Brimisol PR 100 mg Prolonged-Release Tablets
Brimisol PR 200 mg Prolonged-Release Tablets
(tramadol hydrochloride)
PL 17907/0134 & 0136

UK Public Assessment Report

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Brimisol PR 200 mg Prolonged-Release Tablets
(tramadol hydrochloride)
PL 17907/0134 & 0136

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products, Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets (PL 17907/0134 & 0136) on 1st November 2011. These are prescription-only medicines (POM).

Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets contain the active ingredient, tramadol, which is a painkiller, belonging to the class of opioids that acts on the nervous system. It relieves pain by acting on specific nerve cells of the spinal cord and brain. Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets are used for the treatment of moderate to severe pain.

Based on the data submitted by Bristol Laboratories Limited, Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets were considered to be generic versions of the reference products, Zydol SR 100 mg and 200 mg prolonged-release tablets (PL 21727/0003 and 0005; Grünenthal Limited, UK).

No new or unexpected safety concerns arose from these applications. It was judged that the benefits of Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets outweigh the risks; hence Marketing Authorisations have been granted.
Brimisol PR 100 mg Prolonged-Release Tablets
Brimisol PR 200 mg Prolonged-Release Tablets

(tramadol hydrochloride)

PL 17907/0134 & 0136

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bristol Laboratories Limited Marketing Authorisations for the medicinal products, Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets (PL 17907/0134 & 0136) on 1st November 2011. These are prescription-only medicines (POM).

These are generic applications for Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets, submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applications refer to the UK products, Zydol SR 100mg and 200mg prolonged-release tablets (PL 21727/0003 and 0005), licensed to Grünenthal Limited on 1st December 2004. The cross-referenced products were initially authorised to G D Searle & Co. Ltd. (PL 00020/0227 and 0229) on 22nd August 1995; they underwent a series of Change of Ownership (CoA) procedures to the current Grünenthal Limited licences on 1st December 2004. The UK reference products have been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets are indicated for the treatment of moderate to severe pain.

Tramadol is a centrally acting opioid analgesic (ATC code - N02AX02). It is a non-selective pure agonist at μ, δ and κ opioid receptors with a higher affinity for the μ receptor. 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. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be one tenth to one sixth that of morphine.

The applications are supported by 3 bioequivalence studies comparing the pharmacokinetic profile of the test product, Brimisol PR 200 mg Prolonged-Release Tablets, to that of the clinical reference product, Zydol SR 200mg prolonged-release tablets (Grunenthal GmbH, Germany), as well as a single bioequivalence study comparing the pharmacokinetic profile of the test product, Brimisol PR 100 mg Prolonged-Release Tablets, to that of the clinical reference product, Zydol SR 100mg prolonged-release tablets (Grunenthal GmbH, Germany). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.
The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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.

As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

It is not considered that these medicinal products represent any risk to the environment. There is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. The availability of these medicinal products, which are identical to the cited reference products, will not lead to any increase in environmental exposure concentrations of the active ingredient. An Environmental Risk Assessment (ERA) is not considered necessary.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Tramadol hydrochloride

Nomenclature:
INN: Tramadol hydrochloride

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

Structure:

![Chemical Structure](image)

Molecular formula: C_{16}H_{26}ClNO_{2}

Molecular weight: 299.8 g/mol

CAS No: 36282-47-0

Physical form: White or almost white crystalline powder

Solubility: Freely soluble in water and in methanol, very slightly soluble in acetone

The active substance, tramadol hydrochloride, is the subject of a European Pharmacopeia (Ph. Eur) monograph.

All aspects of the manufacture and control of tramadol hydrochloride are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of tramadol hydrochloride for inclusion in these medicinal products.
MEDICINAL PRODUCT

Description and Composition

Brimisol PR 100 mg Prolonged-Release Tablets are presented as white to off-white, round, biconvex, film coated tablets with “100” embossed on one side and “BL” on the other side. Each prolonged-release tablet contains 100 mg tramadol hydrochloride. Brimisol PR 200 mg Prolonged-Release Tablets are presented as light orange to light pink, round, biconvex, film coated tablets with “200” embossed on one side and “BL” on the other side. Each prolonged-release tablet contains 200 mg tramadol hydrochloride.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, hypromellose, colloidal anhydrous silica and magnesium stearate making up the tablet cores; and hypromellose, macrogol 6000, purified talc and titanium dioxide (E171) making up the film-coatings. The film-coating for the 200 mg strength tablets also contains quinoline yellow (E104) and ferric oxide red. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph. Eur monographs, with the exceptions of red ferric oxide which complies with the USP monograph, and quinoline yellow (E104), which is controlled to satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic formulations, bioequivalent to the reference products, Zydol SR 100mg and 200mg prolonged-release tablets (Grünenthal Limited).

Comparative dissolution and impurity data were provided for batches of the test and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory. A commitment has been made by the MAH that full process
validation will be conducted on commercial scale batches in accordance with the process validation protocol.

