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

(Diclofenac sodium and misoprostol)

UK/H/5263/001-2/DC

UK licence no: PL 33100/0008-9

Cipla (UK) Limited
LAY SUMMARY

On 31st May 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) to Cipla (UK) Limited for the medicinal products Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets (PL 33100/0008-9, UK/H/5263/001-2/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

<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>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Diclofenac sodium and misoprostol</td>
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<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>
<tr>
<td><strong>MA Holder</strong></td>
<td>Cipla (UK) Limited, The old Post House, Heath Road, Weybridge, Surrey KT13 8TS</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>The Netherlands</td>
</tr>
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<td><strong>Procedure Numbers</strong></td>
<td>UK/H/5263/001-2/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 16th April 2013</td>
</tr>
</tbody>
</table>
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

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING
(CARTON)

1. NAME OF THE MEDICINAL PRODUCT

Diclofenac sodium and misoprostol 50 mg/200 microgram modified release tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains diclofenac sodium 50 mg and misoprostol 0.2 mg.
Each tablet contains lactose also (see leaflet for further information).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release tablets.
30, 60, 90, 100, 120, 140 Tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Tablets should be swallowed whole, not chewed. Use as directed by the physician.
Read the package leaflet before use.

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

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

8. EXPIRY DATE

EXP:
9. **SPECIAL STORAGE CONDITIONS**

No special precautions are recommended for storage.

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

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

MA Holder: <To be completed nationally>

12. **MARKETING AUTHORISATION NUMBER(S)**

13. **BATCH NUMBER**

B. No:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Diclofenac sodium and misoprostol 50 mg/200 microgram modified release tablets
LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

{CARTON}

1. NAME OF THE MEDICINAL PRODUCT
Diclofenac sodium and misoprostol 75 mg/200 microgram modified release tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each tablet contains diclofenac sodium 75 mg and misoprostol 0.2 mg.
Each tablet contains lactose also (see leaflet for further information).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
Modified-release tablets.
30, 60, 90, 100, 120, 140 Tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Oral use.
Tablets should be swallowed whole, not chewed. Use as directed by the physician.
Read the package leaflet before use.

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

8. EXPIRY DATE
EXP:
### 9. SPECIAL STORAGE CONDITIONS

No special precautions are recommended for storage.

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

### 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: <To be completed nationally>

### 12. MARKETING AUTHORISATION NUMBER(S)

### 13. BATCH NUMBER

B. No.

### 14. GENERAL CLASSIFICATION FOR SUPPLY

POM

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE

Diclofenac sodium and misoprostol 75 mg/200 microgram modified release tablets
9. SPECIAL STORAGE CONDITIONS

No special precautions are recommended for storage.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: Cipla (UK) Limited
The Old Post House, Heath Road,
Weybridge, Surrey, KT13 8TS,
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 33100/0008

13. BATCH NUMBER

B. No:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Diclofenac sodium and misoprostol 50 mg/200 microgram modified release tablets
9. SPECIAL STORAGE CONDITIONS

No special precautions are recommended for storage.

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

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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 33100/0009

13. BATCH NUMBER

B. No.

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Diclofenac sodium and misoprostol 75 mg/200 microgram modified release tablets
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 State (CMS) considered that the applications for Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets for patients who require the non-steroidal anti-inflammatory drug diclofenac together with misoprostol, 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 applicant cross-refers to Arthrotec 50 mg and 75 mg modified release tablets (PL 00032/0396-97), originally granted to G D Searle and company Ltd (50 mg only) on 10th June 1992. This reference licence has undergone a Change of Ownership (CoA) procedure to Monsanto PLC (PL 08821/0006) on 7th February 1996 followed by authorisation to the current Marketing Authorisation Holder, Pharmacia, Limited on 15th April 2002. Arthrotec 75 mg modified release tablets was initially granted to Monsanto PLC on 13th May 1996 and then undergone a CoA to the current marketing Authorisation Holder, Pharmacia Limited on 16th October 2002.

With UK as the RMS in these Decentralised Procedures (UK/H/5263/001-2/DC), Cipla (UK) Limited applied for the Marketing Authorisations for Diclofenac sodium and misoprostol 50 mg/200 micrograms and 75 mg/200 micrograms modified release tablets in The Netherlands.

Diclofenac is a potent non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties, it also has some uricosuric effect. Diclofenac inhibits cyclooxygenase activity with a reduction in the tissue production of prostaglandins such as Pgf2α and PgE2.

Diclofenac is an effective anti-inflammatory and analgesic drug in clinical practice and is widely used in the treatment of rheumatoid arthritis and osteoarthritis. It is as effective as indomethacin or aspirin with perhaps fewer side effects than these two agents. Diclofenac is as effective at inhibiting cyclo-oxygenase as indomethacin in therapeutic usage. The duration of inhibition is such that twice-daily dosage is appropriate. Diclofenac reduces joint swelling and relieves pain in patients with rheumatoid arthritis but has no long-term effects on the disease process. Diclofenac inhibits platelet adhesiveness, prolongs the bleeding time and causes gastric erosions. By inhibiting prostaglandin synthesis in the uterus of pregnant women it may delay the onset of labour. Diclofenac has no effect on renal function in normal individuals but can worsen renal function in patients whose renal blood flow is dependent on the vasodilatory prostaglandin E2 (e.g. in hypertension, diabetes and cirrhosis of the liver).

