TRAMADOL HYDROCHLORIDE AND PARACETAMOL 37.5 MG/325 MG
FILM-COATED TABLETS
(tramadol hydrochloride and paracetamol)

PL 30684/0222

UKPAR

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>4</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>13</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td>14</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>15</td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td>15</td>
</tr>
<tr>
<td>Labelling</td>
<td>16</td>
</tr>
</tbody>
</table>
LAY SUMMARY

Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets
(tramadol hydrochloride and paracetamol)

This is a summary of the public assessment report (PAR) for Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets (PL 30684/0222). It explains how the application for Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets was assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets.

For practical information about using Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets and what are they used for?

Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets are a combination of two active ingredients, tramadol hydrochloride and paracetamol. This medicine is used in the treatment of moderate to severe pain when it is considered by the doctor that a combination of tramadol hydrochloride and paracetamol is needed.

Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets are a ‘generic medicine’. This means that this medicine is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Tramacet 37.5 mg/325 mg Film-coated Tablets.

How are Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets used?

This medicine can only be obtained with a prescription from a pharmacy. Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets are for oral use in adults and adolescents over 12 years of age. It is recommended that this medicine should be swallowed whole with a sufficient amount of liquid and without breaking or chewing the tablets. An initial dose of 2 tablets is recommended. Additional doses may be taken on the advice of the doctor, however not exceeding 8 tablets per day (equivalent to 2600 mg paracetamol and 300 mg tramadol hydrochloride). The shortest time between doses must be at least 6 hours.

The doctor may increase the time between doses if the following conditions apply:
- If you are older than 75 years of age
- If you have kidney problems
- If you have liver problems

How do Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets work?

Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets belong to a group of medicines called analgesics (painkillers). This medicine provides relief from moderate to severe pain by acting on specific nerve cells and the brain.

How have Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets been studied?

Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets are a generic medicine, for which studies in patients have been limited to tests to determine that this medicine is bioequivalent.
to the reference medicine, Tramacet 37.5 mg/325 mg Film-coated Tablets. Two medicines are bioequivalent when they produce the same effect in the body.

**What are the benefits and risks of Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets?**

Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets are a generic medicine that is comparable to the reference medicine, therefore the benefits and risks are taken as being the same as the reference medicine.

**Why are Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets approved?**

It was concluded that, in accordance with EU requirements, Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets have been shown to have comparable quality and to be comparable to the reference medicine Tramacet 37.5 mg/325 mg Film-coated Tablets. Therefore, the view was that as for the reference medicine, the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets?**

Safety information has been included in the Summary of Product Characteristics and the package leaflet for Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets**

A Marketing Authorisation was granted in the UK on 13 June 2014. For more information about treatment with Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2014. The full PAR for Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets follows this summary.
TRAMADOL HYDROCHLORIDE AND PARACETAMOL 37.5 MG/325 MG
FILM-COATED TABLETS
(PL 30684/0222)

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction .......................... Page 5
Pharmaceutical assessment ........ Page 6
Non-clinical assessment ............... Page 9
Clinical assessment .................. Page 10
Overall conclusion and benefit/risk assessment  .......... Page 12
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted a Marketing Authorisation for the medicinal product, Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets (PL 30684/0222) on 13 June 2014 to Dawa Limited.

This application for Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets was submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the originator product Zaldiar 37.5 mg/325 mg Film-coated Tablets authorised in France to Laboratories Grunenthal on 05 April 2002. Tramacet 37.5 mg/325 mg Film-coated Tablets is the UK reference product used in the bioequivalence study. Tramacet 37.5 mg/325 mg Film-coated Tablets were originally authorised to Janssen-Cilag Limited (PL 00242/0384) on 25 September 2003. Following a subsequent change of ownership procedure on 30 March 2009, the current Marketing Authorisation Holder is Grunenthal Limited (PL 21727/0039).

Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets can only be obtained with a prescription from a pharmacy (legal status POM) and are indicated for the symptomatic treatment of moderate to severe pain. The use of Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets should be restricted to patients whose moderate to severe pain is considered to require a combination of paracetamol and tramadol.