**Finished product specifications**

Finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets are licensed for marketing in white opaque polyvinylchloride (PVC)-aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 30 or 60 tablets.

Satisfactory specifications and Certificates of Analysis for all packaging components have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 2 years, with the storage instructions ‘Do not store above 25°C’.

**Quality Overall Summary**

A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The user-testing of the PIL has been evaluated and is accepted. The labelling fulfils the statutory requirements for Braille.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

These abridged applications, submitted under Article 10(1) of Directive 2001/83/EC, as amended, are for Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets, products claiming to be generic versions of the UK reference products, Zydol SR 100mg and 200mg prolonged-release tablets (Grünenthal Limited).

No new non-clinical data have been supplied with these applications and none are required for applications of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

There are no objections to approval of these products from a non-clinical point of view.
**CLINICAL ASSESSMENT**

**BACKGROUND**
Tramadol produces analgesia by two mechanisms: an opioid effect and an enhancement of serotonergic and adrenergic pathways. It has fewer of the typical opioid side-effects (notably, less respiratory depression, less constipation and less addiction potential); psychiatric reactions have been reported.

Tramadol is readily absorbed after oral doses but is subject to first-pass metabolism. Tramadol is metabolised by N- and O-demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulfation in the liver. Production of the active metabolite O-desmethyltramadol is dependent on the cytochrome P450 isoenzyme CYP2D6, which exhibits genetic polymorphism.

The metabolite O-desmethyltramadol is pharmacologically active. Tramadol is excreted mainly in the urine, predominantly as metabolites. Tramadol is widely distributed, crosses the placenta, and appears in small amounts in breast milk. The elimination half-life after oral doses is about 6 hours.

**INDICATIONS**
Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets are indicated for the treatment of moderate to severe pain.

The indications are consistent with those for the reference products and are satisfactory.

**POSOLOGY AND METHOD OF ADMINISTRATION**
The usual initial dose is 50-100 mg tramadol hydrochloride twice daily, morning and evening. If pain relief is insufficient, the dose may be titrated upwards to 150 mg or 200 mg tramadol hydrochloride twice daily.

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

**TOXICOLOGY**
The toxicology of tramadol hydrochloride is well-known. No new data have been submitted and none are required for applications of this type.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**
The clinical pharmacology of tramadol hydrochloride is well-known. With the exception of the bioequivalence studies, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

**Pharmacokinetics - Bioequivalence studies**
The applications are supported by 3 bioequivalence studies comparing the pharmacokinetic profile of the test product, Brimisol PR 200 mg Prolonged-Release Tablets, to that of the clinical reference product, Zydol SR 200mg prolonged-release tablets (Grunenthal GmbH, Germany). As per the note for Guidance on Modified
Release Oral and Transdermal Dosage Forms (CPMP/EWP/280/96), for single unit formulations of a medicinal product with multiple strengths, a single dose study under fasting conditions is required for each dose strength. Therefore, a further single dose, fasting study was provided for the 100 mg dose strength comparing the pharmacokinetic profile of the test product, Brimisol PR 100 mg Prolonged-Release Tablets, to that of the clinical reference product, Zydol SR 100mg prolonged-release tablets (Grunenthal GmbH, Germany). The studies were of an appropriate design and were conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for test and reference products. The UK reference products, Zydol SR 100 and 200mg prolonged-release tablets (PL 21727/0003 and 0005, Grünenthal Limited), are considered to be equivalent to the clinical reference products, Zydol SR 100mg and 200mg prolonged-release tablets (Grunenthal GmbH, Germany).

**Study A – 200 mg, fasted, single dose**

This was an open-label, randomised, two-period, two-sequence, two-treatment, single-dose crossover bioequivalence study conducted in healthy adult human male subjects under fasting conditions. Following a fast of more than 10 hours duration, a single dose of either the test or reference product was administered orally to each subject in each period. A satisfactory washout period of 7 days was maintained between the dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 48.0 hours after administration of test or reference product. Plasma levels of tramadol were quantified by a validated LC-MS/MS method.

The primary pharmacokinetic parameters for the study were \(C_{\text{max}}\), \(\text{AUC}_{0-t}\), and \(\text{AUC}_{0-\infty}\). Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed \(C_{\text{max}}\), \(\text{AUC}_{0-t}\), and \(\text{AUC}_{0-\infty}\) for tramadol.

**Results:**

*Safety* - There were no deaths or serious or significant adverse events.

