Public Assessment Report

Decentralised Procedure

Diclopram 75 mg/ 20 mg modified-release hard capsules

(Diclofenac sodium and omeprazole)

Procedure No: UK/H/5465/001/DC

UK Licence No: PL 33616/0002

Pharmaswiss Česká republika s.r.o.
LAY SUMMARY

Diclopram 75 mg/20 mg modified-release hard capsules
(diclofenac sodium 75 mg, omeprazole 20 mg, modified-release hard capsules)

This is a summary of the Public Assessment Report (PAR) for Diclopram 75 mg/20 mg modified-release hard capsules (PL 33616/0002; UK/H/5465/001/DC). It explains how Diclopram 75 mg/20 mg modified-release hard capsules were assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Diclopram 75 mg/20 mg modified-release hard capsules.

For practical information about using Diclopram 75 mg/20 mg modified-release hard capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Diclopram 75 mg/20 mg modified-release hard capsules and what are they used for?

Diclopram 75 mg/20 mg modified-release hard capsules contain two active ingredients in a single capsule. These active ingredients are diclofenac sodium (75 mg), which is one of a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) and omeprazole (20 mg) which belongs to a group of medicines called ‘proton pump inhibitors’. Diclopram 75 mg/20 mg modified-release hard capsules can be used by patients who have symptoms caused by a joint disorder such as osteoarthritis, rheumatoid arthritis or ankylosing spondylitis. In addition, the patient may be at risk of developing peptic ulcers when taking NSAIDs.

How do Diclopram 75 mg/20 mg modified-release hard capsules work?

Diclofenac belongs to a group of medicines called NSAIDs and is used to reduce pain and inflammation of joint disorders.

Omeprazole is a ‘proton pump inhibitor’ which works by reducing the amount of acid that the patient’s stomach produces. Omeprazole reduces the risk of developing peptic ulcers (ulcers in the stomach or duodenum) caused by NSAIDs.

How are Diclopram 75 mg/20 mg modified-release hard capsules used?

The pharmaceutical form of Diclopram 75 mg/20 mg modified-release hard capsules is a hard capsule (modified-release) and the route of administration is oral.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The patient should always take Diclopram 75 mg/20 mg modified-release hard capsules exactly as directed by their doctor. The patient must check with their doctor or pharmacist if they are not sure.

The recommended dose is one capsule daily. If the patient’s symptoms are not controlled by once daily dosing, the patient must talk to their doctor. The patient must never take more than one capsule of this medicine per day as this could increase the risk of side effects.

Diclopram 75 mg/20 mg modified-release hard capsules must be swallowed whole with a drink of water (about half a glass). Do not chew or break open the capsules. The capsules are best taken with or after food. It may help the patient to remember to take their capsules if they take them at the same time every day, perhaps with breakfast or an evening meal.

The patient must tell their doctor if they have any concerns about their treatment.
What benefits of Diclopram 75 mg/20 mg modified-release hard capsules have been shown in studies?

Diclopram 75 mg/20 mg modified-release hard capsules is a fixed combination product of known active substances, studies in patients have been limited to tests to determine that it is bioequivalent to the free combination of diclofenac and omeprazole reference products Difene 75 mg dual release hard capsules (Temmler Werke GmbH, Germany) and Losec 20 mg gastro-resistant hard capsules (AstraZeneca UK Limited, UK), respectively. Medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Diclopram 75 mg/20 mg modified-release hard capsules?

Like all medicines, this medicine can cause side effects, although not everybody gets them. Taking this medicine for the shortest possible time will minimise side effects. Some side effects can be serious. The patient must stop taking Diclopram 75 mg/20 mg modified-release hard capsules and tell their doctor immediately if they notice any of the following symptoms:

Symptoms caused by diclofenac:
- Passing blood in faeces (stool/motions)
- Bleeding from the stomach or intestines (e.g. passing black “tarry” stools)
- Vomiting blood or dark particles that look like coffee grounds.
- Stomach pains or other abnormal stomach symptoms
- Indigestion or heartburn

Symptoms caused by omeprazole:
- Reddening of the skin and painful red areas, blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be ‘Stevens-Johnson syndrome’ or ‘toxic epidermal necrolysis’.
- Yellow skin, dark urine and tiredness which can be symptoms of liver problems.

Your doctor may require you to have occasional check-ups while you are taking this medicine.