Tramadol hydrochloride and Paracetamol Film-coated Tablets is the combination of 37.5 mg of tramadol hydrochloride and 325 mg of Paracetamol. Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non selective agonist of the μ, δ, and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an antitussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, the gastro-intestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine. The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.

With the exception of the bioequivalence study comparing the pharmacokinetics of the applicant’s Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets with those of Tramacet 37.5 mg/325 mg Film-coated Tablets (Grunenthal Limited), no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on the product being a generic medicinal product of a reference product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture and assembly of this product.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Tramadol hydrochloride

INN: Tramadol hydrochloride
Chemical name: (1RS, 2RS)-2[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride

Structure

Molecular formula: C_{16}H_{26}ClNO_{2}
Molecular weight: 299.8
Physical form: White crystalline powder
Solubility: Freely soluble in water and in methanol, very slightly soluble in acetone.

Tramadol hydrochloride is the subject of a European Pharmacopoeia monograph.

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

All potential known impurities have been identified and characterised.

The container–closure system and retest period are satisfactory and comply with the details given on the EDQM Certificate of Suitability.

DRUG SUBSTANCE
Paracetamol

INN: Paracetamol
Chemical name: N-(4-hydroxyphenyl) acetamide
p-hydroxyacetanilide
p-Acetamidophenol
N-acetyl-p-aminophenol
Structure:

![Structure of Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets]

Molecular formula: \( \text{C}_8\text{H}_9\text{NO}_2 \)
Molecular weight: 151.16
Physical form: White crystalline powder
Solubility: Sparingly soluble in water, freely soluble in alcohol, very slightly soluble in ether and in methylene chloride.

Paracetamol is the subject of a European Pharmacopoeia monograph.

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

All potential known impurities have been identified and characterised.

Satisfactory specifications have been provided for all packaging used for storing the active substance paracetamol. The primary packaging has been shown to comply with current legislation concerning materials in contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable. A suitable retest period has been set based on stability data submitted for the active substance when stored in the proposed packaging.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of the following pharmaceutical excipients:

The tablet core consists of:
- Pregelatinised starch, sodium starch glycolate (Type A), microcrystalline cellulose and magnesium stearate.

The tablet coating consists of:
- Opadry yellow 15B82958, which consists of hypromellose (3cP), hypromellose (6cP), titanium dioxide (E171), macrogol 400, iron oxide yellow (E172) and polysorbate 80.

With the exception of Opadry yellow 15B82958 and iron oxide yellow (E172), all excipients used comply with their respective European Pharmacopoeia monographs. Opadry yellow 15B82958 complies with its in-house specification. The individual components of Opadry yellow 15B82958 comply with
their respective European Pharmacopoeia monographs, with the exception of iron oxide yellow (E172), which complies with the national formulary. None of the excipients used contain material of animal or human origin. The magnesium stearate is of vegetable origin.

**Pharmaceutical development**

The objective of the pharmaceutical development programme was to produce a robust and safe product that could be considered a generic medicinal product of Tramacet 37.5 mg/325 mg Film-coated Tablets (Grunenthal Limited). The applicant has provided a suitable product development rationale and data. Comparative *in vitro* dissolution and impurity profiles have been provided for the applicant’s product versus the reference product.

**Manufacture**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on three pilot scale batches of finished product. The results are satisfactory.

**Finished product specification**

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

**Container Closure System**

The finished product is packaged in milky white polyvinylchloride/polyvinylidene chloride and aluminium/polyvinylchloride blister packs of 60 or 100 film-coated tablets. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

**Stability**

Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 3 years, with no special storage conditions.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**

The SmPC, PIL and labels are acceptable from a pharmaceutical perspective.
The results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets were provided. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms

The MAA form is satisfactory from a pharmaceutical perspective.

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 dossier.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of tramadol hydrochloride and paracetamol are well-known, no further non-clinical studies are required and none have been provided.

