Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Lamotrigine Bristol Labs 25mg, 50mg, 100mg and 200mg Tablets

PL 17907/0118-121

PL 17907/0189-192

Bristol Laboratories Limited.

LAY SUMMARY

Lamotrigine 25mg, 50mg, 100mg and 200mg Tablets
(lamotrigine, tablet, 25mg, 50mg, 100mg and 200mg)

This is a summary of the Public Assessment Report (PAR) for Lamotrigine 25mg, 50mg, 100mg and 200mg Tablets (PL 17907/0118-121 and 189-192). It explains how Lamotrigine 25mg, 50mg, 100mg and 200mg 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 Lamotrigine 25mg, 50mg, 100mg and 200mg Tablets.

The products will be referred to as Lamotrigine tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Lamotrigine tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Lamotrigine tablets and what are they used for?
Lamotrigine tablets are a 'generic medicine'. This means that Lamotrigine tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Lamictal 25 mg, 50 mg, 100 mg and 200 mg Tablets (The Wellcome Foundation Limited, UK).

Lamotrigine tablets are used to treat the following two conditions:
Epilepsy:

- For adults and children aged 13 years and over, lamotrigine can be used on its own or with other medicines, to treat epilepsy. Lamotrigine can also be used with other medicines to treat the seizures that occur with a condition called Lennox-Gastaut syndrome.
- For children aged between 2 and 12 years, lamotrigine can be used with other medicines, to treat those conditions. It can be used on its own to treat a type of epilepsy called typical absence seizures.

Bipolar disorder:

- People with bipolar disorder (sometimes called manic depression) have extreme mood swings, with periods of mania (excitement or euphoria) alternating with periods of depression (deep sadness or despair). For adults aged 18 years and over, lamotrigine can be used on its own or with other medicines, to prevent the periods of depression that occur in bipolar disorder.

How do Lamotrigine tablets work?
This medicine contains the active ingredient lamotrigine, which belongs to a group of medicines called anti-epileptics. Lamotrigine treats epilepsy by blocking the signals in the

brain that trigger epileptic seizures (fits). It is not yet known how lamotrigine works in the brain to prevent periods of depression that occur in bipolar disorder.

How are Lamotrigine tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

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

How much lamotrigine to take
It may take a while to find the best dose of lamotrigine for the patient. The dose the patient takes will depend on:

- the age of the patient
- whether the patient is taking lamotrigine with other medicines
- whether the patient has problems with their kidneys or liver

The patient's doctor will start them on a low dose, and gradually increase the dose over a few weeks until they reach a dose that works for them (called the effective dose). The patient must never take more lamotrigine than their doctor tells them to.

The usual effective dose of lamotrigine for adults and children aged over 13 years is between 100mg and 400mg each day.

For children aged 2 to 12 years, the effective dose depends on their body weight usually, it's between 1mg and 15mg for each kilogram of the child's weight, up to a maximum of 200mg daily.

Lamotrigine is not recommended for children aged under 2 years

The patient should take their dose of lamotrigine once or twice a day, as their doctor advises them. The tablets can be taken with or without food.

The patient's doctor may also advise them to start or stop taking other medicines, depending on what condition they are being treated for and the way they respond to treatment.

The tablets should be swallowed whole. Do not break, chew or crush them.
The patient must always take the full dose that their doctor has prescribed. Never take only part of a tablet.

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 Lamotrigine tablets have been shown in studies?
Because Lamotrigine tablets are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Lamictal 25 mg, 50 mg, 100 mg and 200 mg Tablets (The Wellcome Foundation Limited, 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 Lamotrigine tablets?
Because Lamotrigine 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 Lamotrigine tablets, see section 4 of the package leaflet available on the MHRA website.

Why were Lamotrigine tablets approved?
It was concluded that, in accordance with EU requirements, Lamotrigine tablets have been shown to have comparable quality and to be bioequivalent to Lamictal 25 mg, 50 mg, 100 mg and 200 mg Tablets (The Wellcome Foundation Limited, UK). Therefore, the MHRA decided that, as for Lamictal 25 mg, 50 mg, 100 mg and 200 mg Tablets (The Wellcome Foundation Limited, 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 Lamotrigine tablets?
Safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Lamotrigine 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 Lamotrigine tablets
The Marketing Authorisations for Lamotrigine tablets were granted in the UK on 09 November 2006.

The full PAR for Lamotrigine tablets follows this summary.

For more information about use of Lamotrigine tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2016.

TABLE OF CONTENTS

I INTRODUCTION

Please note that the below scientific discussion consists of the original assessment of the product licences, plus a summary of key post approval changes at the end of this introduction section to improve the accuracy of this Public Assessment Report.

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Lamotrigine tablets to Bristol Laboratories Limited on 9 November 2006. These are prescription-only medicines (POM).

These are national applications for Lamotrigine tablets submitted under Article 10.1 of Directive 2001/83, claiming essential similarity to Lamictal Tablets. The 25 mg, 50 mg and 100 mg strengths of Lamictal Tablets (PLs 00003/0272-4) were first licensed to The Wellcome Foundation Limited on 21 October 1991, the 200 mg strength (PL 00003/0297) was licensed to the same foundation on 19 February 1992.

Lamotrigine tablets contain the active substance lamotrigine and are used in the treatment of epilepsy, either as monotherapy or as an adjunct to treatment with other antiepileptic agents. Lamotrigine is used to treat partial seizures and primary and secondary generalised tonic-clonic seizures and can also be used in the treatment of seizures associated with Lennox-Gastaut syndrome, a severe, childhood form of epilepsy.

Summary of key post-approval changes:
The following post-approval variations have been granted for these licences:

1. User test - Changes to leaflet granted on 29 June 2009 (PL 17907/0118 to 120-0006, & 0189 to 0192-0004).
2. To increase the shelf life from 2 years to 3 years granted on 09 July 2010 (PL 17907/0118 to 120-0014 & 0121-0013).
3. To update the name of the medicinal product to include name of the MAH (Bristol labs) as per CHM's advice. As a consequence, the PIL and labels have been updated as well as SmPC Section 1 granted on 06 March 2014 (PL 17907/0118 to 120-0042 , PL 17907/0121-0041, PL 17907/0189-0036, PL 17907/0190-0037, PL 17907/0191-0041, PL 17907/0192-0039).

II QUALITY ASPECTS

II.1 Introduction

These national abridged applications for lamotrigine tablets are made under EC Article 10.1 of the Directive 2001/83/EC, claiming essential similarity to the originator product, Lamictal Tablets (PL 0003/0272-4), first licensed on 21 October 1991 and PL 0003/0297, granted 19 February 1992.

Lamotrigine is an anti-epileptic drug indicated for use in the treatment of epileptic seizures.

A Mutual Recognition procedure is not intended on granting of licences for these products.

REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

The proposed manufacturing site has been inspected by the MHRA in October 2005 and GMP compliance has been confirmed. The batch release site is Bristol Laboratories Limited, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG, UK and a Wholesale Dealer's Licence dated 10 March 2006 has been provided for this site. QC sites have been proposed as Minerva Scientific Ltd, Delves Road, Heanor Gate, Derbyshire DE75 7SG, UK, Global Analysis, Bretby Busniess park, Ashby Park, Burton Upon Trent, Staffordshire, DE150QD, UK and Bristol Laboratories Ltd, Laporte Way, Luton, Beds, LU48WL, UK. Relevant documentation has not been provided for these sites.

The proposed storage sites are in line with the WDI licence issued by the MHRA on 10 March 2006.

II.2 Drug Substance

The drug substance, lamotrigine, is not the subject of a BP or PhEur monograph.

The applicant has submitted a Drug Master File for lamotrigine from the active substance manufacturer. This source of lamotrigine has been approved in September 2005. There have been no further updates. No further assessment is required.

A letter of access dated September 2004 naming the applications is provided.

Specification

The active substance specification used by the finished product manufacturer is provided and is satisfactory.

A multi-point particle size distribution specification for the drug substance is provided. The drug substance manufacturer has confirmed that they will be able to provide the raw

material within the particle size specification limits and have provided the relevant certificates of analysis. Details of the particle size distribution and certificates of analysis for the batches of active substance used in pivotal batches, including biobatch, have been provided.

Analytical test methods
Full details on the test methods used by the finished product manufacturer to control the active substance are provided.

Analytical test method validation
The test methods and specifications used for lamotrigine by the finished product manufacturer are the same as those of the active substance manufacturer, hence no separate validations were undertaken by the finished product manufacturer.

Justification of specification
The test methods and specifications used for lamotrigine by the finished product manufacturer are the same as those of the active substance manufacturer.

Reference standards
Certificates of Analysis for the working standard (obtained from the drug substance manufacturer) used by the finished product manufacturer in control of the active substance are provided.

II.3. Medicinal Product

Description and Composition of the Drug Product
The qualitative composition of the four strengths is given as follows.

Name of ingredients	**Function**	**Reference to standards**
Active Ingredient Lamotrigine	Drug substance	HSE
Inactive ingredients		
Lactose monohydrate	Diluent	
Cellulose, microcrystalline	Diluent	PhEur
Iron oxide yellow	Colourant	USPNF
Polyvinyl pyrollidone (PVPK30)	Binder	PhEur
Purified water	Vehicle	PhEur
Sodium starch glycollate	Disintegrant	PhEur
Purified talc	Lubricant	PhEur
Magnesium stearate	Lubricant	PhEur

The four strengths of pale yellow coloured, flat, round, uncoated tablets are direct scale up or scale down versions of each other and are differentiated by tablet size and markings.

25mg: L25 on one side plain on the other side.
50mg: L50 on one side and B and L either side of the break line on the other.
100mg: L100 on one side and B and L either side of the break line on the other.
200mg: L200 on one side and B and L either side of the break line on the other.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development rationale was to produce a product with characteristics similar to the originator product, Lamictal Tablets. Functions of ingredients are defined, and it is stated that a compatibility study has been carried out however no details have been provided. As the product appears stable in stability studies this is acceptable. Initial development studies were performed on the 100mg strength and the formulation was scaled down to the other tablet strengths. A small number of small scale trial batches of lamotrigine 100mg were produced in which levels of different excipients were varied until the desired dissolution profile and acceptable physical properties were obtained. Trials using different binders and also by direct compression were carried out. The formulation using povidone as a binder and water as the solvent was selected as the final formulation.

Simulated gastric fluid ph 1.2 was chosen as the media for dissolution. No detailed development of the dissolution method has been described, however comparative dissolution testing was performed on a number of proposed product and reference product batches in three media: pH 1.2, buffer pH 4.5 and phosphate buffer pH 6.8.

Batches subjected to dissolution studies (including the 200mg biobatch: BAD4004F) were also subjected to impurity profile comparison in support of the chemical essential similarity. The proposed products (pilot and laboratory scale batches of each strength) showed similar dissolution and impurity profiles to the reference products sourced from UK.

Based on the results obtained with formulation batches, scale up was carried out on the 200mg tablets. Two batches were used in order to optimise the manufacturing process. Sufficient testing on the blend has been conducted (uniformity of content, LOD following dry mixing of the blend, mixing time for granulation, LOD during drying, bulk density and sieve analysis of the unlubricated and lubricated blend, uniformity of content and LOD of lubricated blend, speed of machine and effect on weight variation and hardness during compression and its effect on the friability and dissolution. The critical manufacturing steps of dry mixing (blend analysis of dry mix), lubricated blend and compression were studied and critical parameters including mixing times were optimised.

In addition data has been provided for the manufacturer of three pilot scale batches of the 100mg, 50mg and 25mg strengths. The data provided covers all the in-process controls

and routine product release testing and is considered to be satisfactory and representative of a controlled process.

The effect of particle size of this poorly water soluble drug substance on product quality in relation to dissolution and bioavailability has been studied and details of this study are provided.

Formulation of the lamotrigine tablets for all four strengths is linear. Therefore, for economical reasons, a common blend was produced for tablets of all four strengths. The applicant has provided an explanation for the granule division and maximum batch sizes for all four strengths.