Other side effects caused by diclofenac include:
Common side effects:
- Headache, dizziness and giddiness.
- Sickness, feeling sick, flatulence, diarrhoea, loss of appetite.
- Stomach pains or other abnormal stomach symptoms, indigestion or heartburn.
- Changes in blood tests that check how the liver is working.
- Rash.

Other side effects caused by omeprazole include:
Common side effects:
- Headache.
- Effects on your stomach or gut: diarrhoea, stomach pain, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).

Taking this medicine may also lead to inflammation in the gut (leading to diarrhoea).

If the patient is on this medicine for more than 3 months, it is possible that the levels of magnesium in the blood may fall. Low levels of magnesium can be seen as fatigue, involuntary muscle contractions, disorientation, convulsions, dizziness or increased heart rate. If the patient gets any of these symptoms, they must tell their doctor promptly. Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood. The patient’s doctor may decide to perform regular blood tests to monitor the patient’s levels of potassium.
For the full list of all side effects reported with Diclopram 75 mg/20 mg modified-release hard capsules, see section 4 of the package leaflet available on the MHRA website.

**Why are Diclopram 75 mg/20 mg modified-release hard capsules, approved?**

It was concluded that, in accordance with EU requirements, Diclopram 75 mg/20 mg modified-release hard capsules has been shown to have comparable quality and to be bioequivalent to the free combination of diclofenac and omeprazole reference products Difene 75 mg dual release hard capsules (Temmler Werke GmbH, Germany) and Losec 20 mg gastro-resistant hard capsules (AstraZeneca UK Limited, UK). Therefore, the view was that, as for Difene 75 mg dual release hard capsules and Losec 20 mg gastro-resistant hard capsules, the benefits of Diclopram 75 mg/20 mg modified-release hard capsules, are greater than its risks and it was recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Diclopram 75 mg/20 mg modified-release hard capsules?**

A risk management plan (RMP) has been developed to ensure that Diclopram 75 mg/20 mg modified-release hard capsules are 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 Diclopram 75 mg/20 mg modified-release hard capsules 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 Diclopram 75 mg/20 mg modified-release hard capsules.**

Bulgaria, Cyprus, Estonia, Greece, Hungary, Lithuania, Latvia, Malta, Poland, Romania, Slovenia, Slovakia and the UK agreed to grant a Marketing Authorisation for Diclopram 75 mg/20 mg modified-release hard capsules on 08 September 2014. A Marketing Authorisation was granted in the UK on 09 October 2014.

The full PAR for Diclopram 75 mg/20 mg modified-release hard capsules follows this summary.

For more information about treatment with Diclopram 75 mg/20 mg modified-release hard capsules read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2014.
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Module 1

Information about the initial procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Diclopram 75 mg/ 20 mg modified-release hard capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Fixed combination, Article 10(b)</td>
</tr>
<tr>
<td>Active Substances</td>
<td>Diclofenac sodium and omeprazole</td>
</tr>
<tr>
<td>Form</td>
<td>Modified-release capsule, hard</td>
</tr>
<tr>
<td>Strength</td>
<td>75mg/20mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Pharmaswiss Česká republika s.r.o. Jankovcova 1569/2c 170 00 Praha 7 Czech Republic</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>Bulgaria, Cyprus, Estonia, Greece, Hungary, Lithuania, Latvia, Malta, Poland, Romania, Slovenia and Slovakia.</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/5465/001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>End of procedure (Day 210) – 08 September 2014</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 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 granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

The following text is the approved label text for the product. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

1. NAME OF THE MEDICINAL PRODUCT

DICLOPRAM 75 mg / 20 mg modified-release hard capsules
Diclofenac sodium / Omeprazole
Modified-release capsules, hard

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release capsule, hard contains 75 mg diclofenac sodium and 20 mg omeprazole.

3. LIST OF EXCIPIENTS

---

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release capsule, hard

Blister:
10 modified release capsules, hard
20 modified release capsules, hard
30 modified release capsules, hard
50 modified release capsules, hard
60 modified release capsules, hard
100 modified release capsules, hard

HDPE bottle:
80 modified release capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

---
8. EXPIRY DATE

Expiry-Date

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

* Additional note for HDPE Bottle: Keep the bottle tightly closed in order to protect from moisture.
* Additional note for HDPE Bottle: Shelf life after first opening: 1 month

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

Pharmaswiss Česká republika s.r.o.
Jankovecova 1569/2c
170 00 Praha 7
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

PL 33616/0002

13. BATCH NUMBER

Ch.-B.: 

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

---

16. INFORMATION IN BRAILLE

DICLOPRAM 75 mg / 20 mg
17. FURTHER INFORMATION

---

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PAR Diclopram 75 mg/ 20 mg modified-release hard capsules

1. NAME OF THE MEDICINAL PRODUCT

DICLOPRAM 75 mg / 20 mg modified-release hard capsules
Diclofenac sodium/ Omeprazole
Modified-release capsules, hard

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release capsule, hard contains 75 mg diclofenac sodium and 20 mg omeprazole.

