ENALAPRIL MALEATE 10MG TABLETS
ENALAPRIL MALEATE 20MG TABLETS

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ENALAPRIL MALEATE 10MG TABLETS
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LAY SUMMARY

The MHRA granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Enalapril Maleate 10mg and 20mg Tablets (PL 17907/0267-8) on 1st February 2013. These prescription-only medicines (POM) used to:

- treat high blood pressure (hypertension).
- treat heart failure (weakening of heart function). It can lower the need to go to hospital and can help some patients live longer.
- prevent the signs of heart failure. The signs include: shortness of breath, tiredness after light physical activity such as walking, or swelling of the ankles and feet.

The active ingredient enalapril maleate belongs to a group of medicines known as ACE inhibitors (drugs that lower blood pressure). These medicines work by widening the blood vessels to make it easier for the heart to pump blood through them to all parts of the body. This lowers your blood pressure.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Enalapril Maleate 10 and 20mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal product Enalapril Maleate 10 and 20mg Tablets (PL 17907/0267-8) on 1st February 2013. These prescription-only medicines (POM) are indicated for the following:

- Treatment of Hypertension
- Treatment of Symptomatic Heart Failure
- Prevention of Symptomatic Heart Failure in patients with Asymptomatic Left Ventricular Dysfunction (ejection fraction ≤ 35%).

These are applications for two strengths of enalapril maleate tablets, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of the original products Innovace Tablets 10mg and 20mg (Merck, Sharp and Dohme), which were initially granted licences in the UK in December 1984.

The products contain the active substance enalapril maleate. Enalapril maleate is the maleate salt of enalapril, a derivative of two amino-acids, L-alanine and L-proline. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase that catalyses the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.

No new non-clinical studies were conducted, which is acceptable given that the applications are generic applications based on originator products that have been licensed for over 10 years.

With the exception of one bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are generic applications based on originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products.

PHARMACEUTICAL ASSESSMENT

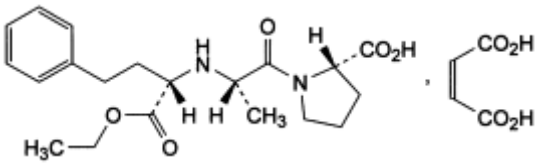
DRUG SUBSTANCE

Enalapril Maleate

INN: Enalapril Maleate

Chemical name: (2S)-1-[(2S)-2-[[(1S)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid (Z)-butenedioate.

Structure:



Molecular formula: $C_{20}H_{28}N_2O_5,C_4H_4O_4$

Molecular weight: 492.5

Physical form: A white or almost white crystalline powder. Sparingly soluble in water, freely soluble in methanol, practically insoluble in methylene chloride

Enalapril maleate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of enalapril maleate are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of enalapril maleate for inclusion in these medicinal products.

Satisfactory specifications have been provided for all materials used in the container-closure of the active substance. Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging. Suitable post approval commitments have been provided to perform follow-up stability studies.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, maleic acid, hypromellose (E464), sodium stearyl fumarate and croscarmellose sodium. All excipients used comply with their respective European Pharmacopoiea monograph. Satisfactory certificates of analysis have been provided for all excipients. With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed it is derived from healthy animals under the same conditions as milk for human consumption.

Pharmaceutical development
The objective of the pharmaceutical development programme was to produce safe, tolerable tablets that could be considered generic medicinal products to the originator products Innovace Tablets 10mg and 20mg (Merck, Sharp and Dohme). The applicant has provided a suitable product development rationale and data.

Satisfactory impurity and dissolution data have been provided, showing that the proposed products are comparable to the originator products Innovace Tablets 10mg and 20mg (Merck, Sharp and Dohme).

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The finished product is packaged in aluminium/polyvinylchloride/polyvinylidene chloride blisters in pack sizes of:

Enalapril Maleate 10mg Tablets - 28, 30, 49, 50, 98 or 100 tablets.
Enalapril Maleate 20mg Tablets – 10, 14, 20, 28, 30, 49, 50, 56, 60, 84, 90, 98, 100 or 500 tablets.

Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

Not all pack sizes are to be marketed. However, the marketing authorisation holder has committed to submitting mock-ups to the regulatory authorities for approval before marketing any pack size.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. The storage conditions ‘Do not store above 25°C. Store in the original container. Keep the container tightly closed’ have been included.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for generic medicinal products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution and impurity profiles have been provided for the proposed and reference products and bioequivalence has been demonstrated to a suitable reference product.

NON-CLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Innovace Tablets 10mg and 20mg (Merck, Sharp and Dohme), which have been licensed within the EEA for over 10 years.

