Public Assessment Report

Scientific discussion

Racecadotril Double-E Pharma
100 mg capsules, hard

(racecadotril)

NL/H/3093/001/DC

Date: 12 October 2015

This module reflects the scientific discussion for the approval of Racecadotril Double-E Pharma 100 mg capsules, hard. The procedure was finalised on 12 January 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Racecadotril Double-E Pharma 100 mg capsules, hard from DOUBLE-E PHARMA Ltd.

The product is indicated for the symptomatic treatment of acute diarrhoea in adults when causal treatment is not possible.

If causal treatment is possible, racecadotril can be administered as a complementary treatment.

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

Racecadotril is a prodrug that needs to be hydrolysed to its active metabolite thiorphan, which is an inhibitor of enkephalinase, a cell membrane peptidase located in various tissues, notably the epithelium of the small intestine. This enzyme contributes both to the hydrolysis of exogenous peptides and to the breakdown of endogenous peptides such as enkephalins. Racecadotril protects enkephalins from enzymatic degradation thereby prolonging their action at enkephalineric synapses in the small intestine and reducing hypersecretion.

Racecadotril is a pure intestinal antisecretory active substance. It decreases the intestinal hypersecretion of water and electrolytes induced by cholera toxin or inflammation, and does not have effects on basal secretory activity. Racecadotril exerts rapid antidiarrhoeal action, without modifying the duration of intestinal transit.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Tiorfan® 100 mg, capsules which has been registered in France by Bioprojet Pharma since 10 July 1992. It is authorised in the Netherlands since August 2011 under the name Hidrasec 100 mg capsules hard (ES/H/0122/001/E/001, NL License RVG 109471).

The concerned member states (CMS) involved in this procedure were Belgium, France, Germany, Portugal and Spain.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Racecadotril Double-E Pharma 100 mg is a yellow opaque-yellow opaque colored capsule, size 2, containing a white or almost white powder.

The capsules are packed in PVC-PVDC/ Aluminium transparent blisters.

The excipients are:
Powder - lactose monohydrate, pregelatinised starch, silica colloidal anhydrous, magnesium stearate
Capsule - yellow iron oxide (E172), titanium dioxide (E171), gelatin.

II.2 Drug Substance

The active substance is racecadotril, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white or almost white powder which is practically insoluble in water. It is a pro-drug of thiorphan. No polymorphism has been detected in this substance. The molecule has one chiral centre. The substance is a racemate.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of
the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

**Manufacturing process**
The manufacturing process involves three steps. The manufacturing process and starting materials have been adequately described. The drug substance is sufficiently characterized with regard to chemical and physical structure.

**Quality control of drug substance**
The MAH’s specification for the drug substance is the same as of the ASMF-holder with additional limits for particle size distribution. The same analytical methods are included, and also the method for particle size is described. The specification of the ASMF-holder is the same as the Ph. Eur. monograph, with additional limits: limits for heavy metals and for residual solvents, and for particle size. Batch analysis results have been submitted of two production batches.

**Stability of drug substance**
Stability data on the active substance have been provided for four production batches stored at 25°C/60% RH (maximum 72 months) and 40°C/75% RH (six months). No significant changes were observed in the stability data, only slight increase of degradation products at 40°C/75% RH. Based on the provided stability data, the proposed re-test period of 60 months, when stored below 25°C, is acceptable.

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**II.3 Medicinal Product**

**Pharmaceutical development**
The development of the product has been described, the choice of excipients is justified and their functions explained. The innovator product was the prototype in the pharmaceutical development studies. The qualitative composition of the proposed generic product is the same as that of the reference product. A drug substance batch was tested for solubility in water at different pH conditions to simulate the physiological range (from pH 1.2 to 6.8) and in a solution of Tween 20 in water. It was found that the active ingredient is insoluble throughout the physiological range and that a surfactant will increase the drug substance solubility. This finding was used in the development of the routine dissolution quality control test. The dissolution medium in this test comprises water with a surfactant. A bioequivalence study was carried out with the product. Bioequivalence was demonstrated. The manufacturing process development is adequately explained.

**Manufacturing process**
The manufacturing process comprises of the following steps: 1) Sieving of raw materials, 2) Dry mixing of materials, 3) Compaction phase (slugging), 4) Slugs breaking and sizing, 5) Preparation of final blend, 6) Filling of capsule with final blend. The manufacturing process is a standard process. The description of the manufacturing process is sufficiently detailed. The process has been sufficiently validated.

