png}
\end{center}}
\]
Molecular Formula: C_{22}H_{38}O_{5}
Molecular Weight: 382.5 g/mol

Appearance: clear, colourless or yellowish oily liquid which is hygroscopic.
Solubility: practically insoluble in water, soluble in ethanol and sparingly soluble in acetonitrile.

Misoprostol is the subject of an active substance master file (ASMF). Satisfactory letters of access have been provided.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications 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 analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for working standards used by the drug substance manufacturer and finished product manufacturer.

The active substance is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

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

**DRUG PRODUCT**

*Other Ingredients*

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, lactose monohydrate, maize starch, povidone (PVP K-30), magnesium stearate, making up the tablet core; and mantle/coat consisting of methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30 percent (containing methacrylic acid-ethylacrylate copolymer (1:1), sodium lauryl sulfate, polysorbate 80, sodium hydroxide pellets, triethyl citrate, talc, crospovidone Type B, silica, colloidal anhydrous, castor oil, hydrogenated, cellulose microcrystalline and hypromellose).

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.
Pharmaceutical Development
The objective of the development programme was to formulate robust, stable modified release tablets that could be considered generic medicinal products of the innovator’s product.

Comparative impurity and dissolution profiles have been presented for the test and reference products.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of these products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packed in a cold form foil/aluminium foil unit dose blisters consisting of 6x1, 7x1, 10x1, 20x1, 30x1, 40x1, 50x1, 56x1, 60x1, 84x1, 90x1, 100x1, 120x1 and 140x1 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months with storage conditions “Do not store above 30°C” and “Store in the original package to protect from moisture” have been set. These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

The Marketing Authorisation Holder has committed to submit mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.
Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

Expert report/Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of diclofenac sodium and misoprostol are well known.

No new non-clinical data have been supplied with these applications and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Suitable justification has been provided for non-submission of an environmental risk assessment. This was satisfactory.

There are no objections to the approval of these products from a non-clinical point of view.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
Pharmacokinetics
In support of these applications, two bioequivalence studies have been submitted:

Study 16556/10-11 (Fed)
This is an open label, randomised, 4 period, 2 sequence, 2 treatment, single dose cross-over bioequivalence study of test product diclofenac sodium 75 mg and misoprostol 200 microgram tablets (Watson Laboratories Inc, USA) with the reference product Arthotec® Forte 75 mg modified-release tablets (Pfizer Pharma, Germany) in healthy male adults under fed conditions.

A total of 21 blood samples consisting of 15 for estimation of diclofenac and 15 for misoprostol acid were collected in each period:
Diclofenac was estimated for the following time points: 0.00 (pre dose), 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00 and 12.00 hours post dose.
Misoprostol acid was estimated for the following time points: 0.00 (pre dose), 0.08, 0.17, 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00 and 6.00 hours post dose. There was a washout period of 7 days between study drug administrations.
**Results**

Table 1. Pharmacokinetic parameters of diclofenac sodium (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$</th>
<th>$\text{AUC}_{0-\infty}$</th>
<th>$C_{\text{max}}$</th>
<th>$t_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test (replicate #1)</strong></td>
<td>2020.97 (537.50)</td>
<td>2173.52 (522.47)</td>
<td>1335.46 (663.05)</td>
<td>4.00 (1.00-8.00)</td>
</tr>
<tr>
<td><strong>Test (replicate #2)</strong></td>
<td>2099.13 (664.05)</td>
<td>2213.36 (626.85)</td>
<td>1385.26 (629.97)</td>
<td>4.00 (1.00-8.00)</td>
</tr>
<tr>
<td><strong>Reference (replicate #1)</strong></td>
<td>2079.16 (652.40)</td>
<td>2230.96 (605.64)</td>
<td>1450.38 (827.60)</td>
<td>4.00 (1.00-10.00)</td>
</tr>
<tr>
<td><strong>Reference (replicate #2)</strong></td>
<td>2055.88 (760.90)</td>
<td>2258.53 (698.20)</td>
<td>1323.55 (733.65)</td>
<td>3.50 (1.00-10.00)</td>
</tr>
</tbody>
</table>

*A Ratio (90% CI) 102.24 (95.08, 109.93) 99.66 (95.07, 104.47) 103.55 (88.78, 120.77)

$\text{AUC}_{0-t}$: Area under the plasma concentration curve from administration to last observed concentration at time $t$.

$\text{AUC}_{0-72h}$ can be reported instead of $\text{AUC}_{0-t}$ in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

$\text{AUC}_{0-\infty}$: Area under the plasma concentration curve extrapolated to infinite time.

