Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Tramadol hydrochloride/Paracetamol 37.5 mg/325 mg Film-coated Tablets

(Tramadol hydrochloride and paracetamol)

UK Licence Number: PL 17907/0392

Bristol Laboratories Limited.

LAY SUMMARY

Tramadol hydrochloride/Paracetamol 37.5 mg/325 mg Film-coated Tablets

(Tramadol hydrochloride 37.5mg and paracetamol 325 mg, tablets)

This is a summary of the Public Assessment Report (PAR) for Tramadol hydrochloride/Paracetamol 37.5 mg/325 mg Film-coated Tablets (PL 17907/0392). It explains how Tramadol hydrochloride/Paracetamol 37.5 mg/325 mg Film-coated Tablets were 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/Paracetamol 37.5 mg/325 mg Film-coated Tablets.

The product will be referred to as Tramadol hydrochloride/Paracetamol Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Tramadol hydrochloride/Paracetamol Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Tramadol hydrochloride/Paracetamol Tablets and what are they used for?
Tramadol hydrochloride/Paracetamol Tablets are a 'generic medicine'. This means that Tramadol hydrochloride/Paracetamol Tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Tramacet 37.5 mg/325 mg film-coated tablets (Grünenthal Ltd, UK).

This medicine is intended for use in the treatment of moderate to severe pain when the patient's doctor recommends that a combination of tramadol and paracetamol is needed.

How do Tramadol hydrochloride/Paracetamol Tablets work?
This medicine is a combination of two analgesics, tramadol and paracetamol, which act together to relieve the patient's pain.

How are Tramadol hydrochloride/Paracetamol Tablets used?
The pharmaceutical form of Tramadol hydrochloride/Paracetamol Tablets is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

The patient should swallow the tablets whole with sufficient liquid. Do not break or chew the tablets.

The dosage should be adjusted to the intensity of the patient's pain and their individual pain sensitivity. In general the lowest pain relieving dose should be taken. The patient should take this medicine for as short a time as possible, and no longer than their doctor has told them.

Adults and adolescents of 12 years and over:
The recommended dosage is to start with 2 tablets, unless otherwise prescribed by the patient's doctor. If required, further doses may be taken, as instructed by their doctor.
The shortest time between doses must be at least 6 hours.
Do not take more than 8 tablets per day.

The patient's doctor may increase the time between doses if:

- the patient is older than 75 years
- the patient has kidney problems
- the patient has liver problems.

This medicine is not recommended for use in children under 12 years of age.

If the patient thinks that the effect of this medicine is too strong (they feel very drowsy or have difficulty breathing) or too weak (they do not have enough pain relief), the patient should contact their doctor.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Tramadol hydrochloride/Paracetamol Tablets have been shown in studies?
Because Tramadol hydrochloride/Paracetamol Tablets are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Tramacet 37.5 mg/325 mg film-coated tablets (Grünenthal Ltd, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Tramadol hydrochloride/Paracetamol Tablets?
Because Tramadol hydrochloride/Paracetamol Tablets are a generic medicine, their benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Tramadol hydrochloride/Paracetamol Tablets, see section 4 of the package leaflet available on the MHRA website.

Why were Tramadol hydrochloride/Paracetamol Tablets approved?
It was concluded that, in accordance with EU requirements, Tramadol hydrochloride/Paracetamol Tablets have been shown to have comparable quality and to be bioequivalent to Tramacet 37.5 mg/325 mg film-coated tablets (Grünenthal Ltd, UK). Therefore, the MHRA decided that, as for Tramacet 37.5 mg/325 mg film-coated tablets (Grünenthal Ltd, UK); the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Tramadol hydrochloride/Paracetamol Tablets?
A risk management plan (RMP) has been developed to ensure that Tramadol hydrochloride/Paracetamol Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Tramadol hydrochloride/Paracetamol Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Tramadol hydrochloride/Paracetamol Tablets
The Marketing Authorisation for Tramadol hydrochloride/Paracetamol Tablets was granted in the UK on 11 May 2016.

The full PAR for Tramadol hydrochloride/Paracetamol Tablets follows this summary.

For more information about use of Tramadol hydrochloride/Paracetamol Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2016.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited, a marketing authorisation for the medicinal product Tramadol hydrochloride/Paracetamol Tablets (PL 17907/0392).

