

**Eprosartan 300 mg, 400 mg and 600 mg Film-coated
Tablets**

(Eprosartan mesilate)

PL 37222/0027-29

UKPAR

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LAY SUMMARY

Eprosartan 300mg, 400mg and 600mg film-coated tablets. (eprosartan mesilate)

This is a summary of the Public Assessment Report (PAR) for Eprosartan 300mg film-coated tablets (PL 37222/0027, previously PL 31746/0006), Eprosartan 400mg film-coated tablets (PL 37222/0028, previously PL 31746/0007) and Eprosartan 600mg film-coated tablets (PL 37222/0029, previously PL 31746/0008). It explains how Eprosartan 300mg, 400mg and 600mg film-coated tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Eprosartan 300mg, 400mg and 600mg film-coated tablets.

For practical information about using Eprosartan 300mg, 400mg and 600mg film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Eprosartan 300mg, 400mg and 600mg film-coated tablets and what are they used for?

Eprosartan 300mg, 400mg and 600mg film-coated tablets are 'generic' medicines. This means that Eprosartan 300mg, 400mg and 600mg film-coated tablets are similar to a reference medicine already authorised in the European Union (EU) called Teveten 300 mg, 400 mg and 600 mg film-coated tablets (SmithKline and Beecham PLC trading as SmithKline Beecham Pharmaceuticals).

Eprosartan 300mg, 400mg and 600mg film-coated tablets contain the active ingredient, eprosartan mesilate which belongs to a group of medicines called 'angiotensin II receptor antagonists.'

This medicine is used to treat high blood pressure, also called hypertension.

The main cause of high blood pressure is narrowing of the blood vessels. This increases the amount of work the heart must do to pump blood around the body. The patient may not feel unwell, but if high blood pressure is not treated, it can lead to heart disease and stroke.

How do Eprosartan 300mg, 400mg and 600mg film-coated tablets work?

- Angiotensin II is a chemical found in the body which makes the blood vessels contract. This makes it more difficult for blood to pass through them.
- This causes the blood pressure to rise.
- This medicine works by preventing the chemical, angiotensin II, from causing the blood vessels to contract. This has the effect of lowering the blood pressure.

The patient may be given eprosartan mesilate on its own or with another medicine used to treat high blood pressure. Using both medicines together will lower the blood pressure more than one on its own.

How are Eprosartan 300mg, 400mg and 600mg film-coated tablets used?

Eprosartan 300mg, 400mg and 600mg film-coated tablets can be obtained only with a prescription. This medicine should be taken exactly as advised by the prescribing doctor. The recommended starting dose for adults is 600mg once a day which may be increased to 800mg once a day (two 400mg tablets) by the patient's doctor.

Eprosartan 300mg, 400mg and 600mg film-coated tablets are taken by mouth at exactly the same time each day. The tablets may be taken with or without food. The patient's doctor will tell the patient how many tablets to take and for how long. It is important that the patient takes the tablets for as long as their doctor has told them to. The patient should only remove a tablet from the blister strip when it is time to take their medicine.

For further information on how Eprosartan 300mg, 400mg and 600mg film-coated tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Eprosartan 300mg, 400mg and 600mg film-coated tablets have been shown in studies?

As Eprosartan 300mg, 400mg and 600mg film-coated tablets are generic medicines; studies in patients have been limited to tests to determine that the tablets are similar to the reference medicine, Teveten 300 mg, 400 mg and 600 mg film-coated tablets (SmithKline and Beecham PLC). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Eprosartan 300mg, 400mg and 600mg film-coated tablets?

Because Eprosartan 300mg, 400mg and 600mg film-coated tablets are generic medicines and are bioequivalent to the reference medicine, the benefits and possible effects are taken as being the same as those for the reference medicine.

For the full list of restrictions, see the package leaflet available on the MHRA website.

Why are Eprosartan 300mg, 400mg and 600mg film-coated tablets approved?

It was concluded that, in accordance with EU requirements, Eprosartan 300mg, 400mg and 600mg film-coated tablets have been shown to have comparable quality and to be bioequivalent to Teveten 300 mg, 400 mg and 600 mg film-coated tablets (SmithKline and Beecham PLC). Therefore, the MHRA decided that, as for Teveten 300 mg, 400 mg and 600 mg film-coated tablets (SmithKline and Beecham PLC) 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 Eprosartan 300mg, 400mg and 600mg film-coated tablets?