Details on the development of the dissolution method parameters are provided.

The discriminatory nature of the dissolution method has been proved by the applicant demonstrating the differences between acceptable and unacceptable batches of the finished product, relevant dissolution profiles are provided with individual tablet data.

No overages have been included in the formulation.

Manufacture of the product

Satisfactory batch formulae have been provided for production scale batches of the tablets. A manufacturing flow chart is provided.

The manufacturing process involves sifting, dry mixing, granulation, milling, drying, milling, lubrication, compression and packaging.

The expiry date given to the finished product is based on the dispensing of the starting materials for manufacturing. The approximate timelines for the manufacturing process, including the time for each stage and between each stage up to and including final packaging, have been provided.

No reprocessing was undertaken during the pivotal batches. The applicant does not advise any reprocessing on commercial batches.

Satisfactory details of in-process controls are provided.

The blisters are subjected to vacuum leak testing and the packaging materials are checked for batch legend details.

Relevant details have been provided on the frequency of in-process control testing.

Relevant details on the collection of samples for the in-process testing, including the quantity and location, are provided.

The process was optimised on batches during manufacturing process development and the process was further validated on batches of lamotrigine tablets of all four strengths. The batches were manufactured using the proposed drug substance source.

For process validation, an undertaking is given that process validation will be carried out on the first full scale production batches. A protocol has been provided. The compressed tablets are tested to drug product specifications. A satisfactory sampling plan has been provided.

The formulation development for Lamotrigine Tablets is based on common granulation concept as the formulation for all four strengths of Lamotrigine tablets is linear. Hence the development studies up to granule stage was undertaken for the 200mg strength. Common granules of 200mg were manufactured, which were then sub-divided for compression into different strengths. Therefore the full inprocess data is presented under 200mg strength and the compression data of the different strengths is presented under the respective strength in the drug product application.

Process validation will be carried out on the first three consecutive full-scale production batches of each strength at the proposed product manufacturer site.

Control of Excipients

Lactose, microcrystalline cellulose, magnesium stearate, povidone, purified talc, sodium starch glycolate and purified water all have European Pharmacopoeia monographs. Ferric oxide yellow is USP/NF grade. Each batch of excipient received is tested to full specification by IPCA. The excipient specifications are supported by certificates of analysis.

Sodium starch glycolate is stated to be Type A.

The suppliers of the excipients have confirmed compliance with BSE/TSE concerns. Lactose monohydrate is specified to be sourced exclusively from healthy animals in the same conditions as for milk sourced for human consumption. The origin of stearic acid in magnesium stearate is specified as being vegetable grade.

Confirmation has been obtained from the supplier of the colourant yellow iron oxide stating that yellow iron oxide is in compliance with E number 172.

Purified water used in the manufacture of the finished product is produced on-site. The description of the manufacturing process with details of the in-process controls, including tests performed, limits, frequency of testing and sampling plan is provided

Finished Product Specifications

The finished product specification of lamotrigine tablets is provided and is satisfactory.

The shelf-life specification covers appearance, identification, average weight, uniformity of weight, disintegration, dissolution, related substances, assay and microbial levels.

As per the ICH guidelines, an identification test solely by a single chromatographic retention time is acceptable if the test is performed using HPLC/UV diode array, hence second identification test is not conducted.

Based on the results obtained on pivotal batches, suitable limits for loss on drying and friability have been set.

The specifications for disintegration, dissolution and impurities all acceptable.

The applicant has confirmed that the reduced testing for microbiology and identification of ferric oxide is only implemented after completion of acceptable results on the first three commercial production scale batches for each strength.

Analytical methods are provided for all tests.

The uniformity of mass test in the finished product specification is in line with the current European Pharmacopoeia.

The HPLC method for assay has been validated: specificity has been demonstrated in relation to placebo and stressed samples. Linearity has also been shown within a suitable range. The method is precise and accurate. Robustness has been demonstrated for changing mobile phase composition, wavelength and pH of the buffer. The method has an acceptable system suitability.

The UV dissolution method has been validated: for specificity, accuracy, precision, linearity and range and ruggedness. Specificity has been demonstrated in relation to placebo. Stability in the dissolution media has been demonstrated for 24 hours. Linearity has been demonstrated within a suitable range.

The robustness of the dissolution method has been demonstrated in line with the guideline on analytical method validation and details of the study undertaken are provided.

The related substances method has been validated: lamotrigine has been used as a reference substance, for specificity, linearity and range, precision, solution stability, ruggedness and robustness. LOD and LOQ values are satisfactory. Linearity has been shown within a suitable range. Specificity has been demonstrated in relation to placebo.

Specification and method of analysis for related substances in the drug product is same as that given in the DMF of the drug substance. The limit for any impurity covers all known and any unknown impurities. In absence of having known impurities in isolated form, as suggested by the DMF, validation of related substances method has been demonstrated

using lamotrigine. Further, it is assumed that the response of all known and unknown impurities are comparable with that of lamotrigine.

Specificity of the related substances method has been demonstrated in relation to the potential known and unknown impurities and also based on the information provided in the DMF about RRTs of known impurities. The data for the specificity study is provided.

The scope of related substance method given in the DMF of the active has been further extended to quantitate the related substances of the finished product. From the accelerated studies of finished product it was confirmed that no new impurities arise from the finished product which have not been characterized in the active substances and hence the robustness study carried out in the DMF holds good for validation of finished product.

Details demonstrating that the validation of the microbiology methods is in-line with the European Pharmacopoeia are provided.

Batch analysis data has been provided for three batches of each tablet strength. Batch histories have been provided and three different batches of drug substance from the active substance manufacturer have been used in these batches manufactured in April 2004. The results are within specification and support the limits set.

The MAA forms state that full testing to finished product specification is performed at the EU QC testing sites.

The impurities in the related substance test are those indicated in the drug master file.

The scope of the related substance method given in the DMF of active includes quantitation of the related substances of finished product. From the accelerated studies of finished product it was confirmed that no new impurities arise from the finished product which have not been characterized in the active substances and hence the robustness study carried out in the DMF holds good for validation of finished product.

Reference Standards or Materials

The working standard certificate of analysis has been provided from the active substance supplier.

Certificates of Analysis of the working standard used in analysis of pivotal batches confirming that it has been characterized with the primary reference standard are provided. The characterization details for the reference standard are provided in the DMF submitted with this application and are satisfactory.

Container Closure System

Lamotrigine tablets are either packed in PVC/aluminium blister strips or HDPE tablet containers with HDPE screw caps.

Upon receipt, the PVC/aluminium foil is subjected to a visual check and identification test and the HDPE containers are verified for dimensions.

The sources and specification of all packaging materials are specified supported by certificates of analysis. Statements have been provided stating that the PVC films and HDPE bottles are in compliance with EC 90/128/EC and aluminium meets EU legislation for food contact.

All packaging materials are tested for identification.

Relevant certification confirming that the packaging components conform to the requirements of the European Pharmacopoeia are provided.

Relevant certification confirming that the packaging components of the bulk tablets comply with the European Pharmacopoeia monograph and the requirements for food contact materials are provided.

Stability of the Product

Three batches of each tablet strength as presented in batch analysis and packed in the proposed blisters and bottles to be marketed have been stored at 25ºC/60%RH and 40ºC/75%RH. Details of the batch numbers of the active substance used in each of the stability batches are provided, stability batches utilised three different batches of active substance.

A stability protocol is provided and the intended duration of the stability study is 36 months at real time. In use stability has not been provided, however, as the product is stable this is acceptable.

The shelf life specification proposed is in line with the 'release' specification.

The physical stability of the tablets was determined during the stability study. Loss on drying and hardness are determined on the batches of all strengths kept on stability and the results of the study are provided.

The parameters monitored on stability are description, disintegration, dissolution, related substances and assay, as well as microbial testing in line with guidelines and using the methods of the drug product specifications. Results are available up to 6 months both at real time and at accelerated storage. Results for related impurities indicate that total impurities increase up to a level of 0.08% at 6 months real time and no significant deterioration in assay is seen up to 6 months.

A commitment has been given that the first three production scale batches will be placed on stability in accordance with the stability protocol post approval. The proposed shelf life is 36 months.

The applicant has confirmed that the post approval stability commitment will include one batch per year of each strength under long term conditions. Stability data up to 24 months has been provided. Storage conditions are in line with available stability data and CPMP/QWP/609/96.

Bioequivalence / Bioavailability

A full bioequivalence study is reported in the clinical documentation. The study was conducted by a clinical research company that has been approved for other generic products. The study is a single dose, open label, randomised, two-treatment, two period, two way crossover study in 26 adult healthy male volunteers with the following products:

Test (A): Lamotrigine 200mg tablets (Batch no.: BAD4004F, man. date: 04/04, batch size: 50,000)

Reference (B): Lamictal 200mg tablets from Wellcome/GSK (UK product, batch no: B119136)

Certificates of analysis have been provided for the test and reference bioequivalence batches.

Bioanalytical methods and validation

The wash out period was 23 days. Pharmacokinetic parameters of AUC_{0-00} and AUC_{0-t}Cmax were determined and analysed by ANOVA for statistical treatment for ratio test/reference and 90% confidence intervals for 24 subjects. These values are within the accepted regulatory range of 80-125% (0.80-1.25 range) indicating that A is bioequivalent to B in this bioequivalence study involving 200mg tablets.

Justification for biowaivers

The applications include several strengths i.e. 25mg, 50mg, 100mg and 200mg lamotrigine tablets. As the four strengths of the proposed product tablets have the same qualitative and quantitative composition and are dose proportional with direct scale-up and scale down versions of each other and exhibit similar dissolution profiles, the results and conclusions of the bioequivalence study on the 200mg strength could be extrapolated to the three lower strengths of 25mg, 50mg and 100mg, tablets.

The bioanalytical method and validation report is provided.

Essential Similarity

This has been discussed under Pharmaceutical Development.

REGIONAL INFORMATION

Process validation scheme for the drug product

This has been provided.

TSE Issues
A certificate for lactose anhydrous has been provided from the applicant.

ASSESSOR'S COMMENTS ON Module I
Name and Appearance (if applicable)
This is acceptable.

SmPC
The Summary of Product Characteristics is satisfactory.

Patient Information Leaflet
The Patient Information Leaflet is satisfactory.

Label
All labelling is satisfactory.

Application Form
The MAA (Marketing Authorisation Application) form submitted with this application is satisfactory.

Samples
Fifty tablet samples of the lowest (25mg) and highest (200mg) strength tablets produced using lamotrigine from the named source accompanied by a Certificate of Analysis have been sent to the MHRA.

Quality Overall Summary
The summary has been completed by a Pharmaceutical and Regulatory Affairs Consultant. The report is a summary of the module.

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

III NON-CLINICAL ASPECTS

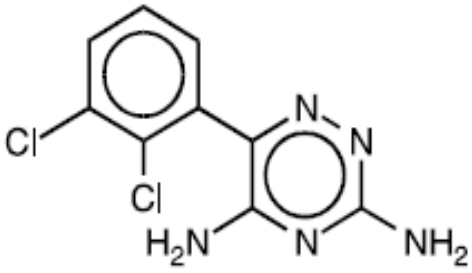
No new non-clinical data have been supplied with this application and none is required for an application of this type.

IV CLINICAL ASPECTS

IV.1 Introduction

These national abridged applications for Lamotrigine tablets are made under EC Article 10.1 of the Directive 2001/83/EC, claiming essential similarity to the originator product, Lamictal Tablets (PL 0003/0272-4), first licensed on 21 October 1991 and PL 0003/0297, granted 19 February 1992).

Lamotrigine, a phenyltriazine derivative, is a well-established anticonvulsant agent that has also been shown to be effective in the prevention of mood episodes in adult patients with bipolar disorder.



The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. The relevance of these models to human epilepsy, however, is not known.

One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. In vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g. glutamate and aspartate). The mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established.