Tramadol hydrochloride/Paracetamol Tablets is a Prescription Only Medicine (POM) indicated for symptomatic treatment of moderate to severe pain

The use of Tramadol hydrochloride/Paracetamol Tablets should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol (see section 5.1 of the SmPC).

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Tramacet 37.5 mg/325 mg film-coated tablets, which was originally granted to Janssen-Cilag Ltd (PL 0242/0384) on 25 September 2003 via an incoming mutual recognition procedure with France as reference member state (RMS) and underwent a change of ownership procedure to the current marketing authorisation holder (MAH) Grünenthal Ltd (PL 21727/0039) on 30 March 2009.

Tramadol is a synthetic, centrally acting analgesic agent with two distinct, synergistic mechanisms of action, acting as both a weak opioid agonist and an inhibitor of monoamine neurotransmitter reuptake. The two enantiomers of racemic tramadol function in a complementary manner to enhance the analgesic efficacy and improve the tolerability profile of tramadol.

Paracetamol is an aniline derivative, which has analgesic and antipyretic, but not anti-inflammatory properties. Although the precise mechanism of action of paracetamol has not been elucidated, its analgesic effects are thought to be largely central and mediated via several mechanisms, including the inhibition of prostaglandin synthesis, supraspinal activation of descending serotonergic pathways, inhibition of the nitric oxide pathway (mediated by substance P or N-methyl-D-aspartate) and by the interaction of active paracetamol metabolites with the endogenous cannabinoid system.

Results from a single bioequivalence study were submitted to support this application conducted under fasting conditions. The applicant has stated that the bioequivalence study was conducted in accordance with EMEA guidelines, Directive 2001/20/EC and ICH-Good Clinical Practice (GCP) including the archiving of essential documents and the current version of the Declaration of Helsinki.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on being a generic medicinal product of an originator product that has been in clinical use 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 this product.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Tramadol hydrochloride/Paracetamol Tablets outweigh the risks and a Marketing Authorisation was granted.

II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains tramadol hydrochloride 37.5 mg and paracetamol 325 mg. Other ingredients consist of the pharmaceutical excipients:

Tablet core:

Powdered cellulose, pregelatinised maize starch, sodium starch glycolate (Type A), maize starch and magnesium stearate.

Film-coating (opadry yellow 15B32209):

Hypromellose, titanium dioxide (E171), macrogol 400, iron oxide yellow (E172) and polysorbate 80.

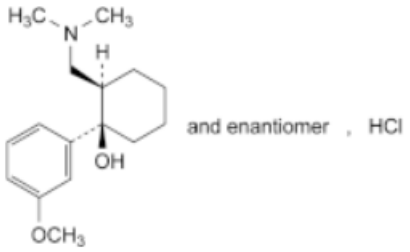
The finished product is packed into opaque polyvinyl chloride (PVC)/aluminium blister packs of 2, 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 tablets. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substances

(1) Tramadol hydrochloride

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

Structure:



Molecular formula:	$C_{16}H_{26}ClNO_2$
Molecular weight:	299.8
Appearance:	White or almost white, crystalline powder.
Solubility:	freely soluble in water and methanol, very slightly soluble in acetone

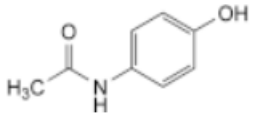
Tramadol hydrochloride is the subject of a European Pharmacopoeia monograph.

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.

(2) Paracetamol

INN:	Paracetamol
Chemical name:	*N*-(4-Hydroxyphenyl)acetamide.

Structure:



Molecular formula:	$C_8H_9NO_2$
Molecular weight:	151.2
Appearance:	White or almost white, crystalline powder.
Solubility:	Sparingly soluble in water, freely soluble in alcohol, very slightly soluble 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.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, tablets containing tramadol hydrochloride 37.5 mg and paracetamol 325 mg per tablet that are a generic version of the reference product Tramacet 37.5 mg/325 mg film-coated tablets (Grünenthal Ltd, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the film coating, opadry yellow 15B32209, which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale batch size and has shown satisfactory results. The Marketing Authorisation Holder has committed to perform process validation on future commercial scale batches and a satisfactory validation protocol has been provided.

Finished Product Specification

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

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 3 years with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of tramadol hydrochloride and paracetamol are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Tramadol hydrochloride/Paracetamol Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of tramadol hydrochloride and paracetamol is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of tramadol hydrochloride and paracetamol.