3. LIST OF EXCIPIENTS

---

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release capsule, hard
30 modified release capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

---

8. EXPIRY DATE

Expiry-Date

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture.
Shelf life after first opening: 1 month

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**

Pharmaswiss Česká republika s.r.o.
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15. **INSTRUCTIONS ON USE**

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16. **Information in BRAILLE**

---

17. **Further information**

Grey marked fields are not printed.
<p>| PARTICULARS TO APPEAR ON &lt;THE OUTER PACKAGING&gt; &lt;AND&gt; &lt;THE IMMEDIATE PACKAGING&gt; |
| { Blister } |
| NAME OF THE MEDICINAL PRODUCT |
| DICLOPRAM 75 mg / 20 mg modified-release hard capsules |
| Diclofenac sodium / Omeprazole |
| Modified-release capsules, hard |
| NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
| Pharmaswiss Česká republika s.r.o. |
| EXPIRY DATE |
| Expiry-Date: see embossing |
| BATCH NUMBER |
| Ch.-B.: see embossing |</p>
<table>
<thead>
<tr>
<th>FURTHER INFORMATION</th>
</tr>
</thead>
</table>

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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 Member States considered that the application for Diclopram 75 mg/ 20 mg modified-release hard capsules (PL 33616/0002; UK/H/5465/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis in patients who are at risk of developing NSAID-associated gastric and/or duodenal ulcers.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Bulgaria, Cyprus, Estonia, Greece, Hungary, Lithuania, Latvia, Malta, Poland, Romania, Slovenia and Slovakia as Concerned Member States (CMS). The application was submitted under Article 10(b) of Directive 2001/83/EC, as amended, applicable for a fixed combination product of known active substances.

Diclopram 75 mg/ 20 mg modified-release hard capsules contain the active ingredients diclofenac and omeprazole.

Diclofenac is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase (cyclo-oxygenase).

Omeprazole, a racemic mixture of two enantiomers, reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H+ K+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

The applicant makes reference to the ‘Guideline on clinical development of fixed combination medicinal products (CPMP/EWP/240/95 Rev.1; 19 February 2009)’ to justify the development rationale of this fixed combination product. The objective of the development programme was to combine the currently approved doses of the active substances diclofenac sodium and omeprazole in to a fixed-dose combination product to provide simplification of therapy and improved safety.

In addition, to support this application, the applicant has provided evidence that the combination of a non-steroidal anti-inflammatory drug (NSAID) and proton pump inhibitor (PPI) is widely recommended by various national and international guidelines, including:

- Key elements for the SmPCs of non-selective NSAIDs, EMEA/CHMP/343456/2005
- Guidelines for Prevention of NSAID-Related Ulcer Complications (Lanza et al 2009)
- Osteoarthritis: The care and management of osteoarthritis in adults (NICE CG59)

The applicant has provided adequate justification for the chosen strengths and once daily posology:

**Diclofenac**
The diclofenac component is 75 mg as modified release pellets (25 mg as gastro-resistant pellets and 50 mg as prolonged release pellets). The applicant states that this dose, provided once daily, would meet the requirements of a relevant portion of patients with osteoarthritis, rheumatoid arthritis or ankylosing
spondylitis. Reference is also made to a published clinical study (Schmitt et al 1998). The study was double-blind, randomised placebo-controlled and parallel in design to assess the therapeutic dose response and safety of a modified-release diclofenac 75 mg formulation (taken once daily) versus a modified-release 150 mg formulation (taken once daily) versus an immediate release 50 mg formulation (taken 3 times a day) versus placebo in patients suffering from osteoarthritis of the knee and/or the hip. The primary outcome was pain assessed by visual analogue scale. All treatments were statistically significantly superior to placebo. There was no statistically significant difference between the active treatments.

**Omeprazole**

The omeprazole component is 20 mg as gastro-resistant pellets. This once daily dose is equal to the dose approved in Europe for the prevention of NSAID-associated gastric and duodenal ulceration.