IV.2 Pharmacokinetics

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug administration.

Estimates of the mean apparent volume of distribution (Vd/F) of lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of dose and is

similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Data from *in vitro* studies indicate that lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 μg/mL (10 μg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely.

Lamotrigine is extensively metabolised in the liver, predominantly via *N*-glucuronidation (the rate-limiting step in elimination of the drug). Clearance is 1.6–2.6 L/h and the mean plasma elimination half-life is 25–35 hours. The major metabolite is an inactive 2-N-glucuronide conjugate.

In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose administered over the range of 50 to 400 mg.

Population pharmacokinetic analyses involving patients aged 2 to 18 years demonstrated that lamotrigine clearance was influenced predominantly by total body weight and concurrent anticonvulsant therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in paediatric patients than in adults.

	Tmax (hours)	Half-life (hours)
Ages 10 months-5.3 years		
Patients taking enzyme-inducing antiepileptic drugs	3.0	7.7
Patients taking antiepileptic drugs (AEDs) with no known effect on drug-metabolising enzymes	5.2	19.0
Patients taking valproate only	2.9	44.9
Ages 5-11 years		
Patients taking enzyme-inducing antiepileptic drugs	1.6	7.0
Patients taking enzyme-inducing antiepileptic drugs plus valproate	3.3	19.1
Patients taking valproate only	4.5	65.8

A single dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31, 0.24, 0.10 mL/min/kg in patients with Grade A, B or C (Child-Pugh Classification) hepatic impairment respectively, compared to 0.34 mL/min/kg in the healthy controls. Reduced doses should generally be used in patients with Grade B or C hepatic impairment.

The mean plasma half-lives determined in one study were 42.9 hours (chronic renal failure), 13.0 hours (during haemodialysis), and 57.4 hours (between haemodialysis) compared to 26.2 hours in healthy volunteers. Pharmacokinetic studies using single doses in subjects with renal failure indicate that plasma concentrations of the major glucuronide metabolite increase almost eight-fold due to reduced renal clearance.

The mean half-life of lamotrigine in elderly subjects was 31.2 hours (range, 24.5 to 43.4 hours) and the mean clearance was 0.40 mL/min/kg (range, 0.26 to 0.48 mL/min/kg). The clearance of lamotrigine is not affected by gender. The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than Caucasians.

Assessment
The Summaries of Product Characteristics of all the four strengths and of the two sets of applications under assessment are identical. In this assessment a comparison was made between the Summary of Product Characteristics of the index products under assessment and the SPC of the brand leader in the UK. Comparison is also made with the Euro-SPC approved following the recent mutual recognition procedure when the UK was the Reference Member State when appropriate

The Summaries of Product Characteristics are satisfactory.

Bioequivalence
The bioequivalence study was performed by a clinical research group and the details are as follows:

Study period:	May 2004 – August 2004
Reference product used:	Lamictal 200mg Tablets Wellcome Foundation Ltd, UK (Batch B119136)
Test product used:	Lamotrigine 200mg Tablets manufactured by IPCA Laboratories Ltd (Batch BAD4004F)
Study design:	Open randomised two-way crossover, single dose study

26 healthy male volunteers of whom 24 completed the study.

Sampling to 96 hours. Washout period 23 days.

Results

N = 24

Arithmetic mean ± SD (range)

Parameter	Test	Reference
Cmax (μg/mL)	3.4047 ± 0.5446	3.2815 ± 0.5643
Tmax (h)	1.89 ± 1.12	2.03 ± 1.44
AUC(o-t) (μg.h/mL)	113.1503 ± 21.3989	114.5312 ± 20.8263
AUC(o-α) (μg.h/mL)	127.0087 ± 31.7688	128.9188 ± 30.9067
AUC(o-t) / AUC(o-α)	89.1 %	88.8 %
t1/2 (h)	28.54 ± 6.35	28.59 ± 6.93

Geometric mean

Parameter	Test	Reference	% Ratio (T/R)	90% CI (%)
Cmax μg/mL	3.4055	3.2847	103.68	96.81-110.55
AUC(o-t) μg.h/mL	113.5180	114.5251	99.12	95.90-102.34
AUC(o-α) μg.h/mL	127.5819	128.9095	98.97	95.05-102.89

In terms of peak concentrations (Cmax) and exposure (AUC), the test product used is bioequivalent to the reference product used.

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 these applications.

IV.6 Discussion on the clinical aspects

There are no major clinical public health issues arising from these applications and the recommendation is to grant marketing authorisation.

VI Overall conclusion, benefit/risk assessment and recommendation

QUALITY

The important quality characteristics of Lamotrigine 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.

EFFICACY

No new or unexpected safety concerns arise from this application.

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

BENEFIT-RISK ASSESSMENT

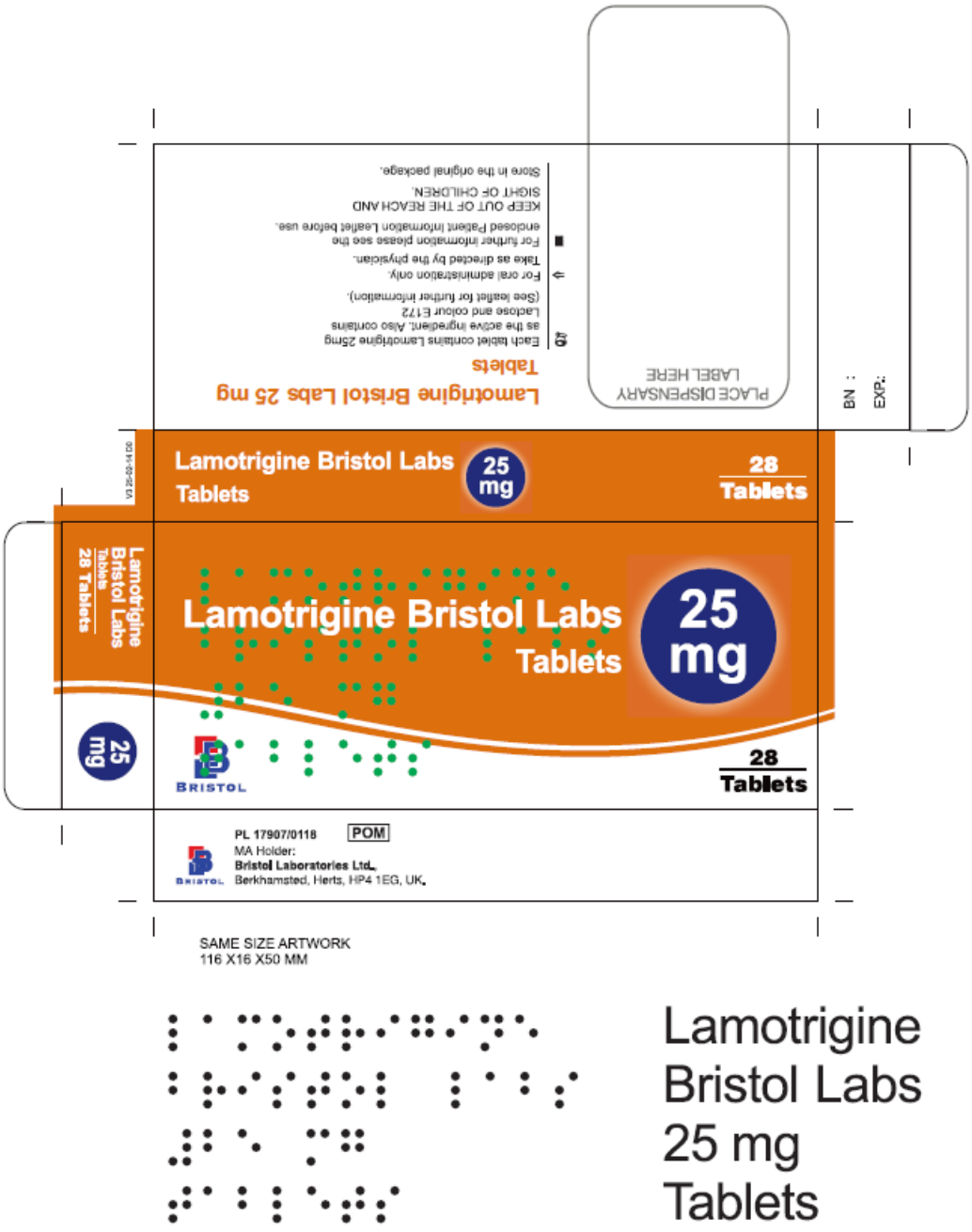
The quality of the product is acceptable, no significant non-clinical or clinical safety concerns were identified, and benefit has been shown to be associated with Lamotrigine tablets. The benefit-risk is therefore considered to be positive.

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 current approved labelling for this medicine is presented below:

PL 17907/0118:



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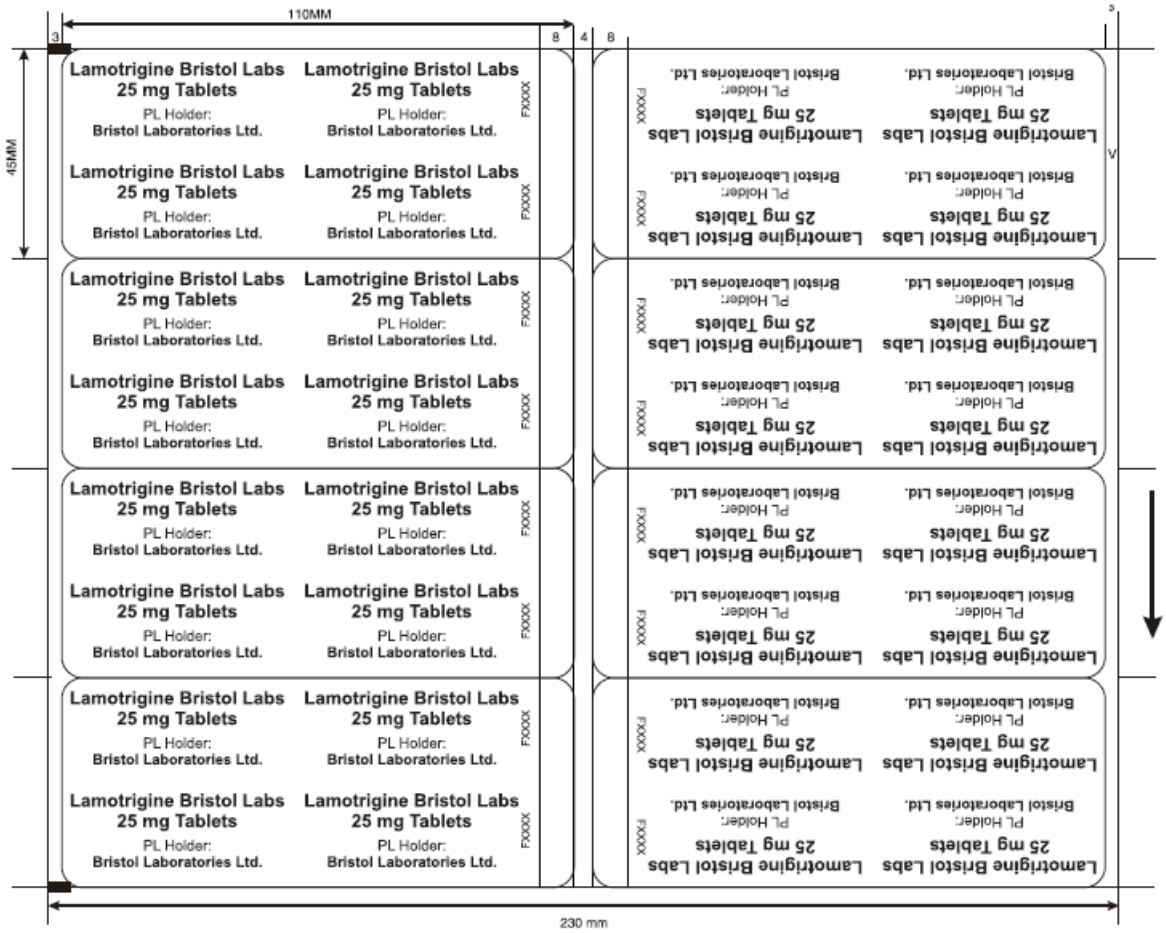
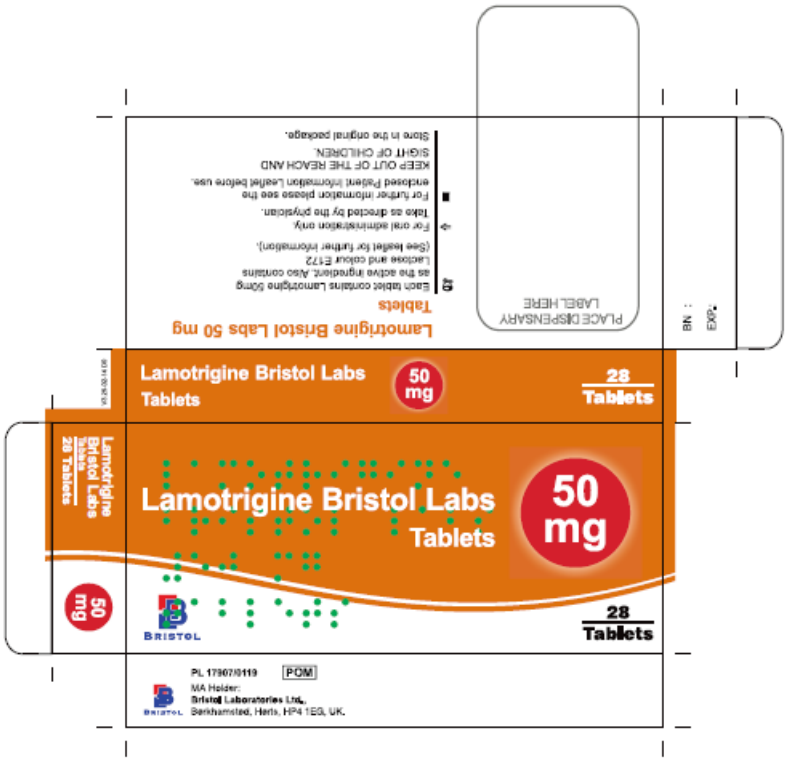
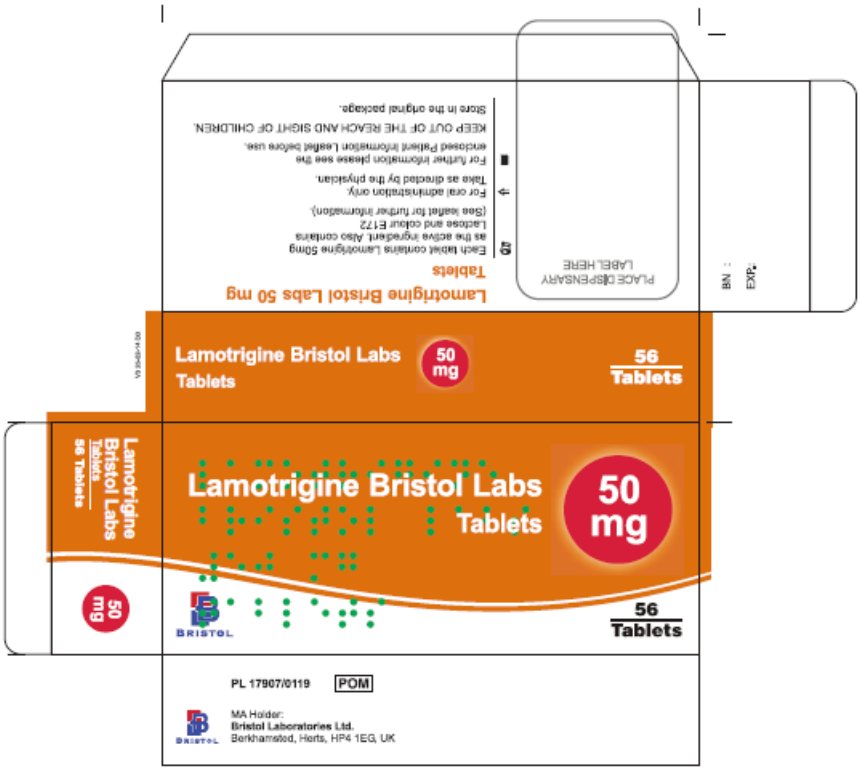
Size : 116 x 22 x 50 mm

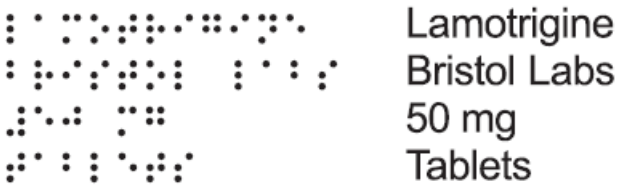

110MM
45MM
230 mm
Lamotrigine Bristol Labs
25 mg Tablets
PL Holder:
Bristol Laboratories Ltd.
FXXXX

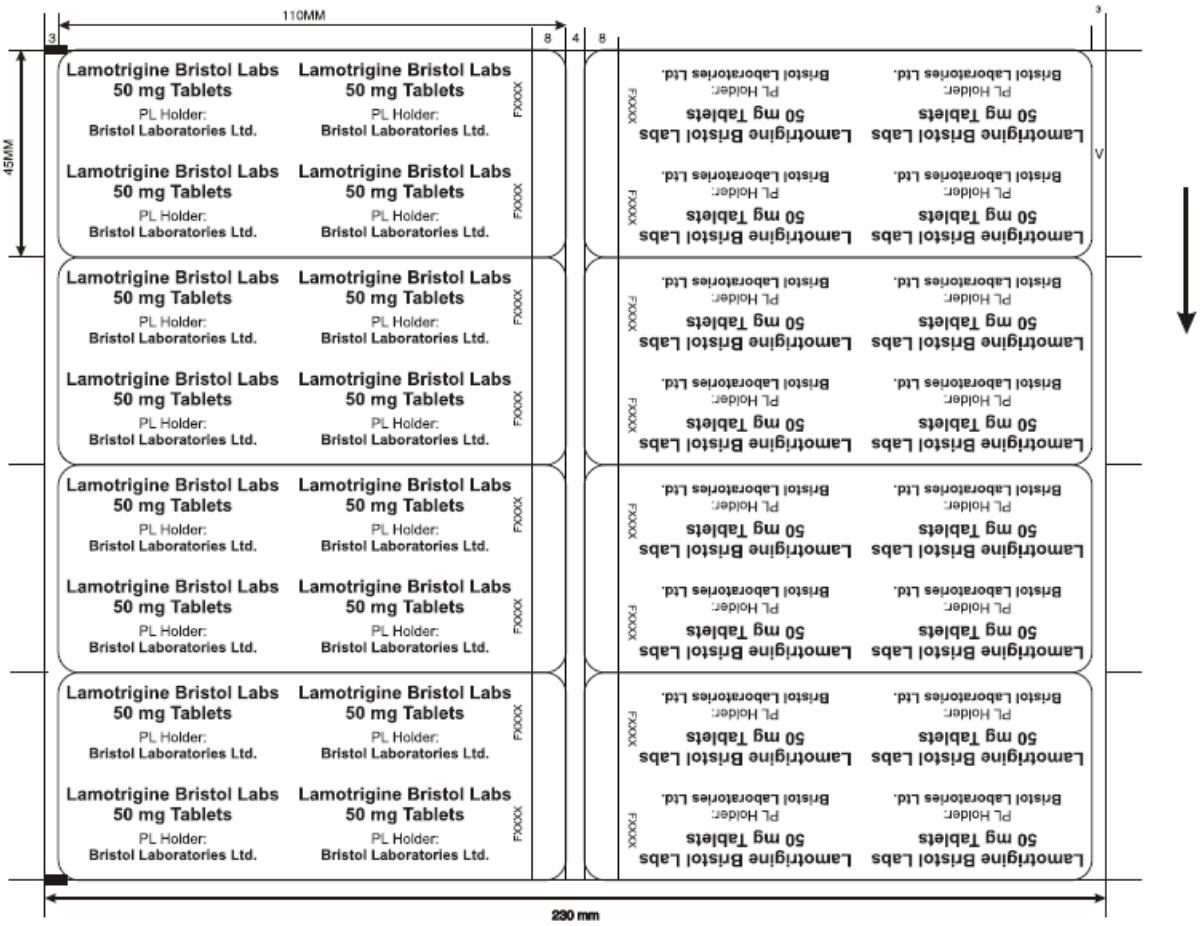
PL 17907/0119:



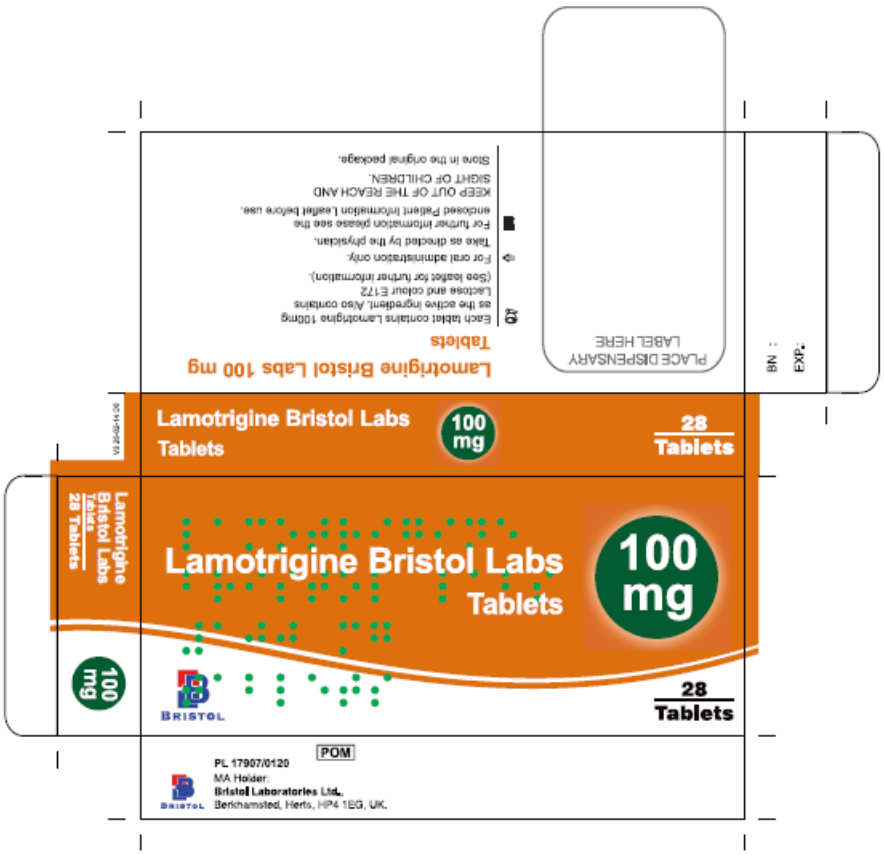
Lamotrigine
Bristol Labs
50 mg
Tablets


Lamotrigine Bristol Labs 50 mg
Tablets
Each tablet contains Lamotrigine 50mg as the active ingredient. Also contains Lactose and colour E172 (See leaflet for further information).
For oral administration only.
Take as directed by the physician.
For further information please see the enclosed Patient Information Leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Store in the original package.
PLACE DISPENSARY LABEL HERE
EXP.
BN
Lamotrigine Bristol Labs
Tablets
50 mg
56 Tablets
Lamotrigine Bristol Labs
Tablets
50 mg
56 Tablets
BRISTOL
PL 17907/0119
POM
MA Holder:
Bristol Laboratories Ltd.
Berkhamsted, Herts, HP4 1EG, UK


