PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Diclofenacnatrium EC 25, gastro-resistant tablets 25 mg
Diclofenacnatrium EC 50, gastro-resistant tablets 50 mg
Disphar International B.V., the Netherlands

diclofenac sodium

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states. It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation. This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1442/001-002/MR
Registration number in the Netherlands: RVG 100157, 100163

22 February 2010

Pharmacotherapeutic group: anti-inflammatory and anti-rheumatic products, non-steroids; acetic acid derivatives and related substances
ATC code: M01AB05
Route of administration: oral
Therapeutic indication: inflammatory and degenerative forms of rheumatoid arthritis; periarthritis humeroscapularis; acute gout; painful postoperative and posttraumatic inflammation and swelling; symptomatic treatment of primary dysmenorrhea; diseases accompanied by fever, particularly for short-term use as an adjuvant to chemotherapy for an infectious disease.

Prescription status: prescription only
Date of first authorisation in NL: 13 August 2007
Concerned Member States: Mutual recognition procedure with PL
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Diclofenacnatrium EC 25 and EC 50, gastro-resistant tablets 25 and 50 mg, from Disphar International B.V. The date of authorisation was on 13 August 2007 in the Netherlands.

The product is indicated for:
- inflammatory and degenerative forms of rheumatoid arthritis: chronic polyarthritis, juvenile chronic polyarthritis, arthrosis including spondylarthrosis.
- periarthritic humeroscapularis.
- acute gout.
- painful postoperative and posttraumatic inflammation and swelling, e.g. following dental or orthopaedic surgery.
- symptomatic treatment of primary dysmenorrhea.
- diseases accompanied by fever, particularly for short-term use as an adjuvant to chemotherapy for an infectious disease. Fever on its own is not an indication.

A comprehensive description of the indications and posology is given in the SPC.

Diclofenacnactrium EC contains the prostaglandin synthetase inhibiting substance diclofenac sodium. This is a phenylacetic acid derivative with antiphlogistic, antipyretic and analgesic properties. A significant part of the mechanism of action is ascribed to the (experimentally proven) inhibition of prostaglandin biosynthesis. Prostaglandins play a key role in the aetiology of inflammation, pain and fever.

The anti-inflammatory and analgesic properties of diclofenac sodium are expressed clinically in rheumatic disease by a significant improvement of symptoms such as rest pain, movement pain, morning stiffness, joint swelling and by functional improvement. In painful postoperative and posttraumatic inflammation and swelling diclofenac sodium leads to a fast decrease of spontaneous pain and movement pain and a decrease of inflammation and swelling.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Voltaren 25 mg gastro-resistant tablets (NL license RVG 07003) registered in the Netherlands by Novartis Pharma B.V. since 15 October 1976, and Voltaren 50 mg tablets, which has been registered in Denmark by Novartis healthcare A/S since 5 October 1977. In addition, reference is made to Voltaren authorisations in the individual member states (reference product). In the Netherlands, Voltaren enteric-coated tablets 50 mg (NL RVG 07708) were registered since 1978, but withdrawn in 2006 for commercial reasons.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Voltarène 50 mg enteric coated tablets, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.
No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a generic application.

II  SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is diclofenac sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or slightly yellowish, crystalline powder, which is slightly hygroscopic. The substance is sparingly soluble in water.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
The manufacturing process is covered by the CEP, and therefore not described by the MAH.

Quality control of drug substance
The drug substance specification is in line with the CEP and the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided on three batches stored at room temperature (for 48 months), three batches at 40°C/75% RH (for six months) and three more recent batches stored for 48 months at 25°C/60%RH and 6 months at 40°C/75% RH. The batches were adequately stored, protected from light. At normal and accelerated conditions all results complied and no trends were observed. In view of that, the proposed re-test of 4 year was granted, with the storage condition ‘protect from light’. Stability studies will be performed on the first 3 production-scale batches of drug substance.

* Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition
Diclofenacnatrium EC 25 and EC 50 contain as active substance 25 mg and 50 mg of diclofenac sodium per tablet, respectively.

Diclofenacnatrium EC 25 is a yellow, coated tablet inscribed with ‘D25’.
Diclofenacnatrium EC 50 is a brown, coated tablet inscribed with ‘D50’.

The gastro-resistant tablets are packed in PVC-PVDC/Aluminium blister strips.
The excipients are: maize starch, lactose monohydrate, sodium starch glycolate, pregelatinized starch (maize), microcrystalline cellulose (E460), magnesium stearate (E470b), talc (E553b), macrogol 6000, methylacrylic acid copolymer – ethyl acrylate copolymer, dimeticone, polysorbate 80, sorbic acid (E200), titanium dioxide (E171), iron oxide yellow (E172), 50 mg only: iron oxide red (E172).