In principle, the fixed combination of the active substances diclofenac and omeprazole is acceptable. The approved posology of omeprazole products is 20 mg once daily for the prevention of NSAID-associated gastric and duodenal ulceration. Therefore the daily dose of diclofenac must also be fixed. The choice of the 75 mg strength could be considered low for the proposed target population with chronic rheumatic disease. However, this dose is within the approved posology for diclofenac-containing products authorised in Europe for the same rheumatic disease indications. In addition, the applicant has provided data from the literature in support of the diclofenac daily dose. Furthermore, it is recommended that patients should take the lowest effective dose of NSAIDs in order to minimise undesirable effects (Key elements for the SmPCs of non-selective NSAIDs, EMEA/CHMP/343456/2005).

It is considered that the chosen strength of diclofenac could provide an acceptable level of benefit in the target population. The applicant has revised the product information to include text to advise prescribers and patients if symptoms are not controlled, then an alternative product may be required; since twice daily dosing with this fixed combination product would lead to over-exposure to omeprazole.

Five bioequivalence studies (two pilot and three pivotal) were submitted to support this application, comparing the fixed combination test product Diclopram 75 mg/20 mg modified-release hard capsules (Pharmaswiss Česká republika s.r.o) and the free combination of diclofenac and omeprazole reference products Difene 75 mg dual release hard capsules (Temmler Werke GmbH, Germany) and Losec 20 mg gastro-resistant hard capsules (AstraZeneca UK Limited, UK). The bioequivalence study reports provide the statement that the studies were conducted in accordance with the Helsinki Declaration (1964 and following amendments), ICH-GCP (1996), EEC rule No. 91/507/EEC and Directive 2001/20/EC of The European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulation and administrative provisions of the Member States relating to the implement of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that this application was for a fixed combination product containing well-known active substances for a substitution indication. Additional clinical and non-clinical studies are not warranted from a scientific or ethical perspective.

Under Article 7 of the Paediatric Regulation, the following waiver applies to this application and a copy of this waiver has been supplied:

- A product-specific waiver for the proposed indication of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis is covered by EMEA-000820-PIP01-09.

The waiver has been granted by the European Medicines Agency (EMA) for all subsets of the paediatric population from birth to less than 18 years of age on the grounds that the specific medicinal product does
not represent a significant therapeutic benefit over existing treatments, as both products are available separately and paediatric patients with arthritic conditions benefit from a flexible therapy.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. 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 of satisfactory inspection summary reports as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 08 September 2014. After a subsequent national phase, a licence was granted in the UK on 09 October 2014.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name(s) of the product in the Reference Member State</th>
<th>Diclopram 75 mg/ 20 mg modified-release hard capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Diclofenac sodium and omeprazole</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Acetic acid derivatives and related substances (M01AB55; diclofenac combinations)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Modified-release capsule, hard; 75 mg/20 mg</td>
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<tr>
<td>Reference number for the Mutual Recognition Procedure</td>
<td>UK/H/5465/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
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<tr>
<td>Concerned Member States</td>
<td>Bulgaria, Cyprus, Estonia, Greece, Hungary, Lithuania, Latvia, Malta, Poland, Romania, Slovenia and Slovakia.</td>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 33616/0002</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Pharmaswiss Česká republika s.r.o. Jankovcova 1569/2c 170 00 Praha 7 Czech Republic</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substances
The product contains two active substance, diclofenac sodium and omeprazole.

(1) Diclofenac sodium
INN: Diclofenac sodium

Structure:

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\text{\includegraphics{diclofenac_structure.png}}
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Molecular formula: \( \text{C}_{14}\text{H}_{10}\text{Cl}_{2}\text{NaO}_{2}; (\text{C}_{14}\text{H}_{10}\text{Cl}_{2}\text{NO}_{2})\text{Na}^+ \)
Molecular weight: 318.13 g/mol
Appearance: Diclofenac sodium is an odourless white, or slightly yellow, slightly hygroscopic crystalline powder. Sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96%) and slightly soluble in acetone.

(2) Omeprazole
INN: Omeprazole

Structure:

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\text{\includegraphics{omeprazole_structure.png}}
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Molecular formula: \( \text{C}_{17}\text{H}_{19}\text{N}_{3}\text{O}_{3}\text{S} \)
Molecular weight: 345.4 g/mol
Appearance: Omeprazole is a white to almost white powder, which is very slightly soluble in water, soluble in methylene chloride, sparingly soluble in ethanol (96 %) and in methanol. It dissolves in dilute solutions of alkali hydroxides.