Lamotrigine
Bristol Labs
50 mg
Tablets


110MM
45MM
230 mm
Lamotrigine Bristol Labs
50 mg Tablets
PL Holder:
Bristol Laboratories Ltd.
FXXXX

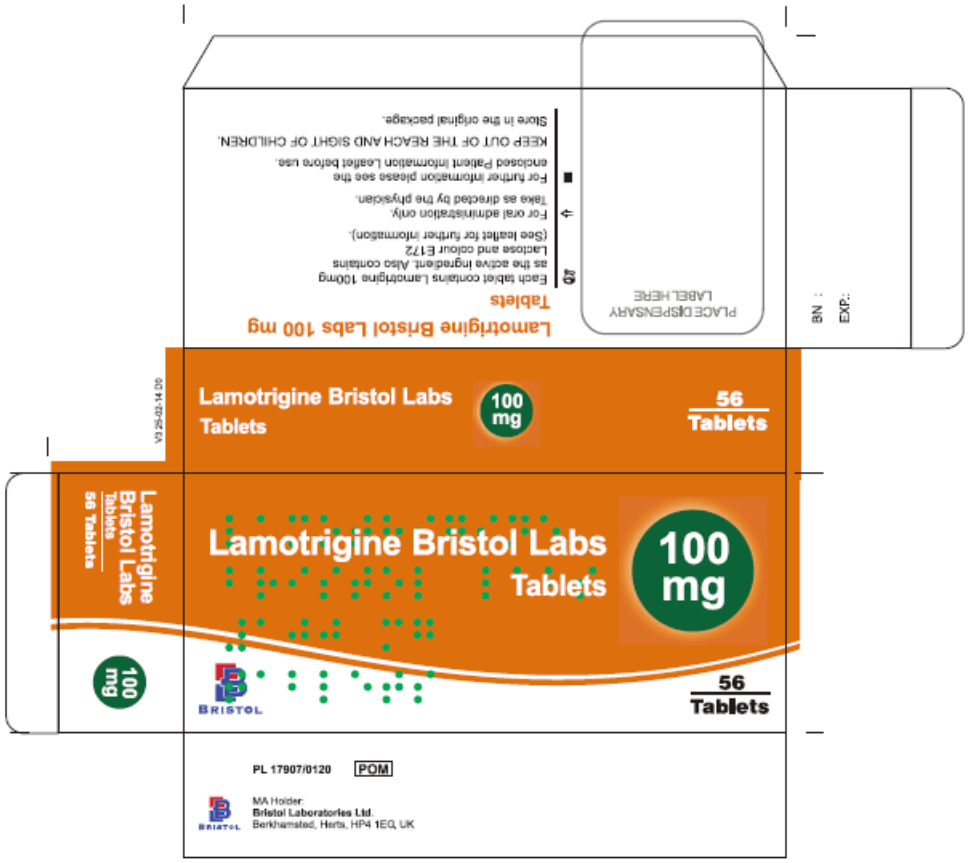
PL 17907/0120:



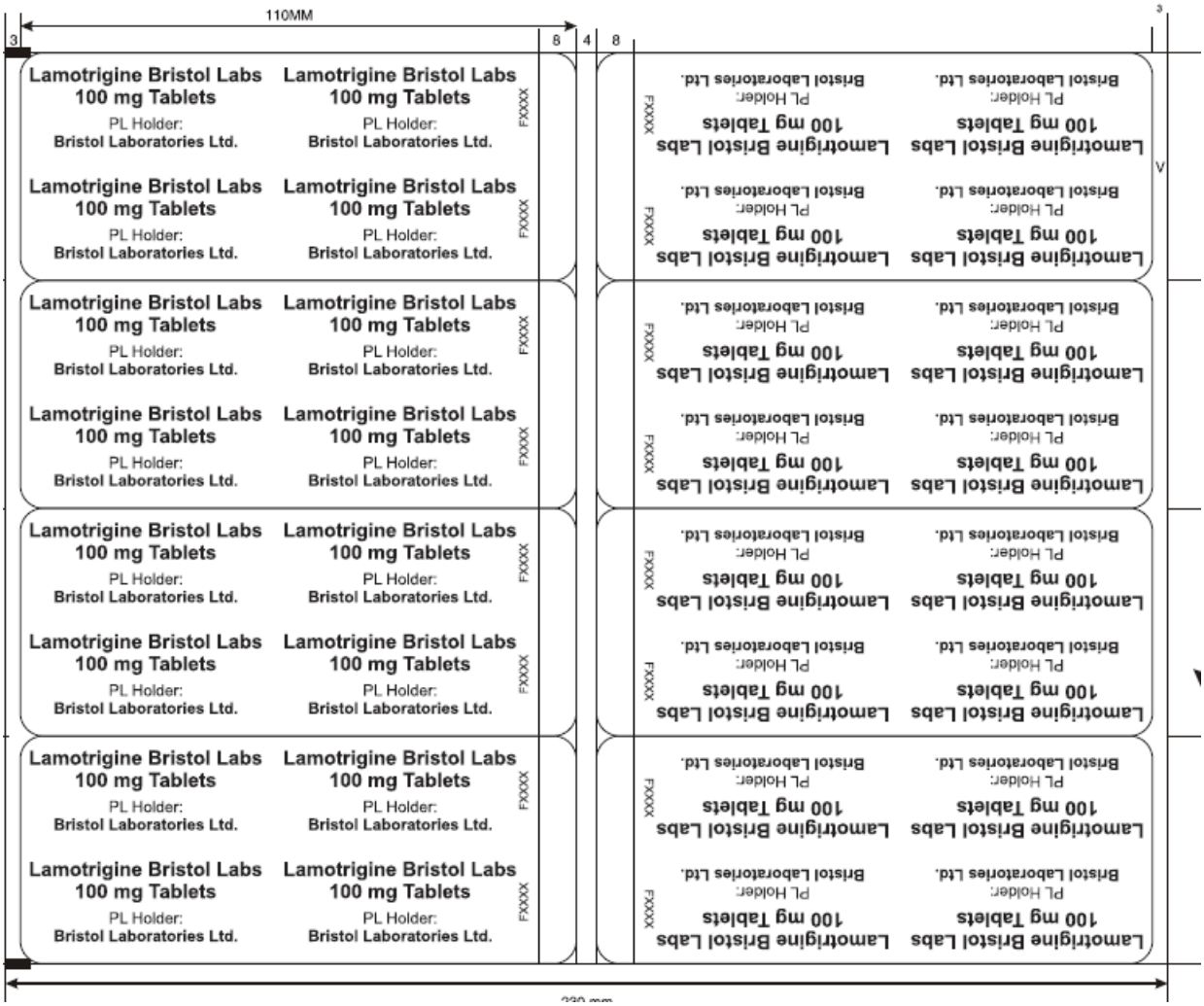
SAME SIZE ARTWORK
116 X16 X50 MM

Kaypee Design
23 11 11

Lamotrigine
Bristol Labs
100 mg
Tablets


Lamotrigine Bristol Labs
Tablets
100 mg
56 Tablets
Lamotrigine Bristol Labs
Tablets
100 mg
56 Tablets
PL 17907/0120
POM
MA Holder:
Bristol Laboratories Ltd.
Berkhamsted, Herts, HP4 1EQ, UK
BRISTOL
PLACE DISPENSARY LABEL HERE
BN
EXP:
Lamotrigine Bristol Labs 100 mg
Tablets
Each tablet contains Lamotrigine 100mg as the active ingredient. Also contains Lactose and colour E172
(See leaflet for further information).
For oral administration only.
Take as directed by the physician.
For further information please see the enclosed Patient Information Leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Store in the original package.

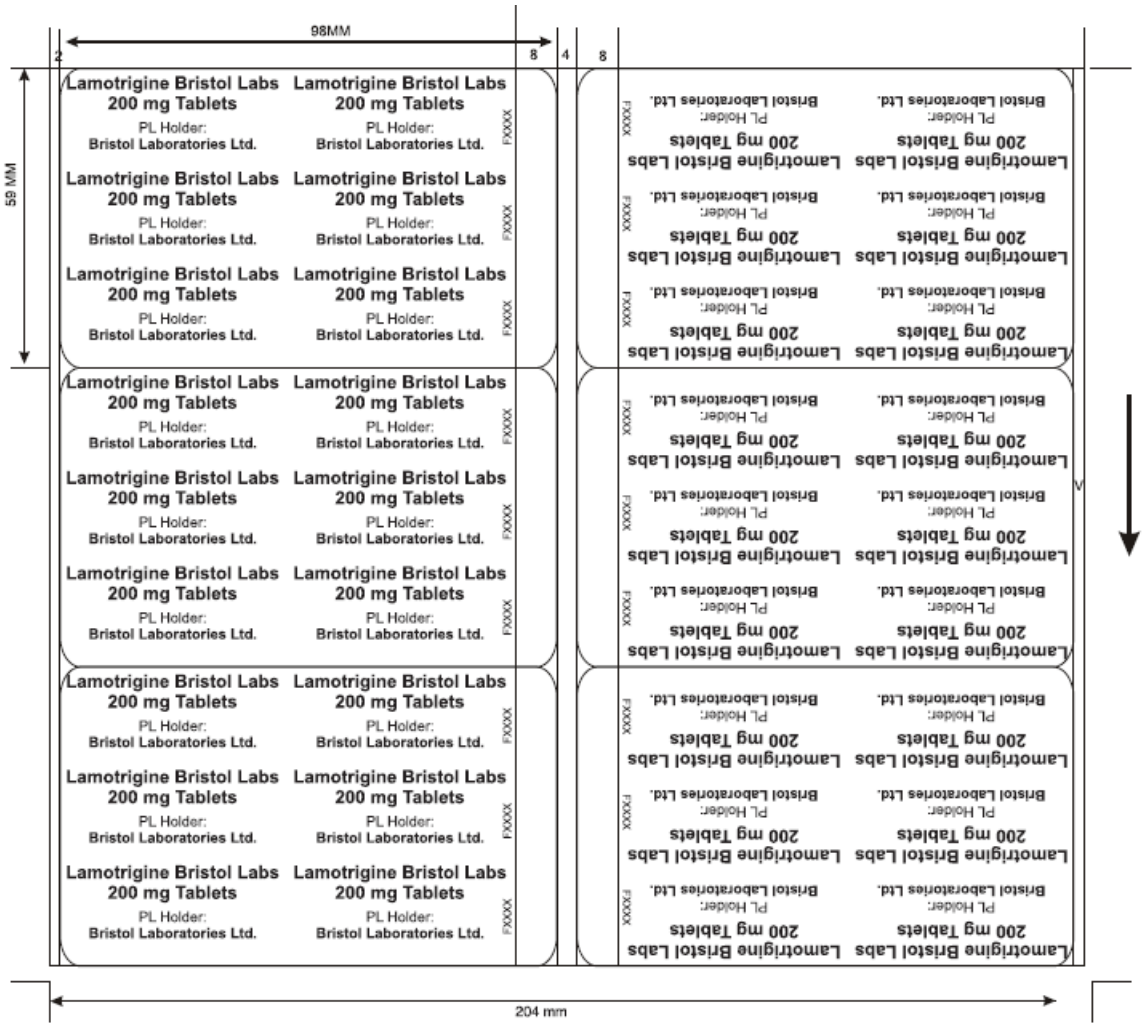

Lamotrigine
Bristol Labs
100 mg
Tablets


110MM
3
8
4
8
Lamotrigine Bristol Labs
100 mg Tablets
PL Holder:
Bristol Laboratories Ltd.
FXXXX
Lamotrigine Bristol Labs
100 mg Tablets
PL Holder:
Bristol Laboratories Ltd.
FXXXX
V