An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric mean</th>
<th>% Ratio</th>
<th>90 % Confidence Interval for Log-transformed data</th>
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</thead>
<tbody>
<tr>
<td>(\text{AUC}_{0-\text{inf}})</td>
<td>5350.70</td>
<td>5480.83</td>
<td>97.65</td>
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<tr>
<td>(\text{AUC}_{0-t})</td>
<td>5211.18</td>
<td>5330.57</td>
<td>97.76</td>
</tr>
<tr>
<td>(C_{\text{max}})</td>
<td>405.93</td>
<td>363.79</td>
<td>111.58</td>
</tr>
</tbody>
</table>

**Conclusion**

Bioequivalence has been demonstrated between the 200 mg strength test and reference products for a single-dose study conducted under fasting conditions.
Study B – 200 mg, fed, single dose

This was an open-label, randomised, two-period, two-sequence, two-treatment, single-dose crossover bioequivalence study conducted in healthy adult human subjects under fed conditions. Following an overnight fast of at least 10 hours, subjects were given a high-fat, high-calorie breakfast before receiving the dose. A single dose of either the test or reference product was administered orally to each subject in each period. A satisfactory washout period of 7 days was maintained between the dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 48.0 hours after administration of test or reference product. Plasma levels of tramadol were quantified by a validated LC-MS/MS method.

The primary pharmacokinetic parameters for the study were $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ for tramadol.

Results:

Safety - There were no deaths or serious or significant adverse events.

An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The summary of the results of the bioequivalence study are tabulated below:

Summary pharmacokinetic data for tramadol for a randomised, open-label, 2-way, single-dose crossover study; healthy subjects, dosed fed; $t=48$ hours; washout period 7 days

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<tr>
<th>Parameters</th>
<th>*Geometric mean</th>
<th>% Ratio</th>
<th>90% Confidence Interval for Log-transformed data</th>
</tr>
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<tbody>
<tr>
<td>$\text{AUC}_{0-\infty}$</td>
<td>6816.06</td>
<td>6807.35</td>
<td>100.13</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$</td>
<td>6627.56</td>
<td>6622.14</td>
<td>100.08</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>531.14</td>
<td>488.47</td>
<td>108.73</td>
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</table>

Conclusion

Bioequivalence has been demonstrated between the 200 mg strength test and reference products for a single-dose study conducted under fed conditions.

Study C – 200 mg, fasted, multiple dose

This was an open-label, randomised, two-period, two-sequence, two-treatment, multiple-dose crossover bioequivalence study conducted in healthy adult human subjects under fasting conditions. Following an overnight fast of at least 10 hours, a single oral dose was administered from day 01 to day 05. Subjects were dosed with the test or the reference product in each period as determined by the randomisation schedule. A satisfactory washout period of 7 days was maintained between the dosing phases in each group.
On each day from day 01 to 04, blood samples were taken pre-dose and at 12.0 hours after administration of test or reference product. On day 05, blood was collected pre-dose and at specified time points up to 48 hours after drug administration. Plasma levels of tramadol were quantified by a validated LC-MS/MS method.

The primary pharmacokinetic parameters for the study were $C_{\text{max}}$, $C_{\text{min}}$ and $\text{AUC}_{0-t}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed $C_{\text{max}}$, $C_{\text{min}}$ and $\text{AUC}_{0-t}$ for tramadol.

**Results:**

**Safety** - There were no deaths or serious or significant adverse events.

An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The summary of the results of the bioequivalence study are tabulated below:

**Summary pharmacokinetic data for tramadol for a randomised, open-label, 2-way, multiple-dose crossover study; healthy subjects, dosed fasted; washout period 7 days**

<table>
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<tr>
<th>Parameters</th>
<th>*Geometric mean</th>
<th>% Ratio</th>
<th>% Intra-CV</th>
<th>90% Confidence Interval for Log-transformed data</th>
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<td>$\text{AUC}_{\text{tau}}$</td>
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<td>$C_{\text{max}}$</td>
<td>614.18</td>
<td>558.94</td>
<td>109.88</td>
<td>10.14</td>
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<tr>
<td>$C_{\text{min}}$</td>
<td>108.57</td>
<td>119.81</td>
<td>90.62</td>
<td>13.64</td>
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</tbody>
</table>

**Conclusion**

Bioequivalence has been demonstrated between the 200 mg strength test and reference products for a multiple-dose study conducted under fasting conditions.

**Study D – 100 mg, fasted, single dose**

This was an open-label, randomised, two-period, two-sequence, two-treatment, single-dose crossover bioequivalence study conducted in healthy adult human subjects under fasting conditions. Following a fast of more than 10 hours duration, a single dose of either the test or reference product was administered orally to each subject in each period. A satisfactory washout period of 11 days was maintained between the dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 36.0 hours after administration of test or reference product. Plasma levels of tramadol were quantified by a validated LC-MS/MS method.

The primary pharmacokinetic parameters for the study were $C_{\text{max}}$ and $\text{AUC}_{0-t}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed $C_{\text{max}}$ and $\text{AUC}_{0-t}$ for tramadol.
Results:

Safety - There were no deaths or serious or significant adverse events.