Both tablet formulation are not dose proportional, only the chosen excipients are the same.

**Pharmaceutical development**

The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients and packaging are usual for this type of dosage form. The MAH’s objective was to obtain a formulation of gastro-resistant diclofenac sodium tablets, which is similar to the innovator’s product Voltaren.

Diclofenac EC 50 mg test tablets are not completely dose-proportional with the 25 mg strength. This is also the case for Voltaren 25 mg and 50 mg. Both formulations Diclofenacnatrium EC 25 mg and 50 mg contain about the same ingredients as Voltaren 25 mg and 50 mg and the total weights are also about equal for each formulation. During the development phase, it was decided to replace wheat starch by maize starch in order to avoid gluten intolerance. The bioequivalence study was performed with Diclofenac sodium EC 50 mg tablets containing wheat starch instead of maize starch. The RMS is of the opinion that this difference does not have an effect on the outcome of the bioequivalence study. Dissolution profiles were found to be comparable.

The final composition was tested by comparative dissolution studies versus the innovator product in several EU countries (NL, FR, BE, DK, DE, UK) and found to be comparable. The pharmaceutical development of the product has been adequately performed.

**Manufacturing process**

The tablets are manufactured by wet granulating the drug substance with the excipients followed by compressing into tablets cores. The tablet cores are gastro-resistant coated. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product have been presented for nine full-scale batches.

**Excipients**

The excipients comply with the Ph.Eur., iron oxide is conform the United States Pharmacopoeia. These specifications are acceptable.

**Quality control of drug product**

The product specification includes tests for appearance, average mass, uniformity of dosage units, disintegration, identity, assay, related substances, dissolution, identification of the colorants, loss on drying and microbial quality. The shelf-life specifications on average mass are broadened because of the hygroscopic nature of the tablets. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on one lab-scale and two full-scale batches of each strength, demonstrating compliance with the release specification.

**Stability of drug product**

Stability data on the active substance have been provided for 19 full-scale batches stored at 25°C/60%RH (48 months), 30°C/65%RH (12 months) and 40°C/75%RH (10 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC/Aluminium blister packs. For 48 months storage at 25°C/60%RH all results complied.

An increase in average mass was seen under all conditions. At 30°C/65%RH and 40°C/75%RH out of specification results are encountered. In view of the stability data a shelf life of 48 months could be granted, but the product should be stored below 25°C in PVC/PVDC/Aluminium blisters.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

A TSE declaration for lactose monohydrate has been provided; it is derived from milk from healthy cows. Magnesium stearate is derived from vegetable origin.
II.2 Non clinical aspects

These products are generic formulations of Voltaren tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of diclofenac released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Diclofenac sodium is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted two bioequivalence studies, one study under fasted and one study under fed conditions, in which the pharmacokinetic profile of the test product Diclofenacnaatrium EC 50 (Disphar International B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Voltarène 50 mg enteric coated tablets (Novartis, France). As the product is a gastro-resistant tablet, bioequivalence should be demonstrated under both fasted and fed conditions.

The choice of the reference product
The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is similar to the formula proposed for marketing, except that wheat starch was used instead of maize starch. The dissolution data of the current formula and the one used in the bioequivalence study were compared. The results show that the profiles are similar. There is no objection to using the formulation with wheat starch in the bioequivalence studies.

Bioequivalence study 1 under fasted conditions

Design
A single-dose, open-randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 19-37 years. Each subject received a single dose (50 mg) of one of the 2 diclofenac sodium formulations. The tablet was orally administered in solid form with 200 ml water after an overnight fast of at least 10 hours. Intake of water was allowed until 1 hour before drug intake. Fasting was continued for 4 hrs after dosing. There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 and 9 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 24 subject completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{max} \) (median, range)) of diclofenac under fasted conditions.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ (ng.h/ml)</th>
<th>C$_{max}$ (ng/ml)</th>
<th>t$_{max}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1105 ± 255</td>
<td>1227 ± 416</td>
<td>2.00 (1.00-4.33)</td>
</tr>
<tr>
<td>Reference</td>
<td>1092 ± 269</td>
<td>1334 ± 489</td>
<td>2.00 (1.33-3.67)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)*

|        | 1.012 (0.958-1.070) | 0.921 (0.812-1.044) |

CV (%)

|        | 11 | 26 |

AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
C$_{max}$ maximum plasma concentration
t$_{max}$ time for maximum concentration

*ln-transformed values

The 90% confidence intervals calculated for AUC$_{0-t}$ and C$_{max}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of diclofenac under fasted conditions, it can be concluded that Diclofenacnatrium EC 50 and Voltarène 50 mg enteric-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study 2 under fed conditions