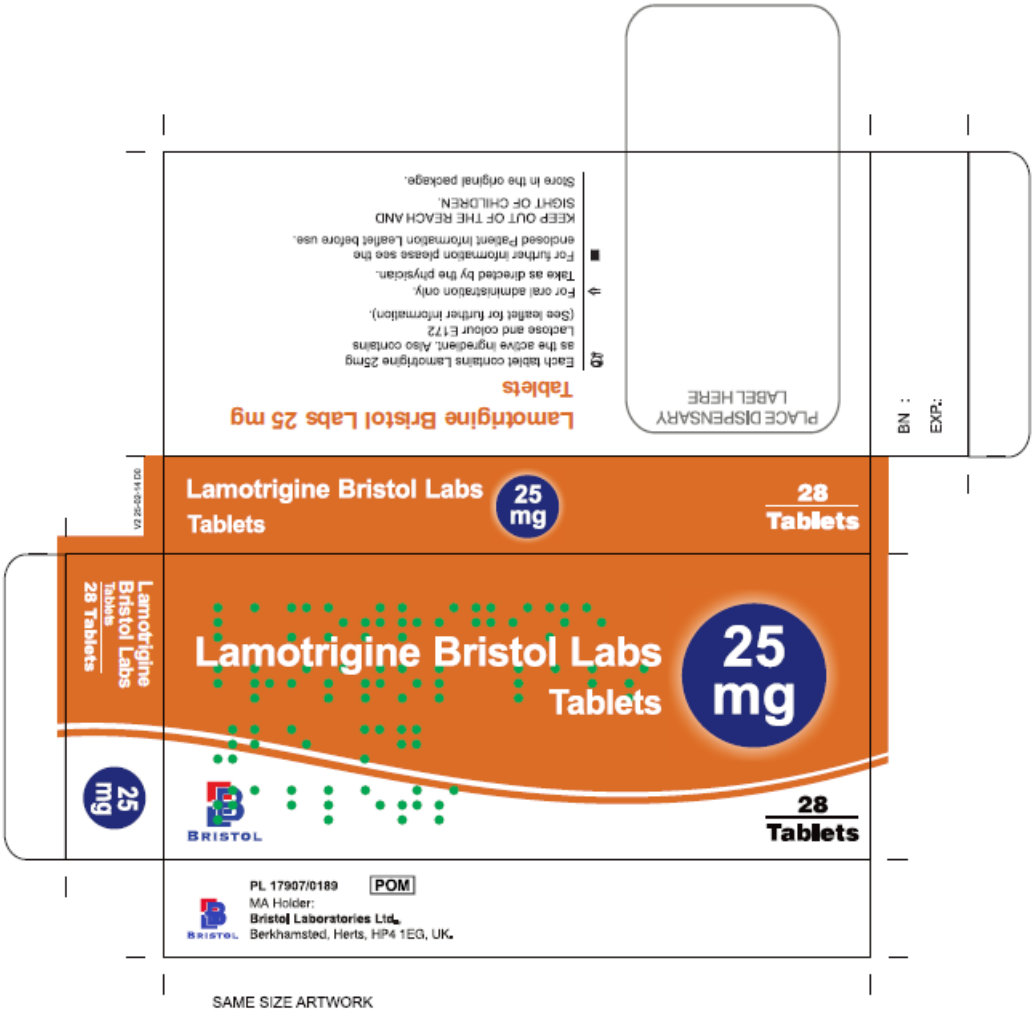
PL 17907/0121:


Lamotrigine Bristol Labs 200 mg Tablets
Each tablet contains Lamotrigine 200mg as the active ingredient. Also contains Lactose and colour E172 (See leaflet for further information).
For oral administration only.
Take as directed by the physician.
For further information please see the enclosed Patient Information Leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Store in the original package.
PLACE DISPENSARY LABEL HERE
BN :
EXP:
V3 25-02-14 DD
Lamotrigine Bristol Labs Tablets
200 mg
56 Tablets
Lamotrigine Bristol Labs Tablets 56 Tablets
Lamotrigine Bristol Labs Tablets
200 mg
BRISTOL
56 Tablets
PL 17907/0121
POM
MA Holder:
Bristol Laboratories Ltd.
Berkhamsted, Herts, HP4 1EG, UK


Lamotrigine
Bristol Labs
200 mg
Tablets


98MM
2
8
4
8
59 MM
Lamotrigine Bristol Labs
200 mg Tablets
PL Holder:
Bristol Laboratories Ltd.
FXXXX
204 mm

PL 17907/0189:



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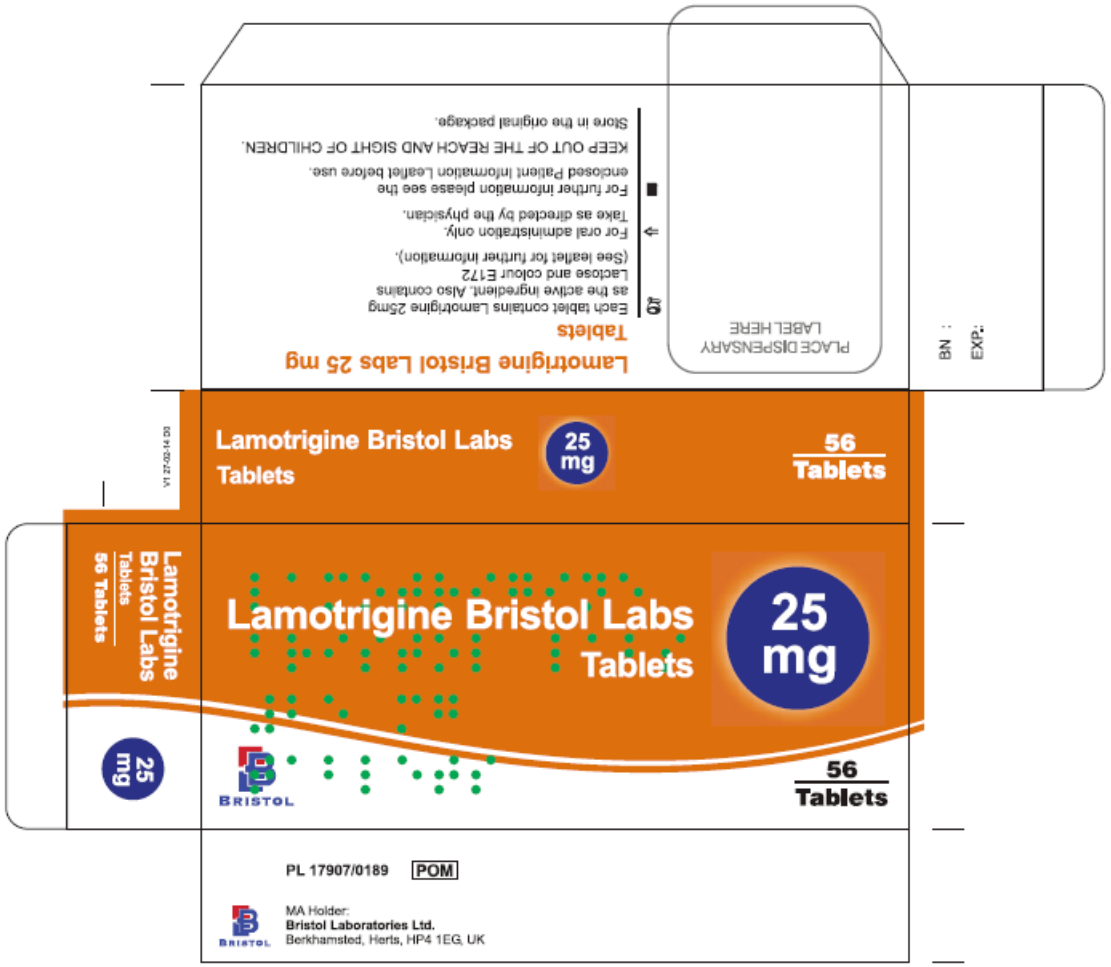
116 X16 X50 MM