Both active substances are the subject of European Pharmacopoeia monographs.

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

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, povidone K 25, colloidal anhydrous silica, methacrylic acid ethyl acrylate copolymer (1:1) Type A neutralised with (6 mol%) sodium hydroxide, propylene glycol, ammonio methacrylate copolymer type A, ammonio methacrylate copolymer type B, mannitol, magnesium carbonate heavy, hydroxypropylecellulose (75-150 mPas/5% sol.), sodium laurilsulfate, hypromellose (6mPas), methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30% (dry substance), polysorbate 80, triethyl citrate, talc and the capsule Shell [comprised of titanium dioxide (E171), iron oxide red (E 172), iron oxide yellow (E 172) and gelatin].

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the colourings in the capsule shell, iron oxide red (E 172), iron oxide yellow (E 172) which are controlled in line with regulation (EU) 231/2012 (regulation laying down specifications for food additives). Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that it is manufactured in line with current European guidelines concerning minimising the risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to combine the currently approved doses of the active substances diclofenac sodium and omeprazole into a robust, stable, single, modified-release hard capsule in order to provide a fixed-dose combination of the two actives for symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis in patients who are at risk of developing NSAID-associated gastric and/or duodenal ulcers. A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution profiles have been provided for the proposed and originator product.

Manufacturing Process

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

Finished Product Specification

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

Container-Closure System

The finished product is packaged in:

- High density polyethylene (HDPE) bottles with a tamper-evident polypropylene screw cap with integrated desiccant containing 30 modified-release hard capsules.
- Oriented polyamide (OPA)-aluminium-polyvinyl chloride (PVC)/aluminium blisters in pack sizes of 10, 20, 30, 50, 60 and 100 modified-release hard capsules.

Not all pack sizes may be marketed.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Regulation (EU) No. 10/2011) concerning materials in contact with foodstuff.

**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. The data from these studies support a shelf-life of 30 months for the blisters and 2 years for the unopened HDPE bottle which reduces to one month once the bottle has been opened with the storage conditions ‘Do not store above 30°C’ (both presentations). Keep the container tightly closed in order to protect from moisture (HDPE bottle only).

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

**Bioequivalence/bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies. The bioequivalence studies are discussed in Section III.3, Clinical Aspects.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

**Marketing Authorisation Application (MAA) Form**
The MAA form is 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 this application from a pharmaceutical viewpoint.

**III.2 NON-CLINICAL ASPECTS**
The pharmacological rationale for developing this fixed dose combination product is that omeprazole is able to reduce the risk of developing NSAID-induced peptic ulcers due to its reduction of gastric acid.

The applicant has submitted a reference from the published literature (Andersson et al 1988) which concluded that no drug interactions occur between omeprazole and diclofenac, such that diclofenac can be administered together with omeprazole without need for dosage adjustment.

Since there is extensive clinical experience with both diclofenac and omeprazole further non-clinical studies of the individual compounds are unnecessary. The applicant states that the efficacy and safety of diclofenac and omeprazole combination therapy is supported by the results of published clinical trials. This clinical data would supersede any non-clinical information.

In summary, the applicant has reviewed the published literature related to the non-clinical safety of diclofenac and omeprazole and used these data to support this application without conducting any
additional non-clinical studies with the fixed combination product. Since the pharmaco-toxicological profiles of both diclofenac and omeprazole are well characterised by reference to the published literature this approach is acceptable.

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

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application was submitted as a fixed combination product of known active substances intended as a substitution therapy. It is not expected that the environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics

The clinical pharmacology of diclofenac sodium and omeprazole is well-known. No new pharmacodynamic or pharmacokinetic data was required for this application.

Clinical Development Programme

According to the CHMP Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev.1), ‘bioequivalence should be demonstrated between the free combination of the recognised reference formulations of the individual monocomponents and the marketing formulation (fixed combination)’. To be in line with this guideline, and also the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation) (CPMP/EWP/280/96 Corr*) and Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party (EMA/618604/2008 Rev.7), the applicant has submitted three pivotal bioequivalence studies, one single dose fasting, one single dose fed, and one multiple dose fasting (see Section IV). The applicant also submitted reports from two pilot studies designed to estimate intra-subject variability and adequacy of blood sampling times for the active substances diclofenac and omeprazole.