Based on the data provided, Tramadol hydrochloride/Paracetamol Tablets can be considered bioequivalent to Tramacet 37.5 mg/325 mg film-coated tablets (Grünenthal Ltd, UK).

IV.2 Pharmacokinetics

In support of this application, the applicant submitted results from the following bioequivalence study:

STUDY 1

An open-label, randomised, two-treatment, two-period, two-sequence, balanced, single-dose, crossover bioequivalence study to compare the pharmacokinetics of the applicant's test product Tramadol hydrochloride/Paracetamol 37.5 mg/325 mg Film-coated Tablets (Bristol Laboratories Limited) versus the reference product, Tramacet 37.5 mg/325 mg film-coated tablets (Grünenthal Ltd, UK), in healthy adult subjects under fasting conditions.

The subjects were administered a single dose (1 x tramadol hydrochloride 37.5 mg and paracetamol 325 mg tablet) of either the test or the reference product with 240 mL of water under fasting conditions.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was at least 7 days. The pharmacokinetic results are presented below:

Table: Pharmacokinetic data for tramadol (geometric means and 90% confidence interval):

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC_{0-t}	894.49	916.01	97.6499	95.5629	99.7826
C_{max}	114.97	114.55	100.3740	96.7204	104.1655

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.

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

Table: Pharmacokinetic data for paracetamol (geometric means and 90% confidence interval):

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC_{0-t}	16395.55	16648.80	98.4789	95.8710	101.1577
C_{max}	4234.21	4490.97	94.2828	88.0120	101.0003

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.

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

Conclusion

The 90% confidence intervals of the test/reference ratio for AUC_{0-t}, and C_{max} values for tramadol and paracetamol lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Tramacet 37.5 mg/325 mg film-coated tablets (Grünenthal Ltd, UK).

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tramadol hydrochloride/Paracetamol Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	• Simultaneous use of tramadol and paracetamol tablets with medicines acting on brain (Concomitant use of drugs acting on central nervous system) • Simultaneous use of tramadol and paracetamol tablets with medicines used in treatment of depression called monoamine oxidase (MAO) inhibitors (Concomitant use of MAO inhibitors) • Use in patients with liver problems (Use in patients with hepatic impairment) • Use in patients with kidney problems (Use in patients with renal insufficiency) • Use in patients experiencing fits or likely to develop to develop fits (Use in patients with epilepsy or susceptible to develop convulsions) • Use in patients dependant on opioid type pain relievers (Use in patients with opioid dependency) • Use in patients with brain injury (Use in patients with cranial trauma) • Use in patients with diseases of the organs and ducts that make and store bile (a fluid made by the liver that helps digest fat), and release it into the small intestine [biliary system] (Use in patients with biliary tract disorders) • Use in patients in a life-threatening condition that occurs when the body is not getting enough blood flow (Use in patients in

Summary of safety concerns	
	a state of shock) • Use in patients with change in consciousness due to unknown reasons (Use in patients with an altered state of consciousness for unknown reasons) • Use in patients with problems affecting breathing functions (Use in patients with problems affecting the respiratory centre or their respiratory function) • Use in patients with an increased pressure within skull (Use in patients with an increased intracranial pressure) • Habituation and dependence (Addiction and drug dependence) • Effects on driving and operating machines (Effects on ability to drive and use machines) • Use of the medicine in more than the medically recommended dose (Overdose) • Reactions that occur after stopping the medicine (withdrawal reactions)
Important potential risks	• Use during pregnancy and breastfeeding (Use during pregnancy and lactation) • Blood disorders (low blood platelet count and severe decrease in white blood cells) (Blood dyscrasias [thrombocytopenia and agranulocytosis]) • Serious skin reactions • Low mood (Depression) • Simultaneous use of tramadol and paracetamol tablets with blood thinning medicines like warfarin (Concomitant use with warfarin like compounds)
Missing information	• Use in children under 12 years of age • Use during a state of temporary loss of sensation and consciousness (Use during general anaesthesia)

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V User consultation

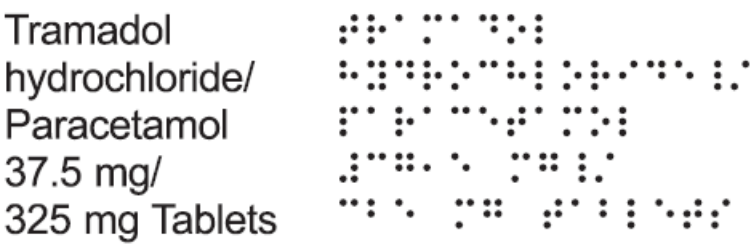
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the product for Co-Codamol tablets (Tillomed laboratories Ltd; PL 11311/0153. The bridging report submitted by the applicant was acceptable.