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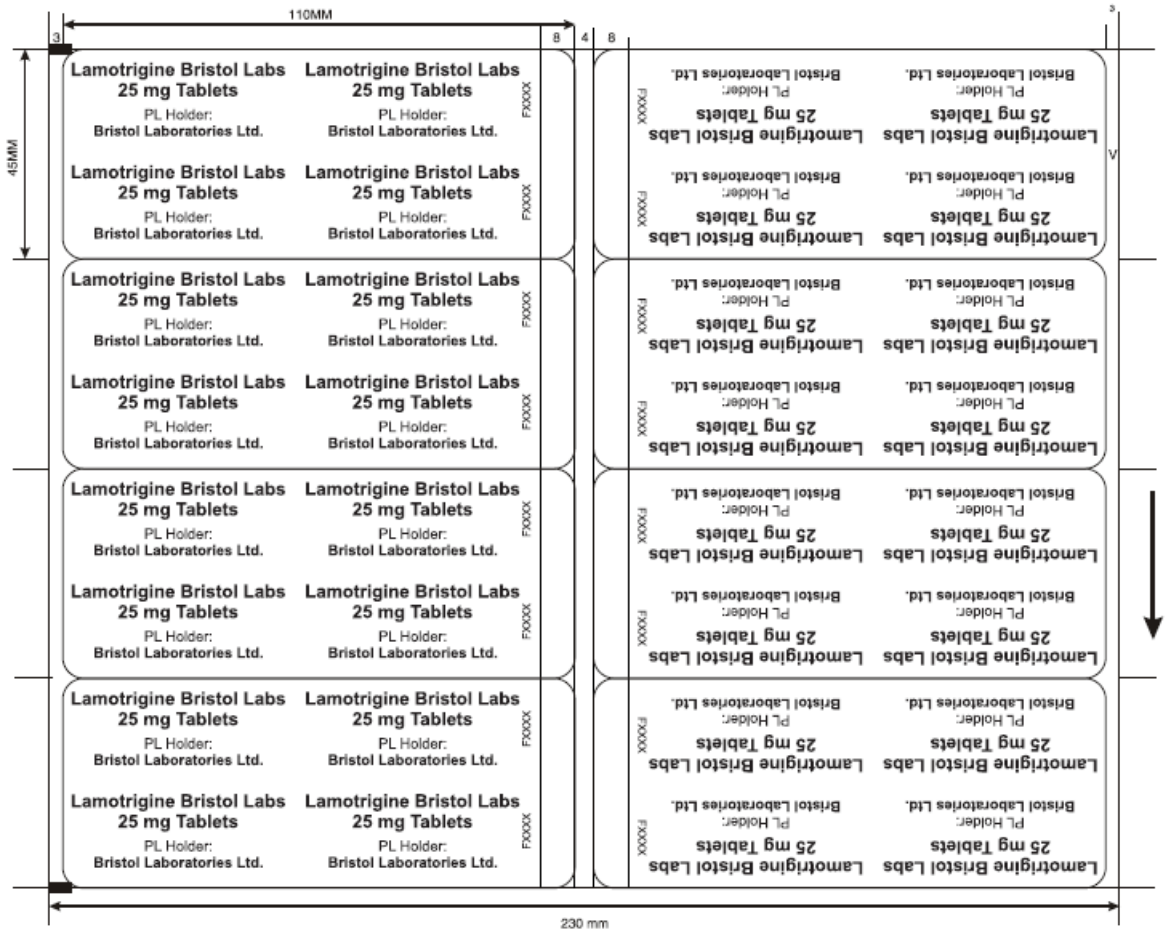
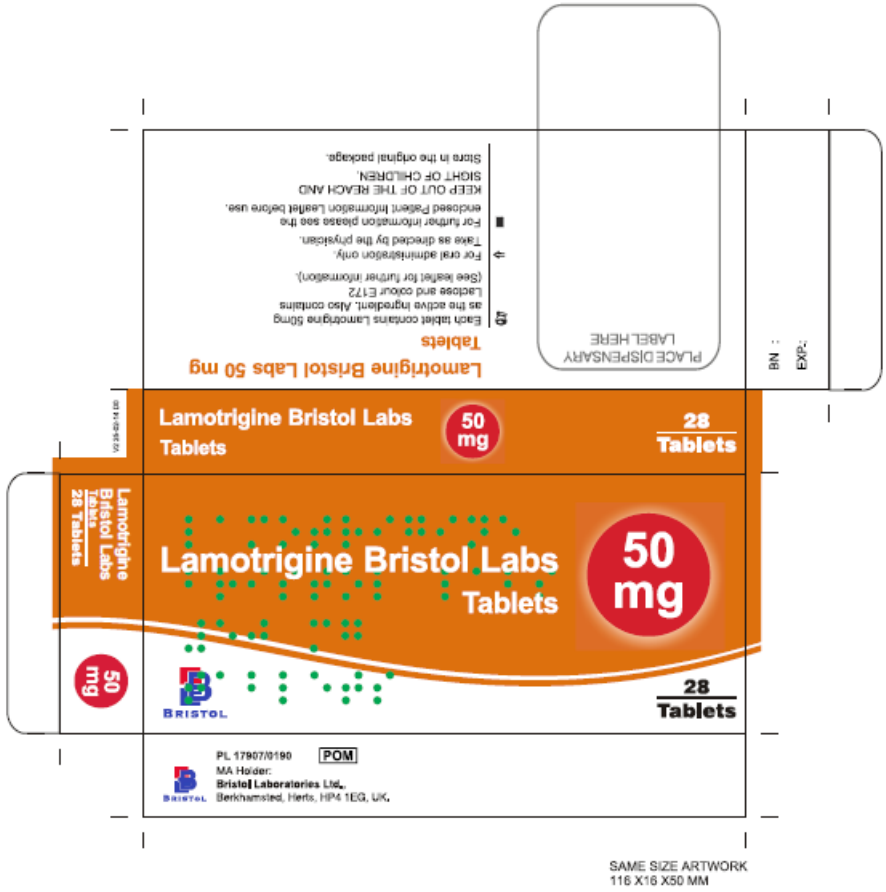
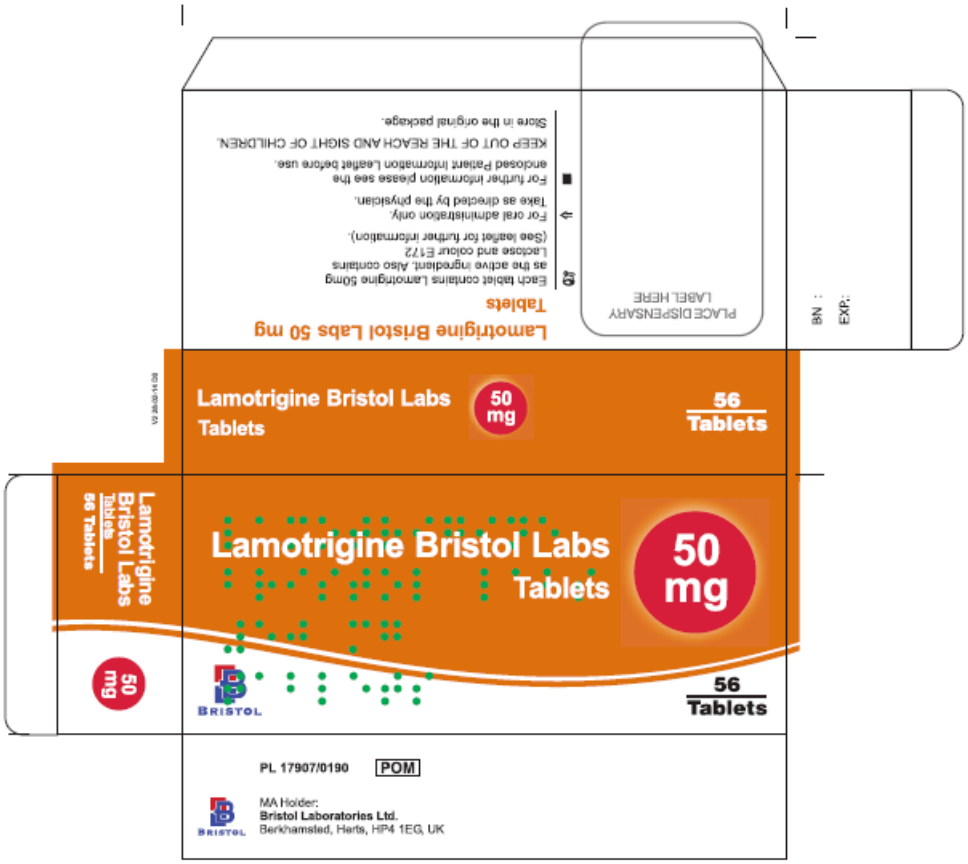
Size : 116 x 22 x 50 mm

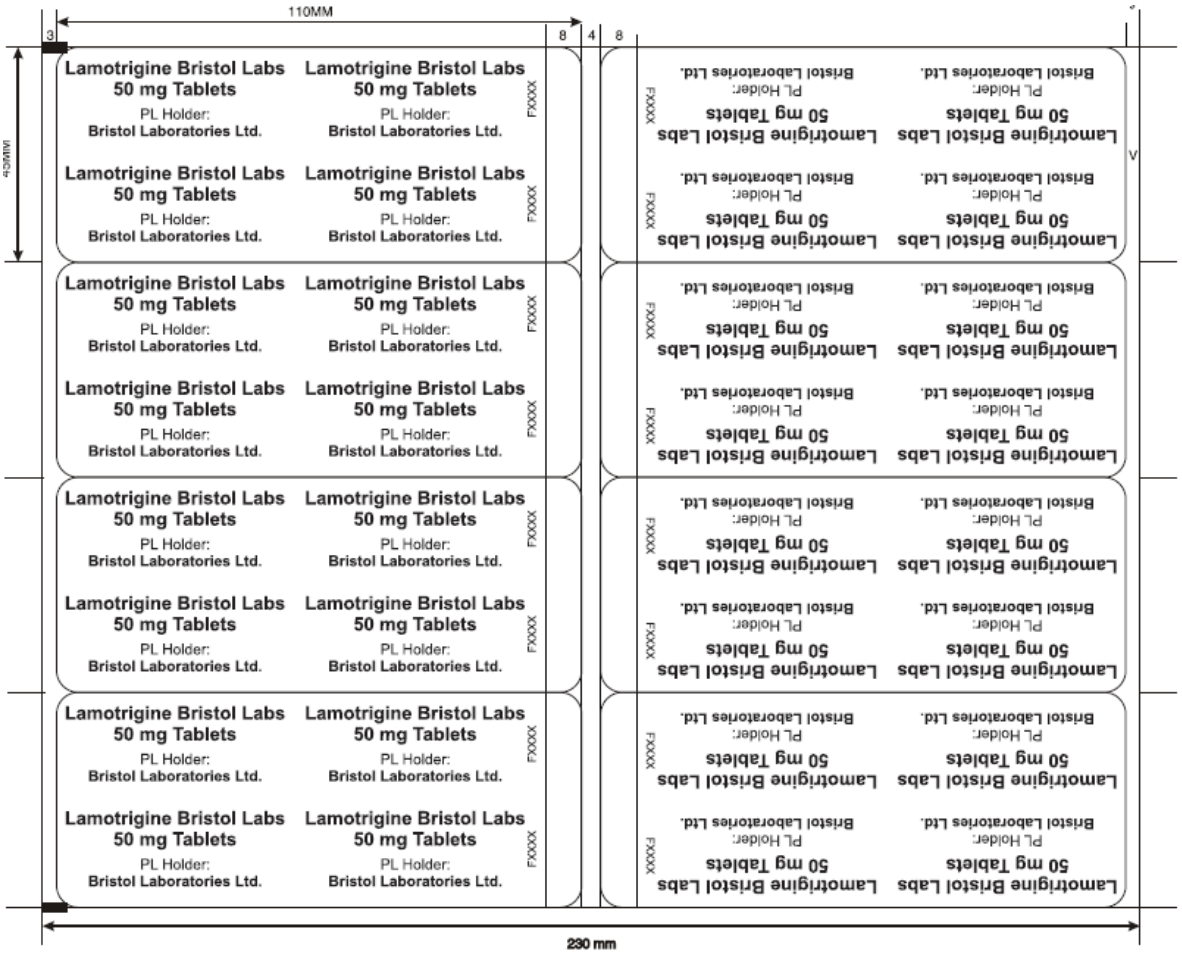

110MM
3
8
4
8
45MM
Lamotrigine Bristol Labs
25 mg Tablets
PL Holder:
Bristol Laboratories Ltd.
FXXXX
230 mm

PL 17907/0190:

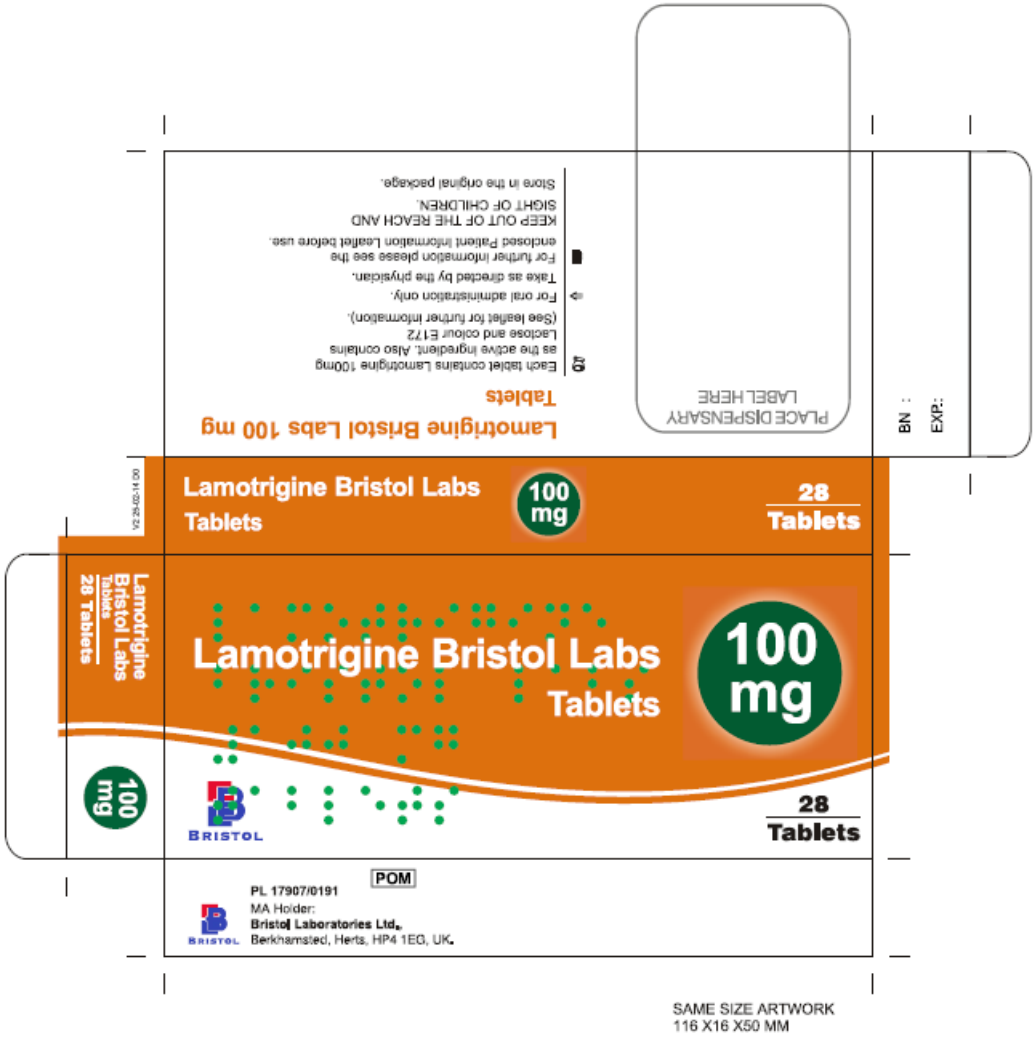



Lamotrigine Bristol Labs 50 mg
Tablets
Each tablet contains Lamotrigine 50mg as the active ingredient. Also contains Lactose and colour E172
(See leaflet for further information).
For oral administration only.
Take as directed by the physician.
For further information please see the enclosed Patient Information Leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Store in the original package.
PLACE DISPENSARY LABEL HERE
BN :
EXP:
Lamotrigine Bristol Labs
Tablets
50 mg
56 Tablets
Lamotrigine Bristol Labs
Tablets
50 mg
56 Tablets
Lamotrigine Bristol Labs
Tablets
50 mg
BRISTOL
56 Tablets
PL 17907/0190
POM
MA Holder:
Bristol Laboratories Ltd.
Berkhamsted, Herts, HP4 1EG, UK