$\text{AUC}_{0-\infty}$ does not need to be reported when $\text{AUC}_{0-72h}$ is reported instead of $\text{AUC}_{0-t}$

$C_{\text{max}}$: Maximum plasma concentration

$t_{\text{max}}$: Time until $C_{\text{max}}$ is reached

*ln-transformed values

Table 2. Pharmacokinetic parameters of misoprostol acid (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$</th>
<th>$\text{AUC}_{0-\infty}$</th>
<th>$C_{\text{max}}$</th>
<th>$t_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test (replicate #1)</strong></td>
<td>266.32 (91.16)</td>
<td>337.06 (173.67)</td>
<td>142.60 (78.27)</td>
<td>0.33 (0.17-5.00)</td>
</tr>
<tr>
<td><strong>Test (replicate #2)</strong></td>
<td>270.64 (95.97)</td>
<td>310.13 (109.65)</td>
<td>141.77 (72.76)</td>
<td>0.33 (0.08-5.00)</td>
</tr>
<tr>
<td><strong>Reference (replicate #1)</strong></td>
<td>277.87 (102.92)</td>
<td>322.10 (109.76)</td>
<td>144.65 (63.43)</td>
<td>0.33 (0.17-5.00)</td>
</tr>
<tr>
<td><strong>Reference (replicate #2)</strong></td>
<td>281.88 (112.30)</td>
<td>323.83 (119.01)</td>
<td>161.24 (93.73)</td>
<td>0.33 (0.17-5.03)</td>
</tr>
</tbody>
</table>

*A Ratio (90% CI) 97.50 (94.69, 100.39) 100.26 (95.16, 105.63) 93.63 (85.73, 102.26)

$\text{AUC}_{0-t}$: Area under the plasma concentration curve from administration to last observed concentration at time $t$.

$\text{AUC}_{0-72h}$ can be reported instead of $\text{AUC}_{0-t}$ in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

$\text{AUC}_{0-\infty}$: Area under the plasma concentration curve extrapolated to infinite time.

$\text{AUC}_{0-\infty}$ does not need to be reported when $\text{AUC}_{0-72h}$ is reported instead of $\text{AUC}_{0-t}$

$C_{\text{max}}$: Maximum plasma concentration

$t_{\text{max}}$: Time until $C_{\text{max}}$ is reached

*ln-transformed values

20
The 90% confidence intervals for AUC$_{0-t}$, AUC$_{0-\infty}$ and C$_{\text{max}}$ for both diclofenac and misoprostol were within the pre-defined limits acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Diclofenac sodium 75 mg and misoprostol 200 micrograms tablets) and the reference formulation (Arthrotec® Forte 75 mg modified-release tablets) under fed state.

**Study 11233/11-12 (Fasting)**
This is an open label, randomised, 4 period, 2 sequence, 2 treatment, single dose cross-over bioequivalence study of test product diclofenac sodium 75 mg and misoprostol 200 micrograms tablets (Watson Laboratories Inc, USA) with the reference product Arthrotec® Forte 75 mg modified-release tablets (Pfizer Pharma, Germany) in healthy male adults under fasting conditions.

A total of 24 blood samples consisting of 15 for estimation of diclofenac and 13 for misoprostol acid were collected in each period:
Diclofenac was estimated for the following time points: 0.00 (pre dose), 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00 and 10.00 hours post dose.
Misoprostol acid was estimated for the following time points: 0.00 (pre dose), 0.08, 0.17, 0.25, 0.42, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67 and 3.00 hours post dose. There was a washout period of 10 days between study drug administrations.

**Table 3 Pharmacokinetic parameters of diclofenac sodium (non-transformed values; arithmetic mean ± SD, t$_{\text{max}}$ median, range)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ (ng/ml/h)</th>
<th>AUC$_{0-\infty}$ (ng/ml/h)</th>
<th>C$_{\text{max}}$ (ng/ml)</th>
<th>t$_{\text{max}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (replicate #1)</td>
<td>2889.236 (642.2653)</td>
<td>2970.135 (649.8276)</td>
<td>2375.908 (723.1214)</td>
<td>1.00 (0.50, 2.50)</td>
</tr>
<tr>
<td>Test (replicate #2)</td>
<td>2789.902 (690.8808)</td>
<td>2908.955 (672.5719)</td>
<td>2157.960 (1007.6432)</td>
<td>1.25 (0.50, 6.00)</td>
</tr>
<tr>
<td>Reference (replicate #1)</td>
<td>2939.943 (847.9518)</td>
<td>3007.459 (638.3094)</td>
<td>2182.702 (733.9401)</td>
<td>1.50 (0.25, 10.00)</td>
</tr>
<tr>
<td>Reference (replicate #2)</td>
<td>2914.148 (640.3073)</td>
<td>2992.793 (657.7272)</td>
<td>2190.173 (722.0410)</td>
<td>1.50 (0.50, 6.00)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