**Design**

A single-dose, open-label randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 24 healthy subjects (12 male/12 female), aged 19-45 years. Each subject received a single dose (50 mg) of one of the 2 diclofenac sodium formulations. The tablets were orally administered in solid form with 200 ml of non-carbonated water, 30 min after the start of a high-fat breakfast which ended 10 min prior to dosing. The breakfast consisted of: 3 slices of wheat bread, 15 gram of butter, 2 slices of cheese (approximately 70 gram), 1 egg and 1 slice of bacon (approximately 15 gram) together fried in 5 gram of butter, 150 ml of high-fat milk, 150 ml of diluted orange juice. Total approximately: 960 kcal, 70 gram fat, 30 gram protein, 40 gram carbohydrate, 350 ml water. There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and at 1, 2, 2.5, 3, 3.5, 4 hours after administration of the products, and from then on every 20 minutes until 15 hours after dosing. Thereafter, samples were collected at 15.5, 16, 16.5, 17, 17.5, 18, 19, 20, 22 and 24 hours after dosing (50 samples).

**Analytical/statistical methods**

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable. The widened bioequivalence range for C$_{max}$ outside 0.75-1.33 is not according to the guideline, but the issue was discussed in April 2007 in the CMD(h) meeting for another procedure (same study was issued for this study) and approved by consensus.

**Results**

One subject withdrew his consent for personal reasons prior to period 2. Twenty-three subjects completed the study and were eligible for pharmacokinetic analysis.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ (median, range)) of diclofenac under fed conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ (ng.h/ml)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$t_{\text{max}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1176 ± 238.0</td>
<td>1330 ± 374</td>
<td>7.33 (4.33-17.00)</td>
</tr>
<tr>
<td>Reference</td>
<td>1256 ± 245.2</td>
<td>1630 ± 436</td>
<td>7.00 (3.00-14.67)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.936 (0.890-0.984)</td>
<td>0.809 (0.723-0.906)</td>
<td>---</td>
</tr>
<tr>
<td>CV (%)</td>
<td>9.9</td>
<td>22.5</td>
<td>---</td>
</tr>
</tbody>
</table>

$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to $t$ hours

$C_{\text{max}}$ maximum plasma concentration

$t_{\text{max}}$ time for maximum concentration

*ln-transformed values

**Conclusion and discussion**

Based on the pharmacokinetic parameters of diclofenac, the reference and test are considered bioequivalent with respect to the extent of absorption after a single 50 mg dose, administered after a high-fat breakfast (see also CMD(h) discussion below). The 90% confidence intervals calculated for $AUC_{0-t}$ was within the normal bioequivalence acceptance range of 0.80 – 1.25. The 90% CI for $C_{\text{max}}$ was within the widened bioequivalence range off 0.70-1.43.

**Food interaction**

There is a considerable delay in absorption of diclofenac observed under fed conditions. A possible explanation is an interaction with food in the stomach (e.g. absorption) and/or a delay in gastric emptying after high-fat breakfast. Taking enteric-coated tablets under fed state is associated with a delay in absorption, and bioequivalence was not achieved.

The fed study was also submitted during the MRP SE/H/600/01-02, in which SE acted as RMS. Since the post-prandial study could not be formally accepted during the MPR (SE/H/600/01-01/MR), it was re-submitted during CMD referral. There was a discussion on 23-24 April 2007 regarding the widening of the acceptance criteria to 70-143%. The RMS argued that such a widening was in accordance with the relevant guideline although the EWP Q&A document was unclear as to whether a widening outside 75-133% would be acceptable. The member states involved in the procedure agreed that the widening of the acceptance criteria in this case did not have any clinical relevance. A contributing fact was that the product is recommended to be administered before a meal, which is also stated in section 4.2 of the SPC. Therefore, consensus about approval was reached.

**Extrapolation to 25 mg strength**

The 25 mg tablet is not completely dose proportional with the 50 mg tablet, but complies with the criteria for extrapolation. The tablets have been manufactured by the same manufacturer and process, the pharmacokinetics is linear over the dose range, and the (quantitative) difference in composition is considered not to affect absorption of diclofenac. Moreover, this was further supported by dissolution data.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

**Risk management plan**

Diclofenac was first approved in 1977, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of diclofenac can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not
adequately covered by the current SPC. Additional risk minimisation activities have not been identified for
the reference medicinal product. Routine pharmacovigilance activities are sufficient to identify actual or
potential risks and a detailed European Risk Management Plan is not necessary for this product.

Pharmacovigilance plan
A description of the pharmacovigilance plan has been submitted in line with chapter 2.2 of Volume 9A of
the Rules governing medicinal products in the European Union. The MAH must ensure that the system of
pharmacovigilance is in place and functioning before the product is placed on the market.