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The applicant has submitted the following bioequivalence study:

A randomized, open-label, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study comparing the pharmacokinetics of Enalapril Maleate 20mg Tablets (Bristol Laboratories Limited, UK) versus Innovace 20mg Tablets (Merck Sharp & Dohme Limited, UK) in healthy human adult subjects, under fasted conditions.

All subjects received one dose of either treatment after at least a 10 hour fast. Blood samples were taken pre- and up to 168 hours post dose. The two treatment periods were separated by a 14-day washout period.

The main pharmacokinetic results are presented below:

Enalapril

Parameters (Units)	Ln-transformed Geometric Least Squares Mean			90% Confidence Interval (ln-transformed)
	Reference Product (R)	Test Product (T)	(T/R)%	
C_{max} (ng/mL)	179.884	187.040	103.98%	95.66% - 113.02%
AUC_{0-t} (ng.h/mL)	264.643	275.191	103.99%	99.19% - 109.02%
$AUC_{0-\infty}$ (ng.h/mL)	273.835	285.855	104.39%	99.73% - 109.27%

Enalaprilat:

Parameters (Units)	Ln-transformed Geometric Least Squares Mean			90% Confidence Interval (ln-transformed)
	Reference Product (R)	Test Product (T)	(T/R)%	
C_{max} (ng/mL)	87.449	90.808	103.84%	97.06% - 111.10%
AUC_{0-t} (ng.h/mL)	819.103	848.562	103.60%	98.00% - 109.51%
$AUC_{0-\infty}$ (ng.h/mL)	852.428	884.104	103.72%	98.56% - 109.14%

The confidence intervals for both enalapril and enalaprilat were within the acceptance criteria of 80-125%. Based on these results, the 20mg strength of the proposed product can be considered as a generic medicinal product of the originator product Innovace 20mg Tablets (Merck, Sharp and Dohme).

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 20mg strength can be extrapolated to the 10mg strength tablets.

EFFICACY
No new data have been provided and none are required.

SAFETY
With the exception of the data collected during the bioequivalence study, no new data have been provided and none are required. No new or unexpected safety issues arose from the bioequivalence study.

EXPERT REPORTS
A clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory

APPLICATION FORMS (MAA)
These are satisfactory.

SUMMARIES OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.

DISCUSSION
Bioequivalence has been satisfactorily demonstrated for the 20mg product, in accordance with CPMP criteria. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 20mg strength can be extrapolated to the 10mg strength tablets.

MEDICAL CONCLUSION
Marketing authorisations are recommended for these applications.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Enalapril Maleate 10mg and 20mg 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

Bioequivalence has been demonstrated between the applicant's Enalapril Maleate 20mg Tablets and Innovace 20mg Tablets (Merck, Sharp and Dohme). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 20mg strength can be extrapolated to the 10mg strength tablets.

No new or unexpected safety concerns arose from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Innovace tablets.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with enalapril maleate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 23 November 2010
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 25 January 2011
3	Following assessment of the applications the MHRA requested further information on 4 May 2011, 5 May 2011, 13 January 2012 and 09 July 2012.
4	The applicant responded to the MHRA's requests, providing further information on 3 November 2011 and 12 April 2012 and 25 July 2012.
5	The applications were determined on 1 February 2013.

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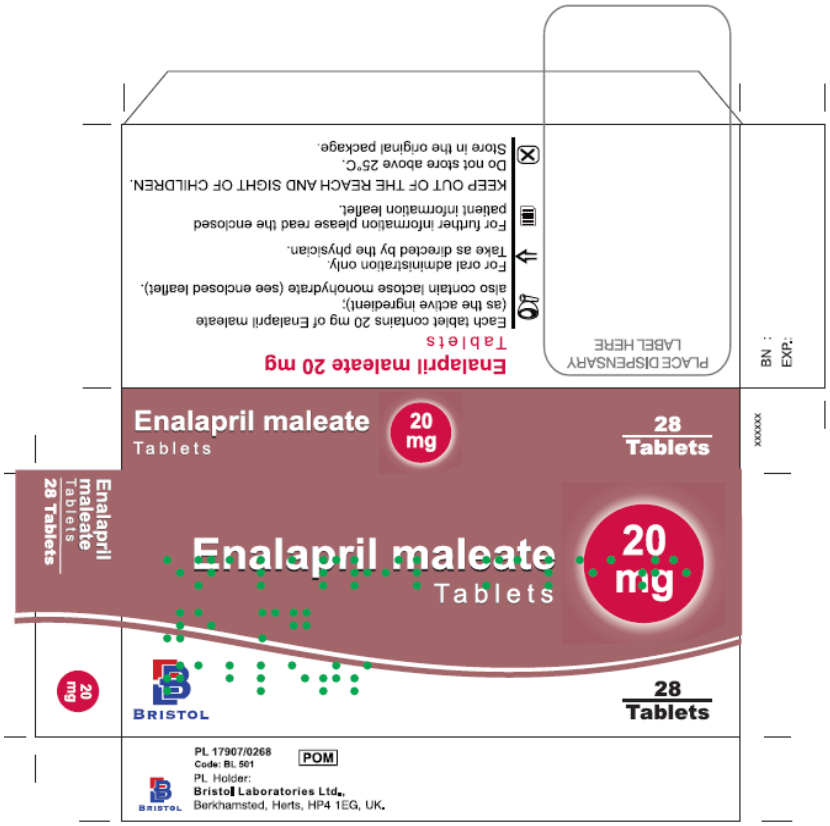
STEPS TAKEN AFTER AUTHORISATION - SUMMARY