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

A suitable justification has been provided for non-submission of an environmental risk assessment. As this product is intended for generic substitution with products currently marketed, the environmental burden is not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

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

CLINICAL PHARMACOLOGY

In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

An open label, randomised, balanced, two-treatment, two-sequence, two-period, single-dose, crossover bioequivalence study comparing the plasma pharmacokinetics of the test product Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets versus the reference product Tramacet 37.5 mg/325 mg Film-coated Tablets (Grunenthal Limited), in healthy, adult subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose of either the test (T) or reference product (R), with 240 ml of water. Blood sampling was performed pre-dose and up to 24 hours post dose. The washout period between each dosing period was 7 days.

A summary of the main pharmacokinetic results is presented below:

Paracetamol

<table>
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<tr>
<th>PK Parameters</th>
<th>Log Transformed PK Values</th>
<th>% Power</th>
<th>% ISCV</th>
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<tr>
<td></td>
<td>Geometric LSM</td>
<td>Ratio T/R (%)</td>
<td>90% Confidence Interval</td>
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<tr>
<td></td>
<td>T</td>
<td>R</td>
<td>Lower Limit</td>
</tr>
<tr>
<td>C_{max}</td>
<td>3874.082</td>
<td>3641.406</td>
<td>106.39</td>
</tr>
<tr>
<td>AUC_{0-t}</td>
<td>15073.751</td>
<td>15078.909</td>
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Tramadol hydrochloride

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<tr>
<th>PK Parameters</th>
<th>Log Transformed PK Values</th>
<th>% Power</th>
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<tr>
<td></td>
<td>T</td>
<td>R</td>
<td>Lower Limit</td>
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<tr>
<td>C_{max}</td>
<td>122.597</td>
<td>120.100</td>
<td>102.08</td>
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<tr>
<td>AUC_{0-t}</td>
<td>1186.042</td>
<td>1174.205</td>
<td>101.01</td>
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AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
The 90% confidence interval of the test/reference ratio for the AUC0-t, and Cmax were within the pre-defined limits of 80.00-125.00% as specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). In conclusion, bioequivalence has been demonstrated between the test and the reference product.

EFFICACY

No new data on efficacy have been submitted and none are required for this type of application.

SAFETY

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

PHARMACOVIGILANCE SYSTEM

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.

Suitable justification has been provided for not submitting a risk management plan for this product.

EXPERT REPORT

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

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

This is consistent with the SmPC for the reference product and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

This is consistent with that for the reference product and is satisfactory.

LABELLING

This is satisfactory.

APPLICATION FORM (MAA)

This is satisfactory.

CONCLUSION

The grant of a Marketing Authorisation is recommended for this application.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL

Bioequivalence has been demonstrated between Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets and Tramacet 37.5 mg/325 mg Film-coated Tablets (Grunenthal Limited).

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and the reference product. Extensive clinical experience with tramadol hydrochloride and paracetamol is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk assessment is, therefore, considered to be positive.
Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets (PL 30684/0222)

**STEPS TAKEN FOR ASSESSMENT**

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<td>1</td>
<td>The MHRA received the marketing authorisation application on 17 July 2012</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant, the MHRA considered the application valid on 24 September 2012.</td>
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<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the dossiers on 22 October 2012, 27 December 2012, 18 April 2013 and 5 November 2013.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 27 December 2012, 27 June 2013 and 03 March 2014</td>
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<td>5</td>
<td>The application was determined on 13 June 2014</td>
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Tramadol hydrochloride and Paracetamol 37.5 mg/325 mg Film-coated Tablets (PL 30684/0222)

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

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Summary of Product Characteristics and Patient Information Leaflet
The current approved UK versions of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for this product are available on the MHRA website.
Labelling

Each film-coated tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol.

Swallow the tablets whole with sufficient liquid.

Do not break or chew the tablets.

Do not take more medicine than the label tells you to.

If you do not get better, talk to your doctor.

Do not take anything else containing paracetamol while taking this medicine.

Talk to a doctor at once if you take too much of this medicine, even if you feel well.

Read the package leaflet before use.

Keep out of the sight and reach of children.