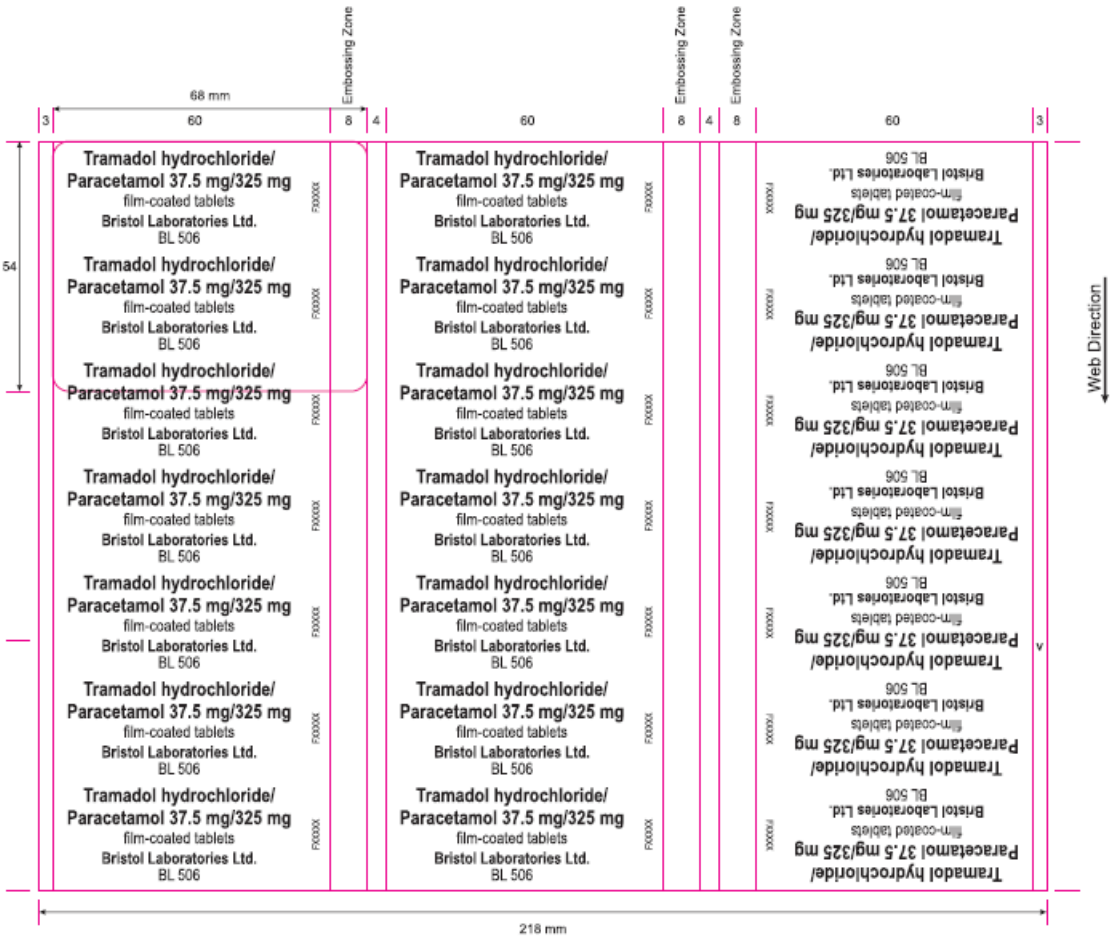
VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. 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.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:




68 mm
Embossing Zone
Embossing Zone
Embossing Zone
3
60
8
4
60
8
4
8
60
3
54
Tramadol hydrochloride/
Paracetamol 37.5 mg/325 mg
film-coated tablets
Bristol Laboratories Ltd.
BL 506
FXXXXX
Web Direction
218 mm