PUBLIC ASSESSMENT REPORT
Scientific Discussion

Zaldiar/Ixprim 37.5 mg/325 mg effervescent tablets
37.5 mg tramadol hydrochloride and 325 mg paracetamol

FR/H/211-212/02/DC

Applicant: Grünenthal

Date of the PAR: December 2008
Information about the initial procedure:

<table>
<thead>
<tr>
<th>Application/Legal Basis</th>
<th>Fixed combination (line-extension)</th>
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<tr>
<td>Active substance</td>
<td>tramadol hydrochloride and paracetamol</td>
</tr>
<tr>
<td>Pharmaceutical form</td>
<td>effervescent tablets</td>
</tr>
<tr>
<td>Strength</td>
<td>37.5 mg tramadol hydrochloride and 325 mg paracetamol</td>
</tr>
<tr>
<td>Applicant</td>
<td>Grünenthal</td>
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<tr>
<td>EU-Procedure number</td>
<td>FR/H/211-212/02/DC</td>
</tr>
<tr>
<td>End of procedure</td>
<td>12 September 2008</td>
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</table>

1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for IXPRIM/ZALDIAR from Grünenthal on September 12th 2008. The marketing authorisation, IXPRIM/ZALDIAR effervescent tablet was granted as a line-extension to the marketing authorisation for IXPRIM/ZALDIAR film-coated tablet.

IXPRIM/ZALDIAR is indicated for the treatment of moderate to severe pain, for patients whose pain is considered to require a combination of tramadol and paracetamol.

This is a decentralised procedure with France acting as Reference Member State. Belgium, Germany, Spain, Portugal, United Kingdom were Concerned Member States for the procedure: FR/H/211/02/DC and Austria, Belgium, Germany, Spain, Hungary, Ireland, Luxembourg, The Netherlands, Slovenia were Concerned Member states for the procedure: FR/H/212/02/DC.

2. QUALITY ASPECTS

2.1 Introduction

The medicinal product is presented in the form of an effervescent tablet containing 37.5 mg of tramadol hydrochloride and 325 mg of paracetamol.

The excipients are monosodium citrate anhydrous, citric acid anhydrous, povidone K30, sodium hydrogen carbonate, macrogol 6000, silica colloidal anhydrous, magnesium stearate, flavour orange, acesulfam potassium, saccharin sodium, sunset yellow E110.

The effervescent tablets are packed in polyethylene terephthalate/aluminium/polyethylene blister strips or polypropylene tubes with wall-integrated molecular sieve and polypropylene cap.

2.2 Drug substance

Both paracetamol and tramadol hydrochloride have monographs in the Ph. Eur. and the corresponding manufacturers hold certificates of suitability of the monograph (CEP).

The Ph. Eur. specifications are used for the control of the drug substances. The specifications of tramadol hydrochloride are completed by an additional test for residual solvents.
Stability studies have been conducted and the data provided are sufficient to confirm the retest periods.

2.3 Medicinal product

The development of the product has been described, the choice of excipients is justified and their functions explained. The manufacturing process is standard for an effervescent form. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

Pharmacopoeia excipients are used. Satisfactory in house-monographs were developed for the control of the flavour and the colorant. There are no excipients of human or animal origin. The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed. The data support the shelf life and storage conditions claimed in the SmPC.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

This DCP application concerns Ixprim/Zaldiar effervescent tablets, which is a fixed combination of the well known substances tramadol hydrochloride and paracetamol. This application is a line-extension of the already marketed Ixprim/Zaldiar film-coated tablets. The pharmacodynamic, pharmacokinetic and toxicological properties of both tramadol hydrochloride and paracetamol and of their combination are well known. No new relevant pharmacodynamic, pharmacokinetic and toxicological data regarding the fixed combination were submitted by the applicant. A timetable has been established by the Applicant regarding the environmental aspects. The Applicant should provide the results of the planned studies as soon as available.

4. CLINICAL ASPECTS

4.1 Introduction

Ixprim/Zaldiar 37.5 mg/325 mg effervescent tablet is a fixed combination of tramadol hydrochloride 37.5 mg and paracetamol 325 mg. Tramadol is an opioid analgesic that acts on the central nervous system as a pure non selective agonist of the μ, δ and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms also contribute to its analgesic effect: inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

The precise mechanism of the analgesic properties of paracetamol is unknown and probably involves central and peripheral effects.