Lamotrigine
Bristol Labs
50 mg
Tablets

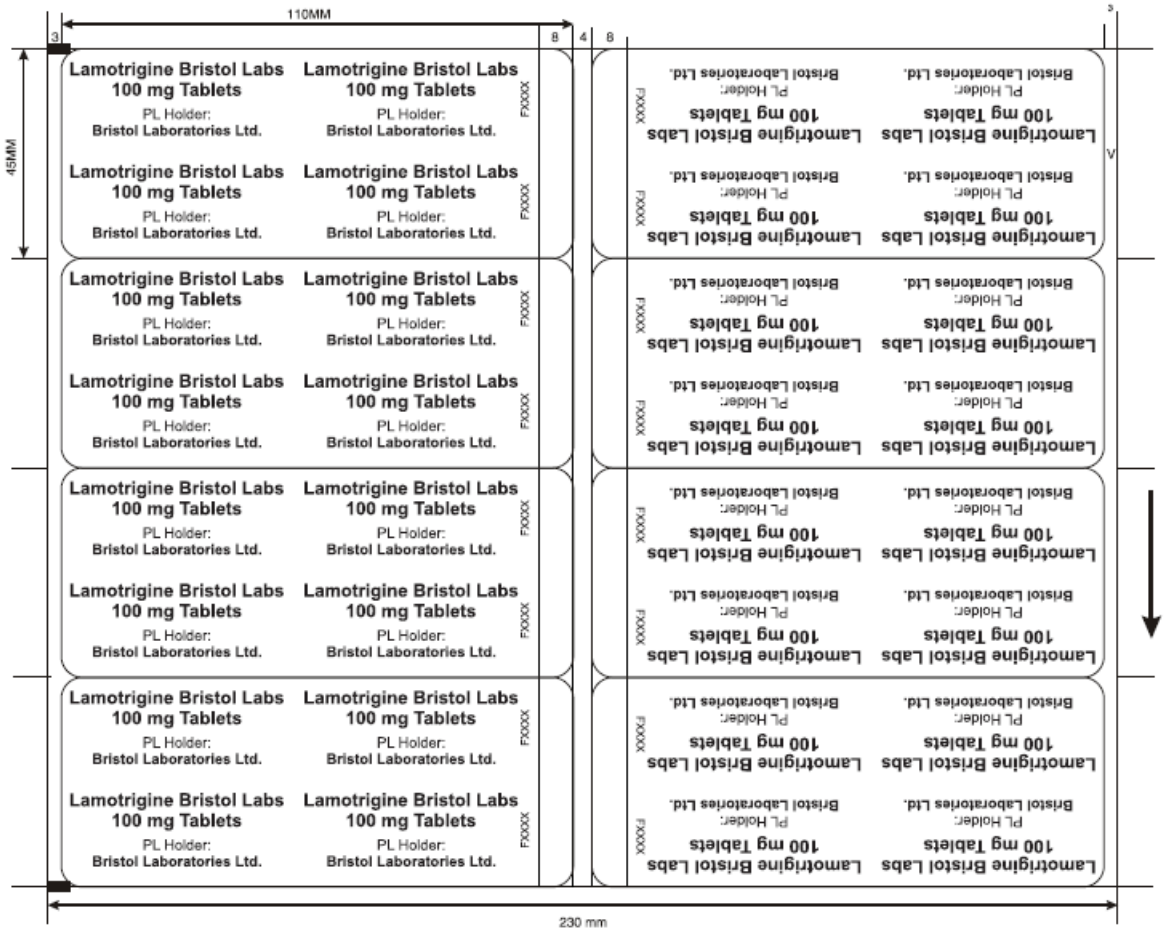

110MM
3
8
4
8
45MM
Lamotrigine Bristol Labs
50 mg Tablets
PL Holder:
Bristol Laboratories Ltd.
FXXXX
230 mm

PL 17907/0191:

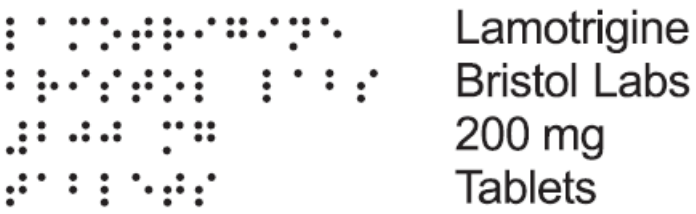



Lamotrigine Bristol Labs 100 mg Tablets
Each tablet contains Lamotrigine 100mg as the active ingredient. Also contains Lactose and colour E172
(See leaflet for further information).
For oral administration only.
Take as directed by the physician.
For further information please see the enclosed Patient Information Leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Store in the original package.
PLACE DISPENSARY LABEL HERE
BN :
EXP:
Lamotrigine Bristol Labs
Tablets
100 mg
56 Tablets
V1 27-02-14 D0
Lamotrigine Bristol Labs
Tablets
100 mg
56 Tablets
BRISTOL
PL 17907/0191
POM
MA Holder:
Bristol Laboratories Ltd.
Berkhamsted, Herts, HP4 1EG, UK

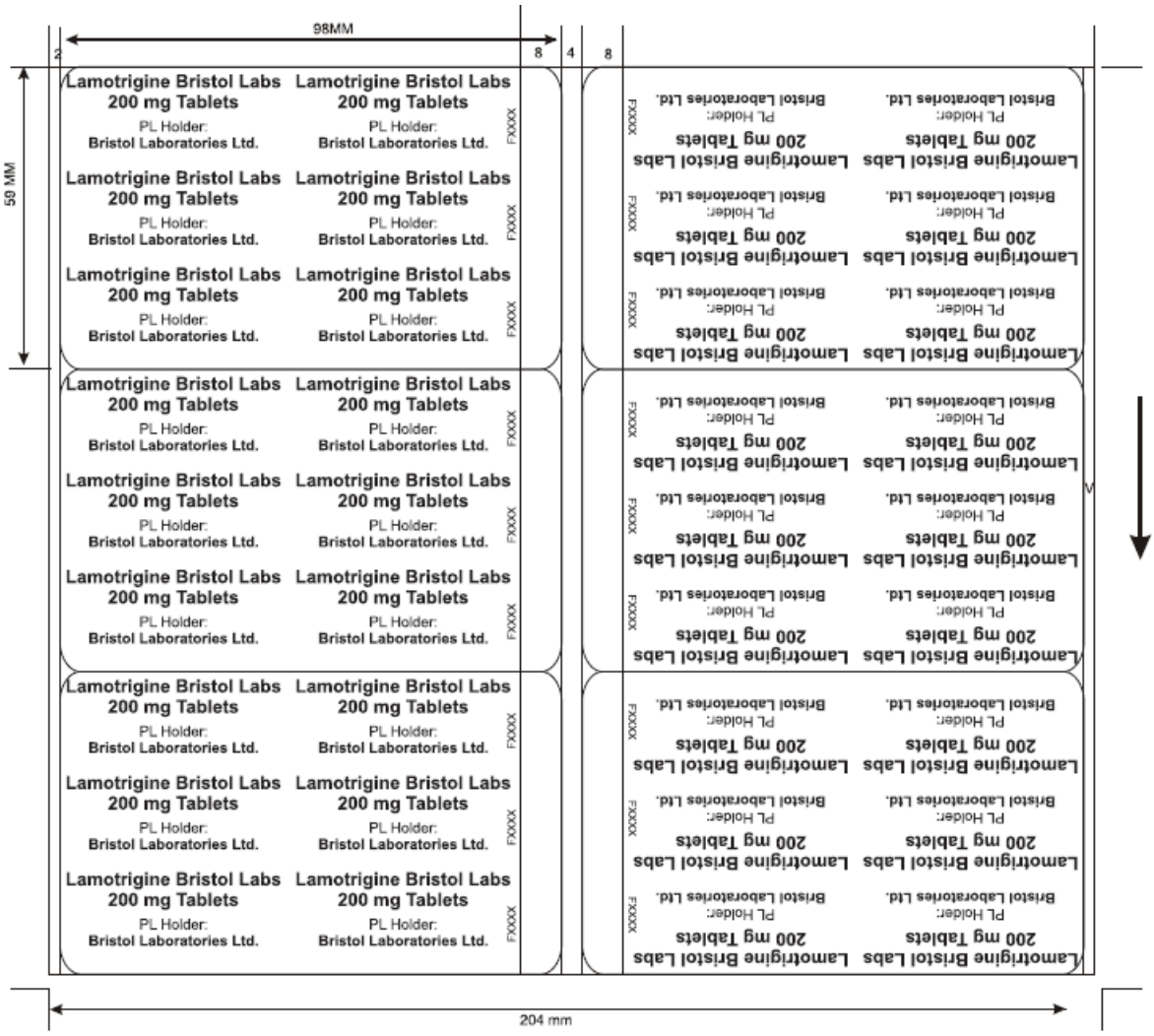

Lamotrigine
Bristol Labs
100 mg
Tablets


110MM
45MM
3
8
4
8
Lamotrigine Bristol Labs
100 mg Tablets
PL Holder:
Bristol Laboratories Ltd.
FXXXX
230 mm

PL 17907/0192:



Lamotrigine
Bristol Labs
200 mg
Tablets


98MM
2
8
4
8
59 MM
Lamotrigine Bristol Labs
200 mg Tablets
PL Holder:
Bristol Laboratories Ltd.
FXXXX
204 mm

Steps Taken After Initial Procedure - Summary

The following table lists non-urgent safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

Date submitted	**Application type**	**Scope**	**Outcome**
03/06/2016	Type 1B	**PL 17907/0118-0054;** **PL 17907/0119-0053;** **PL 17907/0120-0053;** **PL 17907/0121-0052;** **PL 17907/0189-0046 & 47;** **PL 17907/0190-0047;** **PL 17907/0191-0052;** **PL 17907/0192-0050:** To update sections 2,4.2,4.3,4.4,4.5,4.6,4.8,4.9,5.1,5.2, 5.3 of the SmPC in line with the innovator product Lamictal (GlaxoSmithKline). Consequently the leaflet has been updated.	Approved 09/09/2016-see Annex 1.

ANNEX 1

Our Reference:	PL 17907/0118-0054 PL 17907/0119-0053 PL 17907/0120-0053 PL 17907/0121-0052 PL 17907/0189-0046 PL 17907/0189-0047 PL 17907/0190-0047 PL 17907/0191-0052 PL 17907/0192-0050
Product:	Lamotrigine Bristol Labs 25, 50, 100 and 200mg Tablets
Marketing Authorisation Holder:	Bristol Laboratories Limited
Active Ingredient(s):	Lamotrigine
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type IB
Submission Complexity:	Standard
EU Procedure Number (if applicable):	Not applicable

Reason:
To update sections 2,4.2,4.3,4.4,4.5,4.6,4.8,4.9,5.1,5.2, 5.3 of the SmPC in line with the innovator product Lamictal (GlaxoSmithKline). Consequently the leaflet has been updated.

Supporting Evidence
Revised SmPC fragments and PIL.

Evaluation
The proposed changes to the SmPCs and PIL are in line with the reference product. The updated SmPC fragments and PIL have been incorporated into the Marketing Authorisations.

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.

Conclusion
The proposed changes to the SmPCs and PIL are acceptable.

Decision - Approved on 09 September 2016.