An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The summary of the results of the bioequivalence study are tabulated below:

Summary pharmacokinetic data for tramadol for a randomised, open-label, 2-way, single-dose crossover study; healthy subjects, dosed fasted; t=36 hours; washout period 11 days

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<tr>
<th>Parameters</th>
<th>Test (A)</th>
<th>Reference (B)</th>
<th>A/B</th>
<th>90% Confidence Interval for Log-transformed data</th>
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</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-4&lt;/sub&gt;</td>
<td>2652.37</td>
<td>2689.38</td>
<td>98.6236</td>
<td>95.6329 - 101.7077</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>183.66</td>
<td>182.63</td>
<td>100.5598</td>
<td>96.6627 - 104.6140</td>
</tr>
</tbody>
</table>

Conclusion

Bioequivalence has been demonstrated between the 100 mg strength test and reference products for a single-dose study conducted under fasting conditions.

Discussion on Bioequivalence

The results of the bioequivalence studies show that Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets are bioequivalent to their respective clinical reference products, Zydol SR 100mg and 200mg prolonged-release tablets (Grunenthal GmbH, Germany), as the confidence intervals for the pre-defined pharmacokinetic parameters for tramadol fall within the acceptance criteria ranges of 80-125% in line with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CPMP/EWP/QWP/1401/98).

Efficacy

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of tramadol hydrochloride is well-established from its extensive use in clinical practice.

Safety

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of tramadol hydrochloride is well-known.

Product Information:

Summary of Product Characteristics

The approved SmPCs are consistent with those for the reference products and are acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.
Labelling
The labelling is satisfactory.

Clinical overview
A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

CONCLUSIONS
Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was, therefore, recommended.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Brimisol PR 100 mg and 200 mg Prolonged-Release 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 applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets and their respective clinical reference products, Zydol SR 100mg and 200mg prolonged-release tablets (Grunenthal GmbH, Germany). The UK reference products, Zydol SR 100 and 200mg prolonged-release tablets (PL 21727/0003 and 0005, Grüenthal Limited), are considered to be equivalent to the clinical reference products, Zydol SR 100mg and 200mg prolonged-release tablets (Grunenthal GmbH, Germany).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those for the reference products and are satisfactory.

A mock-up PIL has been provided. The package leaflet is in line with the SmPCs and is satisfactory. 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 results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets are generic versions of the UK reference products, Zydol SR 100mg and 200mg prolonged-release tablets (Grüenthal Limited). Extensive clinical experience with tramadol hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit:risk ratio is considered to be positive.
Brimisol PR 100 mg Prolonged-Release Tablets
Brimisol PR 200 mg Prolonged-Release Tablets

(tramadol hydrochloride)

PL 17907/0134 & 0136

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation applications on 3rd July 2009.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 4th September 2009.

3 Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 22nd January 2010 and 11th April 2011 and further information relating to the quality dossier on 4th February 2010 and 11th April 2011.

4 The applicant responded to the MHRA’s requests, providing further information for the clinical and quality sections on 14th March 2011 and 10th August 2011.

5 The applications were determined on 1st November 2011.
Brimisol PR 100 mg Prolonged-Release Tablets
Brimisol PR 200 mg Prolonged-Release Tablets

(tramadol hydrochloride)

PL 17907/0134 & 0136

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets (PL 17907/0134 and 0136) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

- Brimisol PR 100 mg Prolonged-Release Tablet
- Brimisol PR 200 mg Prolonged-Release Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

- Each prolonged-release tablet contains 100mg Tramadol Hydrochloride
- Excipients: Each prolonged-release tablet contains 36.0 mg lactose monohydrate.

- Each prolonged-release tablet contains 200mg Tramadol Hydrochloride
- Excipients: Each prolonged-release tablet contains 20.0 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-Release Tablet

(PR tablet)

- White to off white, round, biconvex, film coated tablets with “100” embossed on one side and “BL” on other side.

- Light orange to light pink, round, biconvex, film coated tablets with “200” embossed on one side and “BL” on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe pain

4.2 Posology and method of administration

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient.

Unless otherwise prescribed, Brimisol PR should be administered as follows:

Adults and adolescents above the age of 12 years:

The usual initial dose is 50-100 mg tramadol hydrochloride twice daily, morning and evening. If pain relief is insufficient, the dose may be titrated upwards to 150 mg or 200 mg tramadol hydrochloride twice daily.

For doses not practicable with this strength, other strengths of this medicinal product are available.

The tablets are to be taken whole, not divided or chewed, with sufficient liquid, independent of meals.

The lowest analgesically effective dose should generally be selected. Daily doses of 400 mg active substance should not be exceeded, except in special clinical circumstances.

Brimisol PR should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Brimisol PR is necessary in view of the nature
and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.

Children

Brimisol PR is not suitable for children below the age of 12 years.

Geriatric patients

A dose adjustment is not usually necessary in elderly patients (up to 75 years) without clinically manifest hepatic or renal insufficiency. In elderly patients (over 75 years) elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Renal Insufficiency/Dialysis and Hepatic Insufficiency

In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage interval should be carefully considered according to the patients requirements. In cases of severe renal and/or severe hepatic insufficiency Brimisol PR prolonged-release tablets are not recommended.