Ixprim/Zaldiar effervescent tablets is a line-extension of Ixprim/Zaldiar film-coated tablets, which has been marketed in Europe since 2003 (FR/H/0211-0212/001). The present product is intended for the symptomatic treatment of moderate to severe pain, for patients whose pain is considered to require a combination of tramadol and paracetamol.

4.2 Discussion on the clinical aspects

As this application concerns a line-extension of an already marketed fixed-combination, the
applicant performed a bioequivalence trial to demonstrate that Ixprim/Zaldiar effervescent tablets is bioequivalent to Ixprim/Zaldiar film-coated tablets (see section 4.3). Tramadol and paracetamol are well known substances marketed for years in the treatment of pain and their fixed combination has been marketed in Europe since 2003 as a film-coated tablet.

The efficacy of the fixed combination has already been evaluated when the file for Ixprim/Zaldiar film-coated tablets has been submitted and no new efficacy data were provided.

The safety of the fixed combination tramadol hydrochloride 37.5 mg/paracetamol 325 mg is well characterised. Since the MA of Ixprim/Zaldiar film-coated tablets, no regulatory actions were taken. The last renewal of Ixprim/Zaldiar film-coated tablets, which ended in June 2007, concluded that the benefit-risk ratio remained positive. The only new information regarding the safety of Ixprim/Zaldiar comes from the bioequivalence study. The treatment emergent AE which occurred during this study were similar between both formulations. The most frequently AE reported were dizziness, headache, nausea, upper abdominal pain and dry mouth. All these AE are listed in the Ixprim/Zaldiar SmPC.

The local tolerance of both treatments was also carefully evaluated. A little more patients receiving the effervescent tablets showed a mild to moderate increase in intensity of the colour of the mucosa immediately after treatment administration: 10 vs 3 receiving the film-coated tablets, 2 of which presenting this sign pre-dose. At three hours, none of the patients having received the effervescent tablets presented with an increased colour of the mucosa whereas this was the case for 3 subjects having received the film-coated tablets (included both patients which presented this sign pre-dose).

The local tolerance of both treatments is thus considered comparable. Even if bioequivalence studies are not designed to evaluate safety of products (limited duration of administration, healthy volunteers, low number of volunteers) the safety profile observed for both treatments does not raise any question regarding the safety of Ixprim/Zaldiar effervescent tablets.

4.3 Pharmacokinetics

A bioequivalence trial was performed in order to show bioequivalence between the new effervescent formulation and the marketed tablet formulation. This study is presented below.

The study was an open label, two-treatment, two periods, two sequence, single dose, crossover study conducted under fasting conditions with a wash out period of at least 5 days between administrations. A 37.5/325 mg single dose was administered in each period with 200ml water. Subjects were confined to the clinical research centre from at least 10 hours prior to drug administration until 24 hour post-dose.

19 Blood samples were collected pre-dosing and up to 24 h post-dosing (at 0.083, 0.166, 0.333, 0.5, 0.75, 1.0, 1.5, 2, 3.0, 4.0, , 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 30 and 24.0 hours) in each period. Samples were assayed for tramadol, 3-O-demethyl-tramadol (M1) and paracetamol by HPLC with tandem MS-MS detection technique.

Test product:
Tramadol 37.5/ Paracetamol 325 mg effervescent tablets dissolved in 200 ml of non–carbonated water. These tablets were manufactured by Grünenthal GmbH, Aachen, Germany, and originate from the batch n° 766026. The batch size is 150,000 tablets.
Reference product:
ZALDIAR 37.5/325 mg current tablets were manufactured by Grünenthal GmbH, Aachen, Germany, and originate from the batch n° 406K01.

Population studied:
Determination of sample size: Based on the estimates of former trials in tramadol Phase I trials (TRAMAP-PHI-001 1989, TRAMAP-PHI-002 1997 and TRAMAP-PHI-003 1997) already available, the intra-individual coefficients of variation were below 20% for the primary parameters. Using the following assumptions for the sample size calculation: \( \mu_T/\mu_R = 0.95 \), \( CV = 0.20 \), acceptance range for equivalence: 0.8 - 1.25, \( \alpha = 5\% \) and \( \beta = 10\% \) a sample size of 26 subjects was needed for the assessment of bioequivalence.