Product information

SPC
The SPC was updated in line with the SPC of the Dutch innovator product. Besides this, the SPC was
brought in line with the document “Key elements for the summaries of product characteristics of non-
selective NSAIDs” adopted by the CHMP during its meeting in October 2005, with respect to the wording
concerning gastrointestinal safety of NSAIDs and skin reactions of NSAIDs.
Additionally, the warning on fertility currently included in section 4.6 was moved to section 4.4, in
accordance with the document (dated 25 May 2004) SPC and PIL Wording for Non-Steroidal Anti-
inflammatory Drugs (NSAIDs) with regard to disturbances of female fertility.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements
of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot phase followed by two
rounds with 10 participants each. The test was conducted in a population of potential diclofenac users.
Respondents from different age groups, educational levels and living environments were selected, next to
an equal distribution of male/female.
Ten product specific questions were formulated, each divided into two subquestions (total of 20
questions). There were sufficient (general and applicability) questions about the critical sections (key
safety aspects) of the leaflet. The quality and number of questions are considered sufficient. After reading
the leaflet the respondents were first asked for a general impression of the leaflet, and were then asked
the product specific questions. After the diagnostic test, an assessment of lay-out followed, using 16
assessment criteria focusing on clarity, fonts and paper, readability, language, completeness and
appearance.
During the first round, for almost all items at least 90% scored well on the diagnostic questions. No critical
issues could be identified. No changes were proposed before the start of the second test round.
One question presented some difficulty: this question concerned the findability of the section "do not use
diclofenac" and scored 80%. This is a critical section in the leaflet. Although the score of this question was
lower, it is advised not to make changes to this section of the leaflet, as the location and wording of this
section is deemed adequate, and in accordance with the template.
In the second round of testing, a 100% score was reached for subjects able to locate the information in
the leaflet. Of those able to locate, a 100% score was reached in answering the questions correctly. The
question which cause some difficulty in the first round, was answered correctly, resulting in a combined
score of 90%.
The results show that the leaflet passes the readability test, as for each question, at least 90% of subjects
were able to locate the relevant information and of those at least 90% were able to demonstrate full
understanding of the information. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Diclofenacnatrium EC 25 and EC 50, gastro-resistant tablets 25 and 50 mg have a proven chemical-pharmaceutical quality and are generic forms of Voltaren 25 and 50 mg gastro-resistant tablets. Voltaren is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence under both fasted and fed conditions has been shown to be in compliance with the requirements of European guidance documents. Under fed conditions the $C_{\text{max}}$ was within the widened bioequivalence range of 0.70-1.43. This widening was excepted during a CMD(h) referral for procedure SE/H/600/01-02, the member states had agreed that the widening of the acceptance criteria was not clinically relevant in this case. Moreover it is advised to take the tablets before a meal..

The MAH will make sure that systems and services are in place to ensure compliance with their pharmacovigilance obligations (see commitment below).

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other diclofenac sodium containing products.

The Board followed the advice of the assessors. Diclofenacnatrium EC 25 and EC 50 were authorised in the Netherlands on 13 August 2007.

The mutual recognition procedure started on 24 June 2008. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Diclofenacnatrium EC 25 and EC 50 gastro-resistant tablets with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finished on 22 September 2008.

A European harmonised birth date has been allocated (11 May 1977) and subsequently the first data lock point for diclofenac sodium is September 2009. The first PSUR will cover the period from September 2008 to September 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 May 2010.

The following post-approval commitments have been made during the procedure:

**Quality - active substance**
- The MAH will provide stability data on the first 3 production-scale batches of drug substance.

**Pharmacovigilance system**
- The MAH committed to ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C\textsubscript{max}</td>
<td>Maximum plasma concentration</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<td>PAR</td>
<td>Public Assessment Report</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PIL</td>
<td>Package Leaflet</td>
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<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>t\textsubscript{1/2}</td>
<td>Half-life</td>
</tr>
<tr>
<td>t\textsubscript{max}</td>
<td>Time for maximum concentration</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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<tr>
<td>Scope</td>
<td>Procedure number</td>
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<tr>
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<tr>
<td>Addition of a primary packaging site with consequential addition of the secondary packaging for the Marketing Authorisation in Poland and in Netherlands.</td>
<td>NL/H/1442/001-002/IA/001</td>
</tr>
<tr>
<td>Addition of a batch release site for the Marketing Authorisation in Poland and in Netherlands.</td>
<td>NL/H/1442/001-002/IA/002</td>
</tr>
<tr>
<td>Change in the name of the product in Poland.</td>
<td>NL/H/1442/001-002/IB/003</td>
</tr>
<tr>
<td>Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the finished product; from a new manufacturer (replacement or addition); other substances.</td>
<td>NL/H/1442/001-002/IA/004</td>
</tr>
</tbody>
</table>