Misoprostol inhibits the acid secretion by a direct action on the parietal cells. The inhibition of adenylate cyclase may be dependent on guanosine-5’-triphosphate (GTP). The significant cytoprotective actions of misoprostol are related to several mechanisms which include; increased secretion of bicarbonate, decrease in the volume and pepsin content of the gastric secretions, and prevention of harmful agents from disrupting the tight junctions between the epithelial cells. This, in turn, stops the subsequent back diffusion of H+ ions into the gastric
mucosa, increases thickness of the mucus layer, and enhances mucosal blood flow, as a result of direct vasodilatation.

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 products that have 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 (Cipla Ltd. India) with the reference product Arthrotec 75 mg tablets (Pharmacia Ltd, UK). 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 licences for the above products at the end of procedure (Day 210 – 16th April 2013). After a subsequent national phase, the UK granted licences for these products on 31st May 2013 (PL 33100/0008-9).
## 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) | ATC Code: M01BX. |
| Pharmaceutical form and strength(s) | modified release tablets |
| Reference numbers for the Decentralised Procedures | UK/H/5263/001-2/DC |
| Reference Member State | United Kingdom |
| Concerned Member State | The Netherlands |
| Marketing Authorisation Number(s) | PL 33100/0008-9 |
| Name and address of the authorisation holder | Cipla (UK) Limited, The old Post House, Heath Road, Weybridge, Surrey KT13 8TS |
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:

![Diclofenac sodium structure](image)

Molecular Formula: C_{14}H_{10}Cl_2NNaO_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:

![Misoprostol structure](image)
Molecular Formula: C\textsubscript{22}H\textsubscript{38}O\textsubscript{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.

The drug substance 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, purified talc, sodium starch glycollate, hydrogenated castor oil making up the tablet core; and the coat consisting of hydroxy propyl methyl cellulose, methacrylic acid-ethyl acrylate copolymer (1:1) (Eudrajit) and triethyl citrate.

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 products Arthrotec 50 mg and 75 mg modified release tablets (Pharmacia, UK).
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 formed aluminium blisters in pack sizes of 30, 60, 90, 100, 120 and 140 (supplied as respective packs of 10 tablets shrink wrapped together) 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 has been set. No special precautions are recommended for storage. 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:

Fasting state study (ARL/10/105)
This is a randomised single-dose, two treatment, two-period, two sequence cross-over bioequivalence study of test product diclofenac sodium 75 mg and misoprostol 200 micrograms tablets (Cipla Ltd., India) with the reference product Arthrotec 75 mg modified-release tablets (Pharmacia Ltd., UK) in healthy adults under fasting conditions.

A total of 23 blood samples were collected from the subjects during the study. Blood samples were collected at 0.083, 0.167, 0.250, 0.333, 0.417, 0.500, 0.750, 1.000, 1.333, 1.666, 2.000, 2.333, 2.666, 3.000, 3.333, 3.666, 4.000, 4.500, 5.000, 6.000, 8.000 and 10.000 hrs post-dose within 2 minutes of scheduled sampling time. Out of the 23 blood samples, 10 blood samples collected at pre dose, at 0.500, 0.750, 1.000, 1.333, 1.666, 2.000, 3.000, 4.000 and at 5.000 hrs post dose were obtained for the estimation of both diclofenac and misoprostol. Five blood samples collected at 0.083, 0.167, 0.250, 0.333 and at 0.417 hrs post dose were obtained for the estimation of misoprostol and 8 samples collected at 2.333, 2.666, 3.333, 3.666, 4.500, 6.000, 8.000 and at 10.000 hrs post dose were obtained for the estimation of diclofenac. There was a washout period of 8 days between study drug administrations.

Results
Table 1. Pharmacokinetic parameters diclofenac sodium (non-transformed values; arithmetic mean ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀₋₇ ng/ml/h</th>
<th>AUC₀₋∞ ng/ml/h</th>
<th>C_max ng/ml</th>
<th>t_max h</th>
<th>T½ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>2347.45</td>
<td>2369.45</td>
<td>1847.06</td>
<td>1.27</td>
<td>1.72</td>
</tr>
<tr>
<td>Standard dev.</td>
<td>558.08</td>
<td>562.48</td>
<td>596.60</td>
<td>0.60</td>
<td>0.40</td>
</tr>
<tr>
<td>Reference</td>
<td>2334.87</td>
<td>2360.45</td>
<td>1837.44</td>
<td>1.56</td>
<td>1.74</td>
</tr>
<tr>
<td></td>
<td>606.87</td>
<td>609.64</td>
<td>652.89</td>
<td>1.00</td>
<td>0.41</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>97.996-104.08%</td>
<td>97.86-103.83%</td>
<td>93.299-111.96</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
The 90% confidence intervals for AUC$_{0-t}$, AUC$_{0-\infty}$ and C$_{max}$ 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 microgram tablets) and the reference formulation (Arthrotec 75 mg modified-release tablets) under fasting state.