4.3 Contraindications

Brimisol PR is contraindicated

- in hypersensitivity to tramadol or any of the excipients (see section 6.1),
- in acute intoxication with alcohol, hypnotics, analgesics, opioids, or psychotropic medicinal products,
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see section 4.5),
- in patients with epilepsy not adequately controlled by treatment,
- for use in narcotic withdrawal treatment

4.4 Special warnings and precautions for use

Brimisol PR may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure.

In patients sensitive to opiates the product should only be used with caution.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered (see section 4.5), or if the recommended dosage is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold (see section 4.5). Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

Tramadol has a low dependence potential. On long-term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment with Brimisol PR should only be carried out for short periods under strict medical supervision.

Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
4.5 Interaction with other medicinal products and other forms of interaction

Brimisol PR should not be combined with MAO inhibitors (see section 4.3).

In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with Brimisol PR.

Concomitant administration of Brimisol PR with other centrally depressant medicinal products including alcohol may potentiate the CNS effects (see section 4.8).

The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur. Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

The combination with mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, and pentazocine) and tramadol is not advisable, because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors, tricyclic anti-depressants, anti-psychotics and other seizure threshold lowering medicinal products to cause convulsions.

In isolated cases there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotoninergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs) or with MAO inhibitors. Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied (see section 4.8).

In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and lactation

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore Brimisol PR should not be used in pregnant women.

Tramadol - administered before or during birth - does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms. During lactation about 0.1% of the maternal dose is secreted into the milk. Brimisol PR is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

4.7 Effects on ability to drive and use machines

Even when taken according to instructions, Brimisol PR may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with alcohol and other psychotropic substances.
4.8 Undesirable effects

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10% of patients.

The frequencies are defined as follows:

Very common: ≥1/10
Common: ≥1/100, <1/10
Uncommon: ≥1/1000, <1/100
Rare: ≥1/10 000, <1/1000
Very rare: <1/10 000
Not known: cannot be estimated from the available data

Cardiovascular disorders:
uncommon: cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.
rare: bradycardia, increase in blood pressure

Nervous system disorders:
very common: dizziness
common: headache, somnolence
rare: changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.
not known: speech disorders

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur.

Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold (see sections 4.4 and 4.5).

Psychiatric disorders:
rare: hallucinations, confusion, sleep disturbance, anxiety and nightmares. Psychic adverse reactions may occur following administration of Brimisol PR which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders). Dependence may occur.

Eye disorders:
rare: blurred vision
not known: mydriasis

Respiratory disorders:
rare: dyspnoea

Worsening of asthma has been reported, though a causal relationship has not been established.


Gastrointestinal disorders:
very common: nausea
common: vomiting, constipation, dry mouth
uncommon: retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea

Skin and subcutaneous disorders:
common: sweating
uncommon (≥1/1000, <1/100): dermal reactions (e.g. pruritus, rash, urticaria)

Musculoskeletal disorders:
rare: motorial weakness

Hepatobiliary disorders:
In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.

Renal and urinary disorders:
rare: micturition disorders (difficulty in passing urine, dysuria and urinary retention)

General disorders:
common: fatigue
rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis; Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, personalisation, derealisation, paranoia).

4.9 Overdose

Symptoms
In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Treatment
The general emergency measures apply. Keep open the respiratory tract (aspiration!) maintain respiration and circulation depending on the symptoms. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

In case of intoxication orally, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities or prolonged-release formulations.

Tramadol is minimally eliminated from the serum by haemodialysis or haemo-filtration. Therefore treatment of acute intoxication with Brimisol PR with haemodialysis or haemofiltration alone is not suitable for detoxification.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other opioids; ATC-code N 02 AX 02

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ opioid receptors with a higher affinity for the μ receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of nor adrenaline and enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

5.2 Pharmacokinetic properties

More than 90% of Brimisol PR is absorbed after oral administration. The mean absolute bioavailability is approximately 70 %, irrespective of the concomitant intake of food. The difference between absorbed and non-metabolised available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

Tramadol has a high tissue affinity ($V_{d,ß}$ = 203 ± 40 l). It has a plasma protein binding of about 20 %.

After administration of Brimisol PR 100 mg the peak plasma concentration $C_{max}$ =141 ± 40 ng/ml is reached after 4.9 h. After administration of Brimisol PR 200 mg $C_{max}$ 260 ± 62 ng/ml is reached after 4.8 hours.

Tramadol passes the blood-brain and placental barriers. Very small amounts of the substance and its O-desmethyl derivative are found in the breast-milk (0.1 % and 0.02 % respectively of the applied dose).

Elimination half-life $t_{1/2,ß}$ is approximately 6 h, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of approximately 1.4.

In humans tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2 - 4. Its half-life $t_{1/2,ß}$ (6 healthy volunteers) is 7.9 h (range 5.4 - 9.6 h) and is approximately that of tramadol.

The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite. Up to now, clinically relevant interactions have not been reported.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90 % of the total radioactivity of the administered dose. In cases of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half-lives of 13.3 ± 4.9 h (tramadol) and 18.5 ± 9.4 h (O-desmethyltramadol), in an extreme case 22.3 h and 36 h respectively, have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 ± 3.2 h and 16.9 ± 3 h, in an extreme case 19.5 h and 43.2 h respectively.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably in isolated cases. A serum concentration of 100 - 300 ng/ml is usually effective.