Process evaluation data were presented for two batches at pilot batch size. All batches complied with the predefined acceptance criteria. An acceptable process validation protocol has been provided for the next production batches after product approval.

**Control of excipients**
All individual excipients comply with the Ph.Eur. where relevant. The colourants comply with the Directive 2009/35 and 231/2012; titanium dioxide also complies with the Ph. Eur. The specifications of the excipients are acceptable.

**Quality control of drug product**
The product specification includes tests for appearance, identification, average mass, water content, dissolution, uniformity of dosage units, related substances/degradation products, assay, and microbial purity. The proposed drug product specification is acceptable with regard to the release and shelf life limits. The limits for degradation products are qualified, based on ICH Q3B, and sufficiently tight.
Analytical methods are adequately described, and have been sufficiently validated. Batch analysis data showing compliance with the proposed release specification have been provided of two pilot batches.

**Stability of drug product**

Stability data on the product was provided for two batches at pilot scale. One batch was stored up to 6 months at accelerated conditions (40°C/75%RH) and up to 18 months at long term conditions (25°C/60%RH). The second batch was stored up to 6 months at accelerated conditions (40°C/75%RH) and up to 12 months at long term conditions (25°C/60%RH).

The conditions used in the stability studies are according to the ICH stability guideline. The capsules were stored in the proposed package (blister). Based on a photostability study the product can be considered photostable.

The proposed shelf-life - 24 months, no special storage conditions - is considered justified, based on the stability results provided.

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

Lactose and gelatin are of animal origin. Regarding lactose statements are provided, including a statement that the milk is sourced from healthy animals in the same conditions as milk collected for human consumption and that the lactose is prepared without the use of other ruminant materials than calf rennet.

Regarding gelatin, several valid EDQM TSE certificates of suitability (CEPs) of the suppliers have been submitted.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**

Based on the submitted dossier, the member states consider that Racecadotril Double-E Pharma 100 mg capsules, hard has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- Process validation and batch analysis release will be carried out for the first three industrial batches.
- The first three production batches will be put into the stability program.

**III. NON-CLINICAL ASPECTS**

**III.1 Ecotoxicity/environmental risk assessment (ERA)**

Since Racecadotril Double-E Pharma is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

**III.2 Discussion on the non-clinical aspects**

This product is a generic formulation of Tiorfan, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

**IV. CLINICAL ASPECTS**

**IV.1 Introduction**
Racecadotril is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Racecadotril Double-E Pharma 100 mg (DOUBLE-E PHARMA Ltd, Ireland) is compared with the pharmacokinetic profile of the reference product Tiorfan 100 mg capsules (Bioprojet Pharma, France).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-treatment, 4-period, replicate crossover bioequivalence study was carried out under fasted conditions in 44 healthy subjects (21 males/23 females), aged 22-71 years. Each subject received a single dose (100 mg) of one of the 2 racecadotril formulations. The capsule was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7 and 8 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate. Fasting conditions has been applied, which is appropriate. The bioavailability of racecadotril is not modified by food, but peak activity is delayed by about one hour and a half.

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.

Racecadotril is a pro-drug that is rapidly hydrolyzed to thiorphan, the active metabolite. According to the European Medicines Agency Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**), pro-drugs that have low plasma concentrations and are quickly eliminated result in difficulties in demonstrating bioequivalence for the parent compound. The Guideline states that in this situation, it is acceptable to demonstrate bioequivalence for the main active metabolite without measurement of the parent compound. In the context of this guideline, and due to the rapid metabolism of racecadotril to the active metabolite thiorphan, it was judged acceptable to quantify the plasma levels of thiorphan and demonstrate bioequivalence based on this active metabolite.

The MAH defined a scaling approach in case the $C_{\text{max}}$ Reference-to-Reference within-subject CV would be greater than 30%. If Test-to-Reference geometric LSmeans ratio was within the bioequivalence range of 0.80-1.25 and the average bioequivalence criterion was not met, the scaling approach was to be used. The acceptance criteria for $C_{\text{max}}$ could have been widened to a maximum of 69.84-143.19%.