Fed state study (ARL/10/106)

This is an open randomised single-dose, two treatment, four-period, two sequence replicate cross-over bioequivalence study of test product diclofenac sodium 75 mg and misoprostol 200 microgram tablets (Cipla Ltd., India) with reference product Arthrotec 75 mg modified-release tablets (Pharmacia Ltd., UK) in healthy, adults under fed conditions.

The subjects were administered the test or the reference product as per the randomization schedule with 240 mL of water at ambient temperature. Out of 22 blood samples, one blood sample was collected as pre dose sample, 7 blood samples were collected at 1.000, 2.000, 2.500, 3.000, 4.000, 5.000 and 6.000 hrs post dose for the estimation of both diclofenac sodium and misoprostol. Seven blood samples were collected at 0.167, 0.333, 0.500, 0.666, 0.833, 1.333 and 1.666 hrs post dose for the estimation of misoprostol acid and 7 blood samples (4 mL each) were collected at 3.500, 4.500, 5.500, 6.500, 7.000, 8.000 and 10.000 hrs post dose for the estimation of diclofenac sodium. Standardized meals were provided to the subjects at 4 hours post-dose (at 12:00 hours, standard lunch) and at 9 hours post-dose (at 17:00 hours, snacks) during each period of the study.
Results

Table 3. Pharmacokinetic parameters diclofenac sodium (non-transformed values; arithmetic mean ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀-t xg/ml/h</th>
<th>AUC₀-∞ xg/ml/h</th>
<th>C_max xg/ml</th>
<th>t_max h</th>
<th>T½ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>2159.94</td>
<td>2215.43</td>
<td>1564.91</td>
<td>4.38</td>
<td>1.59</td>
</tr>
<tr>
<td>Standard dev.</td>
<td>628.94</td>
<td>536.68</td>
<td>818.95</td>
<td>1.64</td>
<td>0.53</td>
</tr>
<tr>
<td>Reference</td>
<td>2105.98</td>
<td>2037.83</td>
<td>1442.95</td>
<td>4.28</td>
<td>1.74</td>
</tr>
<tr>
<td></td>
<td>797.02</td>
<td>579.69</td>
<td>754.92</td>
<td>1.64</td>
<td>0.60</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>93.59-111.25</td>
<td>103.51-114.18</td>
<td>92.95-121.12</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

AUC₀-t area under the plasma concentration-time curve from time zero to t hours
AUC₀-∞ area under the plasma concentration-time curve from time zero to infinity
C_max maximum plasma concentration
T_max time for maximum concentration
T½ half-life

*ln-transformed values

Table 4. Pharmacokinetic parameters misoprostol (non-transformed values; arithmetic mean ± SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀-t xg/ml/h</th>
<th>AUC₀-∞ xg/ml/h</th>
<th>C_max xg/ml</th>
<th>t_max h</th>
<th>T½ (terminal) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>573.30</td>
<td>624.64</td>
<td>288.44</td>
<td>0.99</td>
<td>1.57</td>
</tr>
<tr>
<td>Standard dev.</td>
<td>197.57</td>
<td>240.74</td>
<td>164.93</td>
<td>1.21</td>
<td>1.25</td>
</tr>
<tr>
<td>Reference</td>
<td>551.72</td>
<td>603.81</td>
<td>271.04</td>
<td>0.92</td>
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<td>195.02</td>
<td>316.49</td>
<td>168.35</td>
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<td>1.43</td>
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<td>*Ratio (90% CI)</td>
<td>100.78-109.59</td>
<td>98.22-108.96</td>
<td>100.47-117.03</td>
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AUC₀-t area under the plasma concentration-time curve from time zero to t hours
AUC₀-∞ area under the plasma concentration-time curve from time zero to infinity
C_max maximum plasma concentration
T_max time for maximum concentration
T½ half-life

*ln-transformed values

The 90% confidence intervals for AUC₀-t, AUC₀-∞ 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 micrograms tablets) and the reference formulation (Arthrotec 75 mg modified-release tablets) under fed state.

Satisfactory justification is provided for a bio-waiver for the applicant’s lower strength tablets. According to the Committee for Proprietary Medicinal Products Notes for Guideline on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1 Corr**), the results of the 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/Clinical overview
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 75 mg modified-release tablets under fasting and fed states. According to the Committee for Proprietary Medicinal Products Notes for Guideline on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr*), the results of the 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 PIL are satisfactory and consistent with those of the reference products, where appropriate. 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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