Pilot studies

Two pilot, open-label randomised, single dose, four-period, four-sequence, crossover bioequivalence studies to preliminarily assess the potential for bioequivalence of Dictopram 75 mg/20 mg modified-release hard capsules (PharmaSuisse Česká republika s.r.o) with the reference products Difene 75 mg dual release hard capsules (Temmler Werke GmbH, Germany) and Losec 20 mg gastro-resistant hard capsules (AstraZeneca UK Limited, UK) in healthy adult human volunteers. One study was conducted under fed and fasting conditions and the other study was conducted under fed conditions only. The results of the pilot studies were not considered relevant for the overall assessment of bioequivalence so will not be discussed further.

Pivotal studies.

Study 1

An open-label, randomised, single dose, two period, two-sequence, two-way crossover, study to compare the pharmacokinetics of the test product Dictopram 75 mg/20 mg modified-release hard capsules (PharmaSuisse Česká republika s.r.o) versus equal doses of the reference products Difene 75 mg dual release hard capsules (Temmler Werke GmbH, Germany) and Losec 20 mg gastro-resistant hard capsules (AstraZeneca UK Limited, UK) in healthy adult male volunteers under fasted conditions.
All volunteers received a single oral dose of either the test product or a single dose of each reference product with 240 ml of water under fasting conditions. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 36 hours post dose. The washout period between treatment periods was at least 7 days.

Results

Table 1.  **Diclofenac under fasting conditions**: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ 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>$C_{max}$ (ng/ml)</th>
<th>$t_{max}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1544.319 ± 325.452</td>
<td>1680.041 ± 352.065</td>
<td>613.832 ± 285.716</td>
<td>1.00 (0.25 – 5.00)</td>
</tr>
<tr>
<td>Reference</td>
<td>1529.777 ± 375.489</td>
<td>1651.842 ± 359.493</td>
<td>574.454 ± 260.696</td>
<td>0.75 (0.50-5.50)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>101.29 (97.58 – 105.15)</td>
<td>101.58 (97.93 – 105.36)</td>
<td>106.00 (92.79 – 121.08)</td>
<td></td>
</tr>
</tbody>
</table>

*A ln-transformed values

$AUC_{0-t}$: Area under the plasma concentration curve from administration to last observed concentration at time $t$. $AUC_{0-72h}$ can be reported instead of $AUC_{0-\infty}$ in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable.

Only for immediate release products

$AUC_{0-\infty}$: Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when $AUC_{0,72h}$ is reported instead of $AUC_{0-\infty}$

$C_{max}$: Maximum plasma concentration

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

Table 2.  **Omeprazole under fasting conditions**: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ 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>$C_{max}$ (ng/ml)</th>
<th>$t_{max}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>931.071 ± 1079.158</td>
<td>936.874 ± 1081.499</td>
<td>446.529 ± 304.571</td>
<td>1.50 (0.75 – 3.00)</td>
</tr>
<tr>
<td>Reference</td>
<td>913.191 ± 988.041</td>
<td>918.975 ± 989.904</td>
<td>429.325 ± 261.544</td>
<td>1.50 (0.75 – 4.00)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>100.33 (92.83 – 108.44)</td>
<td>100.29 (92.90 – 108.26)</td>
<td>99.16 (88.56 – 111.02)</td>
<td></td>
</tr>
</tbody>
</table>

*A ln-transformed values

$AUC_{0-t}$: Area under the plasma concentration curve from administration to last observed concentration at time $t$. $AUC_{0,72h}$ can be reported instead of $AUC_{0-\infty}$ in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable.

Only for immediate release products

$AUC_{0-\infty}$: Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when $AUC_{0,72h}$ is reported instead of $AUC_{0-\infty}$

$C_{max}$: Maximum plasma concentration

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

Study 2.

An open-label, randomised, single dose, four period, two-sequence, replicate design study to compare the pharmacokinetics of the test product Diclopram 75 mg/20 mg modified-release hard capsules (Pharmaswiss Česká republika s.r.o) versus equal doses of the reference products Difene 75 mg dual release hard capsules (Temmler Werke GmbH, Germany) and Losec 20 mg gastro-resistant hard capsules (AstraZeneca UK Limited, UK) in healthy adult male volunteers under fed conditions.
Following a supervised fast of 10 hours, all volunteers were given a standard high-fat high calorie breakfast. Thirty minutes after starting breakfast; all volunteers received a single oral dose of either the test product or a single dose of each reference product with 240 ml of water. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 36 hours post dose. The washout period between treatment periods was at least 7 days.