Results

A number of subjects withdrew from the study. However, all subjects received at least one single dose of both test and reference; all 44 subjects were analysed and included in the pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ (median, range)) of thiorphan under fasted conditions.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀⁻⁴</th>
<th>AUC₀⁻∞</th>
<th>C_max</th>
<th>t_max</th>
<th>t₁/₂</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td>276 ± 79</td>
<td>290 ± 76</td>
<td>180 ± 69</td>
<td>1.25 (0.50 – 4.5)</td>
<td>1.1 ± 0.6</td>
</tr>
<tr>
<td><strong>Reference</strong></td>
<td>286 ± 81</td>
<td>299 ± 83</td>
<td>185 ± 64</td>
<td>1.25 (0.33 – 4.5)</td>
<td>1.4 ± 0.8</td>
</tr>
<tr>
<td><em>Ratio (90% CI)</em></td>
<td>0.97 (0.92 – 1.02)</td>
<td>--</td>
<td>0.95 (0.87 – 1.04)</td>
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<tr>
<td><strong>CV (%)</strong></td>
<td>19.1</td>
<td>--</td>
<td>35.9</td>
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</tbody>
</table>

- **AUC₀⁻⁴**: area under the plasma concentration-time curve from time zero to infinity
- **AUC₀⁻∞**: area under the plasma concentration-time curve from time zero to t hours
- **C_max**: maximum plasma concentration
- **t_max**: time for maximum concentration
- **t₁/₂**: half-life
- **CV**: coefficient of variation

*ln-transformed values

**Conclusion on bioequivalence study**

The 90% confidence intervals calculated for AUC₀⁻⁴ and C_max are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence study, Racecadotril Double-E Pharma 100 mg is considered bioequivalent with Tiorfan 100 mg capsules. The scaling approach was not necessary to demonstrate bioequivalence.

The MEB has been assured that the bioequivalence study has 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).

**IV.3 Risk Management Plan**

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Racecadotril Double-E Pharma.

- **Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP**

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimisation activities (routine)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity to the active or any other ingredients contained within the product</td>
<td>Routine PV</td>
<td>SmPC sections 4.3, 4.8</td>
</tr>
<tr>
<td>Adverse reactions of the skin and subcutaneous tissues</td>
<td>Routine PV</td>
<td>SmPC sections 4.8</td>
</tr>
<tr>
<td><strong>Important potential risks</strong></td>
<td></td>
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<tr>
<td>Use in the presence of invasive bacteria or other severe disease</td>
<td>Routine PV</td>
<td>SmPC sections 4.4</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome, Toxic epidermal necrolysis, DRESS</td>
<td>Routine PV</td>
<td>Monitoring of individual case reports received</td>
</tr>
<tr>
<td>Hepatic events</td>
<td>Routine PV</td>
<td>Monitoring of individual case reports received</td>
</tr>
<tr>
<td>Condition</td>
<td>Monitoring</td>
<td>Status</td>
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<td>-----------------------------------------------</td>
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<tr>
<td>Urinary retention</td>
<td>Routine PV</td>
<td>Monitoring of individual case reports received</td>
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<tr>
<td>Epilepsy and convulsion</td>
<td>Routine PV</td>
<td>Monitoring of individual case reports received</td>
</tr>
<tr>
<td>Sub-occlusive syndrome</td>
<td>Routine PV</td>
<td>Monitoring of individual case reports received</td>
</tr>
<tr>
<td>Overdose</td>
<td>Routine PV</td>
<td>SmPC section 4.9</td>
</tr>
<tr>
<td>Dyspnoea and respiratory insufficiency</td>
<td>Routine PV</td>
<td>Monitoring of individual case reports received</td>
</tr>
<tr>
<td>Use in chronic and antibiotic associated diarrhoea</td>
<td>Routine PV</td>
<td>SmPC section 4.4</td>
</tr>
<tr>
<td><strong>Important missing information</strong></td>
<td></td>
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<tr>
<td>Use of the product in patients with renal and hepatic impairment</td>
<td>Routine PV</td>
<td>SmPC section 4.2, 4.4, 5.2</td>
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<tr>
<td>Use in pregnancy and lactation</td>
<td>Routine PV</td>
<td>SmPC section 4.6</td>
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The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Tiorfan 100 mg capsules. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

### V. USER CONSULTATION

The readability of the package leaflet (PL) has been assessed in line with the guidance on user testing. No weaknesses have been identified. The leaflet passed the defined success criteria: 90% of the test participants are able to find the information requested within the package leaflet of which 90% can show that they understand it. Therefore the test was deemed to be successful. The final PL reflects the results of testing with patients to make sure it enables the patient to use the medicinal product safely and effectively.

### VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Racecadotril Double-E Pharma 100 mg has a proven chemical-pharmaceutical quality and is a generic form of Tiorfan 100 mg hard capsules. Tiorfan is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential
similarity has been demonstrated for Racecadotril Double-E Pharma 100 mg capsules, hard with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 January 2015.
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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