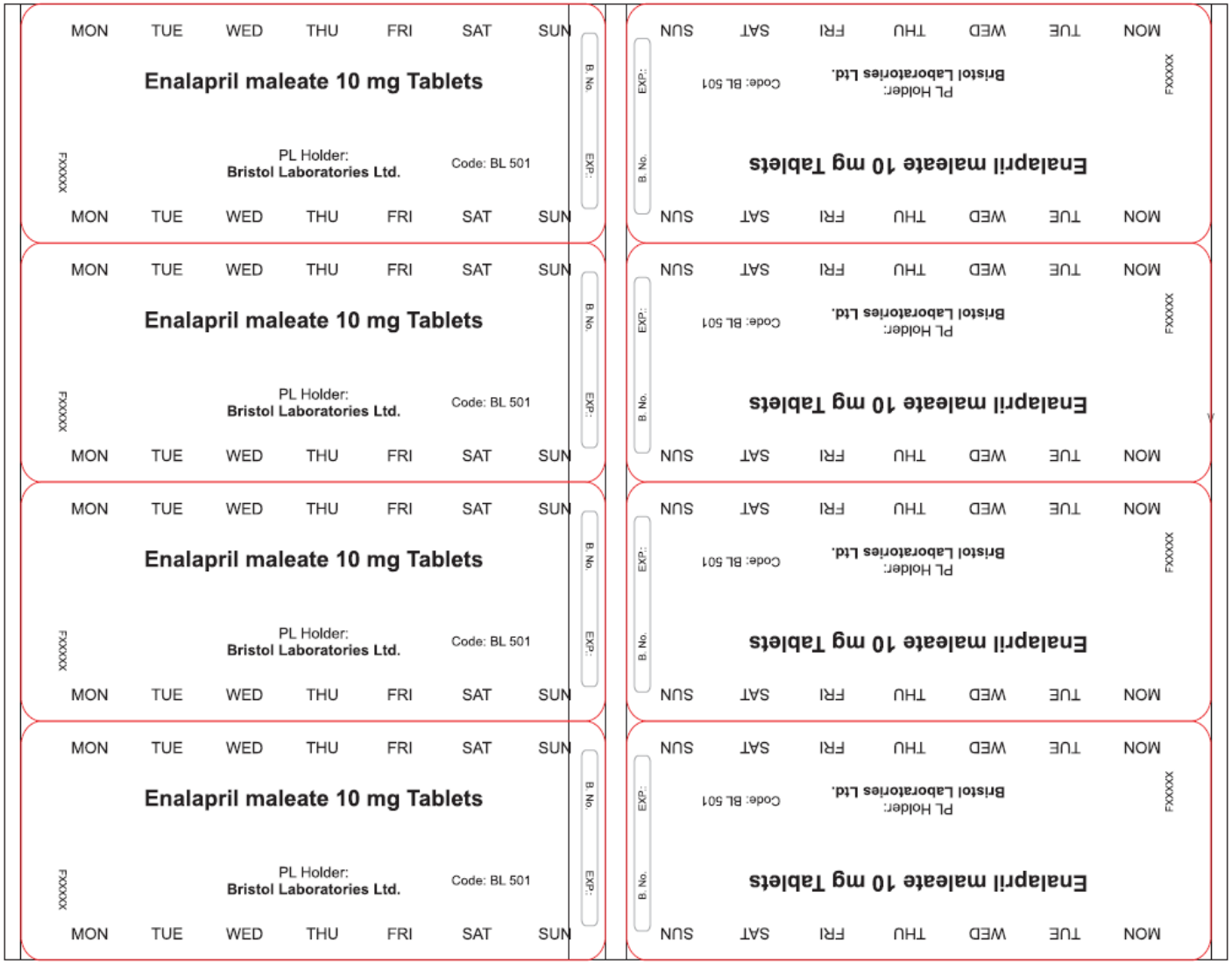
Date submitted	Application type	Scope	Outcome

Summary of Product Characteristics and Patient Information Leaflet

The current approved versions of the SmPC and PIL are available on the MHRA website.