5.3 Preclinical safety data

On repeated oral and parenteral administration of tramadol for 6 - 26 weeks in rats and dogs and oral administration for 12 months in dogs haematological, clinico-chemical and
histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions, and reduced weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and dogs rectal doses of 20 mg/kg body weight without any reactions.

In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

In some in-vitro test systems there was evidence of mutagenic effects. In-vivo studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, non-significant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Lactose Monohydrate
Cellulose, microcrystalline
Hypromellose
Silica, Colloidal Anhydrous
Magnesium Stearate

Film-coating:
Hypromellose
Macrogol 6000
Purified Talc
Titanium Dioxide (E171)

Additionally in the film-coating for the 200 mg strength tablets only (PL 17907/0136):
Quinoline Yellow (E104)
Ferric Oxide Red

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

White, opaque PVC/Aluminium blister packs of 30 or 60 tablets

6.6 Special precautions for disposal

None
7 MARKETING AUTHORIZATION HOLDER
BRISTOL LABORATORIES LIMITED
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom

8 MARKETING AUTHORIZATION NUMBER(S)
17907/0134
17907/0136

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
01/11/2011

10 DATE OF REVISION OF THE TEXT
01/11/2011
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
Brimisol PR 100 mg and 200 mg
Prolonged-release Tablets
Tramadol hydrochloride

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

In this leaflet:
1. What Brimisol PR Tablet is and what it is used for
2. Before you take Brimisol PR Tablets
3. How to take Brimisol PR Tablets
4. Possible side effects
5. How to store Brimisol PR Tablets
6. Further information

1. WHAT BRIMISOL PR TABLET IS AND WHAT IT IS USED FOR
Tramadol-the active substance in Brimisol PR- is a painkiller belonging to the class of opioids that acts on the central nervous system. It relieves pain by acting on specific nerve cells of the spinal cord and brain.
Brimisol PR is used for the treatment of moderate to severe pain.

2. BEFORE YOU TAKE BRIMISOL PR TABLETS
Do not take Brimisol PR:
- if you are allergic (hypersensitive) to Tramadol or any of the other ingredients of Brimisol PR.
- in acute poisoning with alcohol, sleeping pills, pain relievers or other psychotropic medicines (medicines that affect mood and emotions);
- if you are also taking MAO inhibitors (certain medicines used for treatment of depression, examples include tranylcypromine, phenelzine and moclobemide) or have taken them in the last 14 days before treatment with Brimisol PR (see “Taking other medicines”);
- if you are an epileptic and your fits are not adequately controlled by treatment;
- as a substitute in drug withdrawal

Take special care with Brimisol PR:
- if you think that you are addicted to other pain relievers (opioids);
- if you suffer from consciousness disorders (if you feel that you are going to faint);
- if you are in a state of shock (cold sweat may be a sign of this);
- if you suffer from increased pressure in the brain (possibly after a head injury or brain disease);
- if you have difficulty in breathing;
- if you have a tendency towards epilepsy or fits because the risk of a fit may increase;
- if you suffer from a liver or kidney disease;
In such cases please consult your doctor before taking the medicine. Epileptic fits have been reported in patients taking tramadol at the recommended dose level. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400 mg).
Please note that Brimisol PR may lead to physical and psychological addiction. When Brimisol PR is taken for a long time, its effect may decrease, so that higher doses have to be taken (tolerance development). In patients with a tendency to abuse medicines or who are dependent on medicines, treatment with Brimisol PR should only be carried out for short periods and under strict medical supervision. Please also inform your doctor if one of these problems occurs during Brimisol PR treatment or if they applied to you in the past.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Brimisol PR should not be taken together with MAO inhibitors (certain medicines for the treatment of depression).
The pain-relieving effect of Brimisol PR may be reduced and the length of time it acts may be shortened, if you take medicines which contain
- carbamazepine (for epileptic fits);
- pentazocine, nalbuphine or buprenorphine (pain killers);
- ondansetron (prevents nausea).
Your doctor will tell you whether you should take Brimisol PR, and what dose. The risk of side effects increases,

- If you take tranquilizers, sleeping pills, other pain relievers such as morphine and codeine (also as cough medicine), and alcohol while you are taking Brimisol PR. You may feel drowsier or feel that you might faint. If this happens tell your doctor.
- If you are taking medicines which may cause convulsions (fits), such as certain antidepressants. The risk having a fit may increase if you take Brimisol PR at the same time. Your doctor will tell you whether Brimisol PR is suitable for you.
- If you are taking selective serotonin reuptake inhibitors (often referred to as SSRIs) or MAO inhibitors (for the treatment of depression). Brimisol PR may interact with these medicines and you may experience symptoms such as confusion, restlessness, fever, sweating, uncoordinated movement of limbs or eyes, uncontrollable jerking of muscles, or diarrhoea.
- If you take coumarin anticoagulants (medicines for blood thinning), e.g. warfarin, together with Brimisol PR. The effect of these medicines on blood clotting may be affected and bleeding may occur.