**Results**

**Diclofenac under fed conditions:** Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ (ng/ml/h)</th>
<th>$\text{AUC}_{0-\infty}$ (ng/ml/h)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$t_{\text{max}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>$1531.775 \pm 306.866$</td>
<td>$1599.916 \pm 306.784$</td>
<td>$369.937 \pm 136.905$</td>
<td>6.50 (0.25 – 9.00)</td>
</tr>
<tr>
<td>Reference</td>
<td>$1538.628 \pm 314.484$</td>
<td>$1608.254 \pm 318.341$</td>
<td>$339.422 \pm 126.897$</td>
<td>6.25 (1.50 – 10.00)</td>
</tr>
<tr>
<td><em>Ratio (90% CI)</em></td>
<td>$99.68 (97.77 – 101.62)$</td>
<td>$99.67 (97.64 – 101.74)$</td>
<td>$108.47 (100.17 – 117.46)$</td>
<td></td>
</tr>
</tbody>
</table>

*ln-transformed values

**AUC$_{0-t}$** Area under the plasma concentration curve from administration to last observed concentration at time t. AUC$_{0-72h}$ can be reported instead of 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

**AUC$_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. AUC$_{0-\infty}$ does not need to be reported when AUC$_{0-72h}$ is reported instead of AUC$_{0-t}$

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

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

**Omeprazole under fed conditions:** Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ (ng/ml/h)</th>
<th>$\text{AUC}_{0-\infty}$ (ng/ml/h)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$t_{\text{max}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>$483.568 \pm 302.030$</td>
<td>$493.750 \pm 305.016$</td>
<td>$209.283 \pm 123.723$</td>
<td>4.00 (1.17-8.00)</td>
</tr>
<tr>
<td>Reference</td>
<td>$507.580 \pm 296.738$</td>
<td>$515.739 \pm 297.043$</td>
<td>$195.508 \pm 101.326$</td>
<td>4.00 (0.83 – 10.00)</td>
</tr>
<tr>
<td><em>Ratio (90% CI)</em></td>
<td>$90.63 (81.93 – 100.26)$</td>
<td>$91.20 (82.70 – 100.57)$</td>
<td>$101.09 (88.98 – 114.86)$</td>
<td></td>
</tr>
</tbody>
</table>

*ln-transformed values

**AUC$_{0-t}$** Area under the plasma concentration curve from administration to last observed concentration at time t. AUC$_{0-72h}$ can be reported instead of AUC$_{0-\infty}$ in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

**AUC$_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. AUC$_{0-\infty}$ does not need to be reported when AUC$_{0-t}$ is reported instead of AUC$_{0-72h}$

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

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

_Study 3._

An open-label, randomised, multiple dose, two period, two-sequence, two-way crossover study to compare the pharmacokinetics of the test product Diclopram 75 mg/ 20 mg modified-release hard capsules (Pharmaswiss Česká republika s.r.o) versus equal doses of the reference products Difene 75 mg dual release hard capsules (Temmler Werke GmbH, Germany) and Losec 20 mg gastro-resistant hard capsules (AstraZeneca UK Limited, UK) in healthy adult male volunteers under fasting conditions.
On the morning of treatment days 1 to 7, following a supervised fast of 10 hours, volunteers were given a single dose of test product or a single dose of each reference product with 240 ml of water. Blood samples were taken for the measurement of pharmacokinetic parameters at pre-dose (treatment days 1-7) and up to 24 hours post dose (day 7 only). The washout period between treatment periods was at least 16 days.

**Results**

**Diclofenac under fasting conditions: Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-τ&lt;/sub&gt; ng/ml/h</th>
<th>C&lt;sub&gt;max,ss&lt;/sub&gt; ng/ml</th>
<th>C&lt;sub&gt;min,ss&lt;/sub&gt; ng/ml</th>
<th>t&lt;sub&gt;max,ss&lt;/sub&gt; h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1649.918 ± 359.268</td>
<td>768.844 ± 323.785</td>
<td>Not reported</td>
<td>0.5 (0.25 – 4.0)</td>
</tr>
<tr>
<td>Reference</td>
<td>1596.133 ± 396.151</td>
<td>728.193 ± 312.466</td>
<td>Not reported</td>
<td>0.5 (0.25 - 4.0)</td>
</tr>
<tr>
<td><em>Ratio (90% CI)</em></td>
<td>103.88 (99.53 – 108.41)</td>
<td>105.95 (92.46 – 121.42)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ln-transformed values

- AUC<sub>0-τ</sub>: Area under the plasma concentration curve during a dosage interval at steady state
- C<sub>max,ss</sub>: Maximum plasma concentration at steady state
- C<sub>min,ss</sub>: Minimum plasma concentration at steady state
- t<sub>max,ss</sub>: Time until C<sub>max,ss</sub> is reached