Labelling




MON TUE WED THU FRI SAT SUN
Enalapril maleate 10 mg Tablets
PL Holder:
Bristol Laboratories Ltd.
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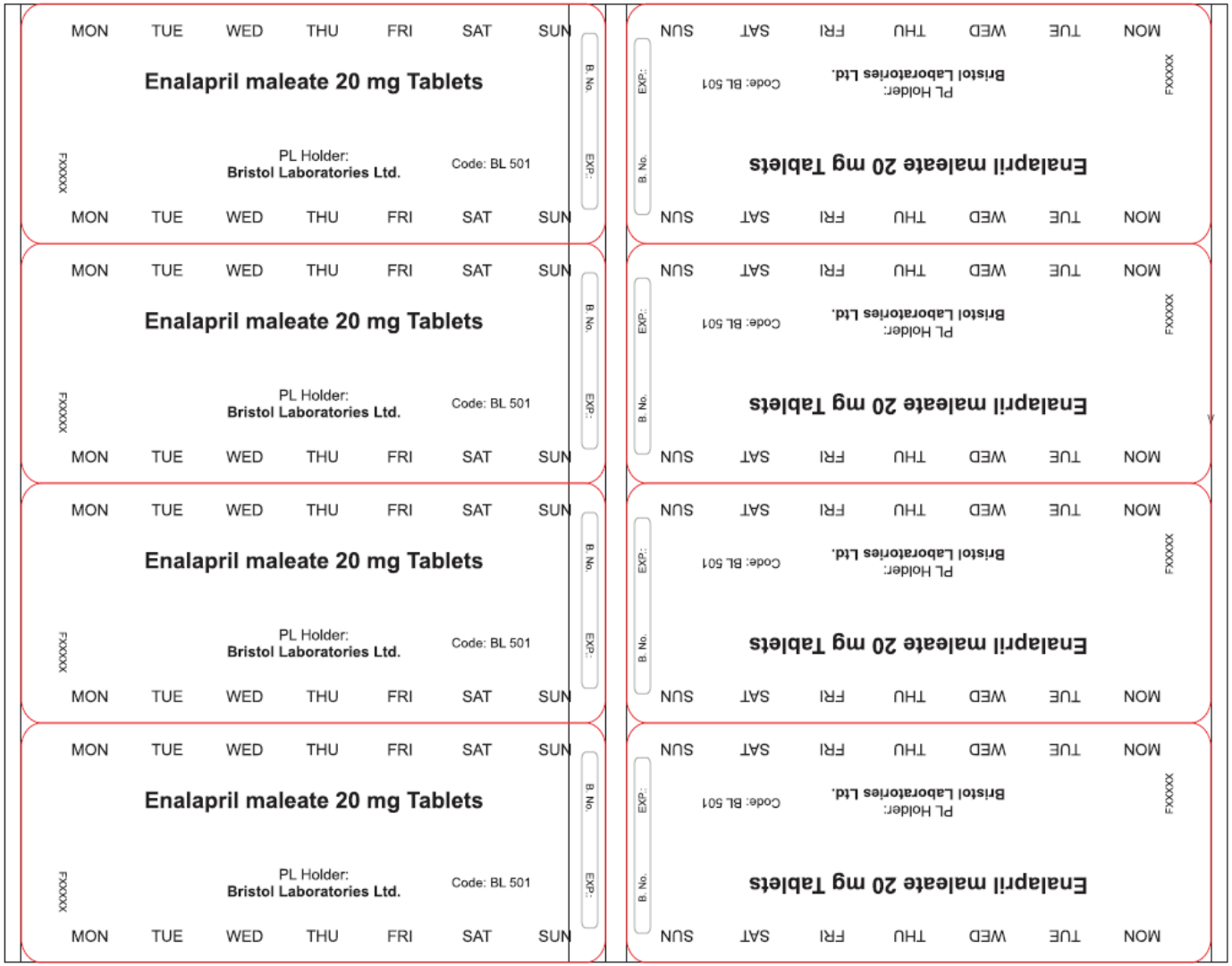
B. No.
EXP.:


MON TUE WED THU FRI SAT SUN
Enalapril maleate 20 mg Tablets
PL Holder:
Bristol Laboratories Ltd.
Code: BL 501
FXXXXX
B. No.
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