<table>
<thead>
<tr>
<th></th>
<th>97.79 (91.65, 104.34)</th>
<th>98.17 (94.67, 101.80)</th>
<th>102.34 (91.04, 115.04)</th>
</tr>
</thead>
</table>

| Intrasubject %CV | 20.01 | 13.24 | 39.96 |

**Notes**

- AUC$_{0-t}$: Area under the plasma concentration curve from administration to last observed concentration at time t.
- AUC$_{0-\infty}$: Area under the plasma concentration curve extrapolated to infinite time.
- C$_{\text{max}}$: Maximum plasma concentration.
- t$_{\text{max}}$: Time until C$_{\text{max}}$ is reached; median (min, max).

*ln-transformed values

NOTE For Diclofenac Sodium, Subject 34 pre dose concentration data is greater than 5% of C$_{\text{max}}$, As per the protocol subject 34 data was excluded from all BE study evaluations.
Table 4  Pharmacokinetic parameters of misoprostol acid (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} pg/ml/h</th>
<th>AUC_{0-∞} pg/ml/h</th>
<th>C_{max} pg/ml</th>
<th>t_{max} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (replicate #1)</td>
<td>305.347 (111.3670)</td>
<td>316.052 (112.7005)</td>
<td>493.917 (212.4507)</td>
<td>0.25 (0.17, 1.00)</td>
</tr>
<tr>
<td>Test (replicate #2)</td>
<td>308.777 (113.8147)</td>
<td>319.022 (114.0096)</td>
<td>489.234 (213.0215)</td>
<td>0.25 (0.08,1.00)</td>
</tr>
<tr>
<td>Reference (replicate #1)</td>
<td>317.890 (157.4299)</td>
<td>328.716 (160.1211)</td>
<td>531.355 (355.9538)</td>
<td>0.25 (0.17, 0.67)</td>
</tr>
<tr>
<td>Reference (replicate #2)</td>
<td>319.470 (120.0302)</td>
<td>337.978 (132.9279)</td>
<td>550.912 (235.9660)</td>
<td>0.25 (0.17, 0.67)</td>
</tr>
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</table>

**Ratio (90% CI)**

<table>
<thead>
<tr>
<th>Intrasubject %CV</th>
<th>AUC_{0-t} (93.47, 101.42)</th>
<th>AUC_{0-∞} (92.72, 100.86)</th>
<th>C_{max} (86.87, 99.81)</th>
</tr>
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<tbody>
<tr>
<td>97.36</td>
<td>16.46</td>
<td>16.94</td>
<td>28.37</td>
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</table>

The 90% confidence intervals for AUC_{0-t}, AUC_{0-∞} and C_{max} for both diclofenac sodium and misoprostol were within the pre-defined limits acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Diclofenac sodium 75 mg and misoprostol 200 microgram tablets) and the reference formulation (Arthrotec ® Forte 75 mg modified-release tablets) under fasting state.

Satisfactory justification is provided for a bio-waiver for the applicant’s lower strength tablets. As Diclofenac sodium 50 mg and misoprostol 200 micrograms tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**), the results and conclusions of the bioequivalence study for 75 mg/200 micrograms formulation can be extrapolated to the other strength, i.e. 50 mg/200 micrograms modified release tablets.

**Pharmacodynamics**

No new data have been submitted and none are required for applications of this type.

**Clinical Efficacy**

No new data have been submitted and none are required.

**Clinical Safety**

No new data have been submitted and none are required.
**Expert Report**
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**
The SmPCs, PILs and labelling are satisfactory from a clinical perspective and consistent with those for the reference products.

**Marketing Authorisation Application (MAA) Forms**
The MAA forms are satisfactory from a clinical perspective.

**Conclusion**
There are no objections to the approval of these products from a clinical point of view.
**IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**
The important quality characteristics of Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets 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 applications of these type.

**EFFICACY**
Bioequivalence has been demonstrated between the applicant’s Diclofenac sodium 75 mg and misoprostol 200 micrograms tablets and the reference product, Arthrotec® Forte 75 mg modified-release tablets under fasting and fed states. As Diclofenac sodium 50 mg and misoprostol 200 microgram tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr*), the results and conclusions of the bioequivalence study for 75 mg/200 micrograms formulation can be extrapolated to the other strength i.e. 50 mg/200 micrograms modified release Tablets.

No new or unexpected safety concerns arose from these applications.

The SmPCs and PILs are satisfactory and consistent with those of the reference product. Satisfactory labelling has also been submitted.

**RISK-BENEFIT 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 sodium and misoprostol is considered to have demonstrated the therapeutic value of the compounds. The risk-benefit is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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