**Table 6. Omeprazole under fasting conditions: Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-τ&lt;/sub&gt; ng/ml/h</th>
<th>C&lt;sub&gt;max,ss&lt;/sub&gt; ng/ml</th>
<th>C&lt;sub&gt;min,ss&lt;/sub&gt; ng/ml</th>
<th>t&lt;sub&gt;max,ss&lt;/sub&gt; h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>945.230 ± 731.873</td>
<td>489.748 ± 279.918</td>
<td>Not reported</td>
<td>1.5 (0.75 – 4.0)</td>
</tr>
<tr>
<td>Reference</td>
<td>943.421 ± 854.787</td>
<td>454.190 ± 230.879</td>
<td>Not reported</td>
<td>1.125 (0.5-5.0)</td>
</tr>
<tr>
<td><em>Ratio (90% CI)</em></td>
<td>100.85 (93.16 – 109.16)</td>
<td>100.80 (90.30 – 112.53)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ln-transformed values

- AUC<sub>0-τ</sub>: Area under the plasma concentration curve during a dosage interval at steady state
- C<sub>max,ss</sub>: Maximum plasma concentration at steady state
- C<sub>min,ss</sub>: Minimum plasma concentration at steady state
- t<sub>max,ss</sub>: Time until C<sub>max,ss</sub> is reached

**Conclusions**

The 90% confidence intervals for AUC and C<sub>max</sub> for test versus reference products for diclofenac and omeprazole are within predefined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr) in fasted and fed subjects after a single dose and in fasted subjects at steady state. Thus, the data from the three studies support the claim that the test product is bioequivalent to the reference products.

No pharmacokinetic interactions are expected for the active substances diclofenac sodium and omeprazole, based on current SmPCs of the reference products. In addition, the applicant has provided a description of a clinical in vivo drug-drug interaction study of diclofenac and omeprazole (Andersson et al 1998). There was no evidence of significant interaction, as measured by AUC ratio.
Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

Efficacy
No new efficacy data were submitted. The clinical overview includes an adequate discussion of literature data relating to the use of diclofenac and omeprazole in combination. In addition, the applicant refers to relevant guidelines which recommend the combination of NSAIDs and gastro-protective agents in high risk patients. It is also noted that the key elements for the SmPCs of non-selective NSAIDs (EMEA/CHMP/343456/2005) recommends combination therapy with gastro-protective agents for patients at risk.

Safety
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this type of application. No new or unexpected safety issues were highlighted by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator products. The PIL is consistent with the SmPC and in line with current guidelines. The labelling is in line with current guidelines.

MAA Form
The MAA form is satisfactory.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
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 has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

An acceptable Risk Management Plan has been provided. Routine risk minimisation is provided through the Summary of Product Characteristics and the Patient Information Leaflet and this is sufficient.

Conclusion
There are no objections to the approval of the product from a clinical view-point.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The quality characteristics of Diclopram 75 mg/ 20 mg modified-release hard capsules 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. Since the pharmaco-toxicological profiles of both diclofenac and omeprazole are well characterised by reference to the published literature; this is acceptable.
The pharmacodynamic, pharmacokinetic and toxicological properties of diclofenac sodium and omeprazole are well-known.

**EFFICACY**
With the exception of the bioequivalence studies, no new data were submitted. Literature data relating to the use of diclofenac and omeprazole in combination have been provided and are acceptable.

Bioequivalence has been demonstrated between the applicant’s Diclopram 75 mg/ 20 mg modified-release hard capsules (Pharmaswiss Česká republika s.r.o) and the mono component reference products administered separately (Difene 75 mg dual release hard capsules and Losec 20 mg gastro-resistant hard capsules).

**SAFETY**
With the exception of the bioequivalence studies, no new data were submitted and none are required for this type of application. As the safety profile of diclofenac sodium and omeprazole is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence studies.

**PRODUCT LITERATURE**
The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

**BENEFIT-RISK ASSESSMENT**
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

The bioequivalence studies support the claim that the applicant’s fixed combination product is bioequivalent with the mono components given separately at the same dose level and that there is no interaction between the two active substances.

The Marketing Authorisation Holder has provided adequate justification for the combination product and the studies supporting this application were acceptable.

Extensive clinical experience with diclofenac sodium and omeprazole in combination is considered to have demonstrated the therapeutic value of the compound. The benefit-risk 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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