32 subjects were planned in order to allow for drop-outs and discontinuers. All subjects were previously characterized as extensive metabolizers with regard to CYP2D6 isoenzyme. One subject (subject n°28) drops out for personal reasons. Two additional subjects were excluded in period two of the study. Subject n° 05 was excluded as two blood samples (30 h and 36 h) could not be drawn due to the subject’s absence.

Subject n° 21 was excluded as he has taken additional paracetamol during the study.

Pharmacokinetic variables:
Relevant PK parameters of Tramadol, M1 metabolite and Paracetamol were estimated. The pharmacokinetic parameters AUC0-t, AUC0-inf, Cmax and Tmax were either observed or calculated. AUC was calculated by the trapezoidal rule. Cmax and Tmax were directly estimated from the individual concentrations: time profiles.

Statistical methods:
GLM ANOVA was performed on the ln-transformed AUC0-t, AUC0-inf and Cmax. The ANOVA model included sequence, subject nested within sequence, period and product. Non-transformed T_{max} was evaluated and tested using a non parametric Mann/Whitney/Wilcoxon test.

The statistical analysis was performed using SAS software (release 6.12 for windows).

Bioequivalence criteria:
90% geometric intervals of the ratio (Test/Reference) of least square means from the ln-transformed values for AUC0-t, AUC0-inf and C_{max} should be within 80-125%.

Results:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t}</th>
<th>AUC_{0-inf}</th>
<th>C_{max}</th>
<th>t_{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hr.ng/ml</td>
<td>hr.ng/ml</td>
<td>ng/ml</td>
<td>h</td>
</tr>
<tr>
<td>Test (S.D.)</td>
<td>688.6 (166.5)</td>
<td>704.7 (173.1)</td>
<td>94.1 (19)</td>
<td>1 (0.75-2)</td>
</tr>
<tr>
<td>Reference (S.D.)</td>
<td>677.5 (187.5)</td>
<td>694.2 (195.2)</td>
<td>94.9 (29.1)</td>
<td>1 (0.75-2)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI) point estimate

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<tbody>
<tr>
<td>Test</td>
<td>[98;107]%</td>
<td>102 %</td>
<td>9.1 %</td>
</tr>
<tr>
<td>Reference</td>
<td>[98;106]%</td>
<td>102 %</td>
<td>9.2 %</td>
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Intra-subject CV

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<tbody>
<tr>
<td></td>
<td>14.8 %</td>
<td></td>
<td></td>
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</table>
Paracetamol Pharmacokinetic parameters (log-transformed values; arithmetic mean ± SD, t\textsubscript{max} median, range)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\textsubscript{0-t}</th>
<th>AUC\textsubscript{0-∞}</th>
<th>C\textsubscript{max}</th>
<th>t\textsubscript{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (S.D.)</td>
<td>12.09 (2.73)</td>
<td>12.66 (2.76)</td>
<td>3.96 (0.78)</td>
<td>0.5 (0.17-1.5)</td>
</tr>
<tr>
<td>Reference (S.D.)</td>
<td>13.71 (9.06)</td>
<td>15.45 (14.64)</td>
<td>4.38 (1.85)</td>
<td>0.5 (0.2-1.5)</td>
</tr>
<tr>
<td>*Ratio (90% CI) Point estimate</td>
<td>[86;104]% 95 %</td>
<td>[83;104]% 93 %</td>
<td>[86;108]% 96 %</td>
<td></td>
</tr>
<tr>
<td>Intra-subject CV (%)</td>
<td>20.8 %</td>
<td>26.1 %</td>
<td>25.5 %</td>
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</tbody>
</table>

*log-transformed values

The data reported above for Tramadol and Paracetamol demonstrate clearly the BE of the new effervescent tablet and the current conventional tablet of Zaldiar 37.5/325 mg. 500 These findings are confirmed by the supportive data (not reported) derived from M1 Tramadol metabolite PK parameters.

5. OVERALL DISCUSSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The fixed combination of tramadol HCL/paracetamol (film-coated tablets) has been marketed for 5 years in the European Community. This application concerns a line-extension of this combination as effervescent tablets. Based on the evidence submitted, the benefit-risk assessment of Ixprim/Zaldiar effervescent tablets is considered favourable.

However, regarding environmental risk assessment the Applicant should provide the results of the planned studies as soon as available.

This application was recommended for approval.