**Taking BRIMISOL PR with food and drink**

Do not drink alcohol during treatment with Brimisol PR as its effect may be intensified. Food does not influence the effect of Brimisol PR.

**Pregnancy and breastfeeding**

Ask your doctor or pharmacist for advice before taking any medicine. There is very little information regarding the safety of tramadol in human pregnancy. Therefore you should not use Brimisol PR if you are pregnant. Chronic use during pregnancy may lead to withdrawal symptoms in newborns. Generally the use of tramadol is not recommended during breast-feeding. Small amounts of tramadol are excreted into breast-milk. On a single dose it is usually not necessary to interrupt breast-feeding. Please ask your doctor for advice.

**Driving and using machines**

Brimisol PR may cause drowsiness, dizziness and blurred vision and therefore may impair your reactions. If you feel that your reactions are affected, do not drive a car or other vehicle, do not use electric tools or operate machinery, and do not work without a firm hold.

**Important information about some of the ingredients of BRIMISOL PR**

These tablets contain LACTOSE. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

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### 3. HOW TO TAKE BRIMISOL PR TABLETS

Always take Brimisol PR exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The dosage should be adjusted to the intensity of your pain and your individual pain sensitivity. In general the lowest pain-relieving dose should be taken. Unless otherwise prescribed by your doctor, the usual dose is:

**Adults and adolescents from the age of 12 years**

The usual initial dose is 50–100 mg prolonged released tablet twice daily, morning and evening. Your doctor may increase this dose up to 150–200 mg twice daily according to your needs.

The **maximum dose** is usually 400 mg daily. Your prescribed daily dose will depend on the severity of your pain.

**Children under 12 years of age**

Brimisol PR is not suitable for children below the age of 12 years.

**Elderly patients**

In elderly patients (above 75 years) the excretion of tramadol may be delayed. If this applies to you, your doctor may recommend prolonging the dosage interval.

**Severe liver or kidney disease (insufficiency)/dialysis patients**

Patients with severe liver and/or kidney insufficiency should not take Brimisol PR. If in your case the insufficiency is mild or moderate, your doctor may recommend prolonging the dosage interval.

**How and when should you take BRIMISOL PR**

Brimisol PR tablets are for oral use. Always swallow Brimisol PR tablets whole, not divided or chewed, with sufficient liquid, preferably in the morning and evening. You may take the tablets on an empty stomach or with meals.

**How long should you take BRIMISOL PR**

You should not take Brimisol PR for longer than necessary. If you need to be treated for a longer period, your doctor will check at regular short intervals (if necessary with breaks in treatment) whether you should continue to take Brimisol PR tablets and at what dose.

If you have the impression that the effect of Brimisol PR is too strong or too weak, talk to your doctor or pharmacist.
If you take more BRIMISOL PR than you should
If you have taken an additional dose by mistake, this will generally have no negative
effects. You should take your next dose as prescribed.
If you (or someone else) swallow a lot of Brimisol PR tablets at the same time you
should go to hospital or call a doctor straight away. signs of an overdose include very
small pupils, being sick, a fall in blood pressure, a fast heart beat, collapse,
unconsciousness, fits and breathing difficulty or shallow breathing.

If you forget to take BRIMISOL PR
If you forget to take the tablets, pain is likely to return. Do not take a double dose to
make up for forgotten individual doses; simply continue taking the tablets as before.

If you stop taking BRIMISOL PR
If you interrupt or finish treatment with Brimisol PR too soon, pain is likely to return.
If you wish to stop treatment on account of unpleasant effects, please tell your doctor.
Generally there will be no after-effects when treatment with Brimisol PR is stopped.
However, on rare occasions, people who have been taking Brimisol PR tablets for
some time may feel unwell if they abruptly stop taking them. They may feel agitated,
angry, irritable or restless. They may be disoriented, hyperactive, have difficulty sleeping
and have stomach or bowel disorders. Very few people may get panic attacks, delusions,
paranoia, hallucinations or feeling of loss of identity. They may experience unusual
perceptions such as itching, tingling and numbness, and “ringing” in the ears (tinnitus).
If you experience any of these complaints after stopping Brimisol PR, please consult
your doctor.
If you have any further questions on the use of this product, ask your doctor or
pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Brimisol PR can cause side effects, although not everybody gets them.
In case one of the following situations occur, see your doctor straight away:
• allergic reactions e.g. difficulty in breathing, wheezing, swelling of skin (occurs rarely),
• swollen face, tongue and/or throat and/or difficulty to swallow or hives together
  with difficulties in breathing (occurs rarely),
• Shock/sudden circulation failure (occurs rarely).
Usually the frequency of side effects is classified as follows:
  - very common (more than 1 out of 10 persons),
  - common (more than 1 out of 100 persons),
  - uncommon (more than 1 out of 1,000 persons),
  - rare (more than 1 out of 10,000 persons),
  - very rare (less than 1 out of 10,000 persons).
The most common side effects during treatment with Brimisol PR are nausea and
dizziness, which occur in more than 1 out of 10 patients.

Heart and blood circulation disorders
Uncommon: effects on the heart and blood circulation (pounding of the heart, fast heart
beat, feeling faint or collapse). These adverse effects may particularly occur in patients
in an upright position or under physical strain.
Rare: slow heart beat, increase in blood pressure.

Nervous system disorders
Very common: dizziness
Common: headaches, drowsiness.
Rare: changes in appetite, abnormal sensations (e.g. itching, tingling, numbness),
trembling, slow breathing, epileptic fits, muscle twitches, uncoordinated movement,
transient loss of consciousness (syncope). If the recommended doses are exceeded, or
if other medicines that depress brain function are taken at the same time, breathing may
slow down.
Epileptic fits have occurred mainly at high doses of Tramadol or when Tramadol was
taken at the same time as other medicines which may induce fits.

Psychiatric disorders
Rare: hallucinations, confusion, sleep disorders, anxiety and nightmares.
Psychological complaints may appear after treatment with Brimisol PR. Their intensity
and nature may vary (according to the patient's personality and length of therapy).
These may appear as a change in mood (mostly high spirits, occasionally irritated
mood), changes in activity (slowing down but sometimes an increase in activity) and
being less aware and less able to make decisions, which may lead to errors in judgement.
Dependence may occur.

Eye disorders:
Rare: blurred vision.

Respiratory disorders:
Rare: shortness of breath (dyspnoea).
Worsening of asthma has been reported, however it has not been established whether
it was caused by Tramadol.
Stomach and bowel disorders:
Very common: feeling sick.
Common: being sick, constipation, dry mouth.
Uncommon: urge to be sick (retching), stomach trouble (e.g. feeling of pressure in the stomach, bloating), diarrhoea.

Skin disorders:
Common: sweating
Uncommon: skin reactions (e.g. itching, rash).

Muscle disorders:
Rare: weak muscles.

Liver and biliary disorders:
Very rare: increase in liver enzyme values.

Urinary disorders:
Rare: passing water difficult or painful, less urine than normal.

General disorders:
Common: tiredness, weariness, weakness, low energy.
There have been some reports of speech disorders and dilated pupils.

If Brimisol PR tablets are taken over a long period of time dependence may occur, although the risk is very low. When treatment is stopped abruptly signs of withdrawal may appear (see "If you stop taking BRIMISOL PR").

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE BRIMISOL PR TABLETS
• Keep out of the reach and sight of children.
• Do not store above 25°C. Store in the original package.
• Do not keep the tablets into another container they might get mixed up.
• Do not remove the tablets from the blister pack or open the blister pack until you are ready to take the medicines.
• Do not use these Tablets after the “Expiry date” which is stated on the carton or blister. The expiry date refers to the last day of that month.
• Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What BRIMISOL PR Tablets contain
Brimisol PR Tablets come in two strengths containing 100mg or 200mg of the active ingredient Tramadol Hydrochloride.
The other ingredients are:
Tablet Core: Lactose Monohydrate, Microcrystalline Cellulose, Hypromellose, Colloidal Anhydrous Silica and Magnesium Stearate.
Film Coating: Hypromellose, Macrogol 6000, Purified Talc and Titanium dioxide(E171).
Each 200mg prolonged release tablet also contains Quinoline yellow lake (E 104) and Ferric oxide red.

What BRIMISOL PR looks like and contents of the pack
• Brimisol PR 100 mg tablets are white to off white, round, biconvex, film-coated tablets with '100' embossed on one side and 'BL' on other side.
• Brimisol PR 200 mg tablets are light orange to light pink, round, biconvex, film-coated tablets with '200' embossed on one side and 'BL' on other side.
Brimisol PR Tablets are available in pack size of 30 Tablets and 60 Tablets.

Marketing Authorization Holder and Manufacturer
Name and address: Bristol Laboratories Ltd,
Unit 3, Canalside, Northbridge Road,
Berkhampstead, Hertfordshire, HP4 1EG
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Brimisol PR 100mg Tablets; PL 17907/0134
Brimisol PR 200mg Tablets; PL 17907/0136

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UKPAR Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets

LABELLING

Brimisol PR 100 mg Prolonged-Release Tablets – PL 17907/0134

Carton – pack size 30
Carton – pack size 60
UKPAR Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets

Braille

Brimisol PR
br im is ol pr
3 0 m g
per tablets
p - r t a b l e t s

Blister foil
Brimisol PR 200 mg Prolonged-Release Tablets – PL 17907/0136

Carton – pack size 30
Carton – pack size 60
UKPAR Brimisol PR 100 mg and 200 mg Prolonged-Release Tablets

PL 17907/0134 & 0136

Braille

brimisol pr
200 mg
per tablets

Blister foil