Safety information has been included in the Summary of Product Characteristics and the package leaflet for Eprosartan 300mg, 400mg and 600mg film-coated 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 as well.

Other information about Eprosartan 300mg, 400mg and 600mg film-coated tablets

Marketing Authorisations (PL 31746/0006-08) were first granted in the UK to Norpharm Regulatory Services on 24 October 2013.

Subsequent to a Change of Ownership procedure, the Marketing Authorisations (PL 31746/0006-08) were granted to Hetero Europe S.L. on 21 January 2014.

The full PAR for Eprosartan 300mg, 400mg and 600mg film-coated tablets follows this summary.

For more information about treatment with Eprosartan 300mg, 400mg and 600mg film-coated tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2014.

Eprosartan 300 mg, 400 mg and 600 mg Film-coated Tablets

PL 37222/0027-29

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Marketing Authorisations (licences) for the medicinal products Eprosartan 300 mg, 400 mg and 600 mg Film-coated Tablets (PL 31746/0006-08) to Norpharm Regulatory Services on 24th October 2013. These prescription only medicines (POM) are indicated for the treatment of essential hypertension.

These are national abridged applications for Eprosartan 300 mg, 400 mg and 600 mg Film-coated Tablets submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applicant cross-refers to Teveten 300 mg, 400 mg and 600 mg film-coated tablets, originally granted to SmithKline and Beecham PLC trading as SmithKline Beecham Pharmaceuticals (PL 10592/0102-04) on 14th July 1998. The reference products have then undergone a Change of Ownership (COA) procedure to the current Marketing Authorisation Holder, Abbott Healthcare Products Limited (PL 00512/0163 – 0165) on 23rd August 1999.

A pharmacovigilance system has been provided with these applications and is satisfactory. A suitable justification for non-submission of the Risk Management Plan has been provided.

Subsequent to a Change of Ownership procedure, the Marketing Authorisations (PL 31746/0006-08) were granted to Hetero Europe S.L. on 21 January 2014.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN: Eprosartan mesilate

Chemical Names: (aE)-Cl-((2-Butyl-1-((4-carboxy phenyl) methyl)-1 H-imidazol-5-yl) methylene)-2- thiophene-propanoic acid monomethane sulfonate

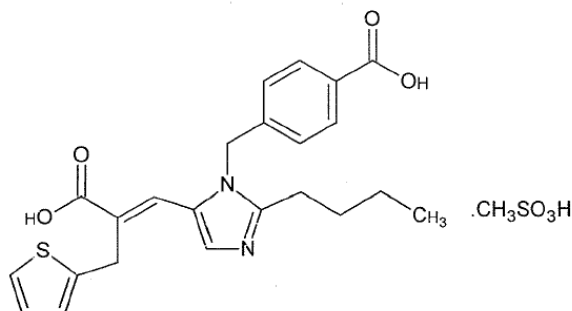
Or (E)-3-(2-butyl- 1-((4-carboxyphenyl) methyl) imidazol-5-yl)-2-(2-thienyl methyl)-2-propanoic acid mono methane sulfonate

Structure:

Molecular Formula : $C_{23}H_{24}N_2O_4S \cdot CH_3SO_3H$

Molecular Weight : 520.62

Structural formula :



Appearance: A white or almost white crystalline powder.

Solubility: Freely soluble in methanol, dimethylformamide, sparingly soluble in ethanol, insoluble in water.

Eprosartan mesilate is the subject of an Active Substance Master File (ASMF).

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof of structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients lactose, microcrystalline cellulose, magnesium stearate, croscarmellose sodium, hydroxypropylcellulose making up the tablet core, and the tablet coat of opadry white (300 mg and 600 mg) and opadry pink (400mg). Opadry white consists of hypromellose, titanium dioxide (E171), macrogol 400 and polysorbate 80. Opadry pink additionally contains Iron oxide red (E172) and Iron oxide yellow (E172).

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of opadry white, opadry pink, Iron oxide red (E172) and Iron oxide yellow (E172). Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose. The applicant has provided a declaration that the milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

Pharmaceutical development

The objective of the development programme was to formulate robust, stable tablets containing eprosartan mesilate that could be considered generic medicinal products of Teveten 300 mg, 400 mg and 600 mg Film-coated tablets (Abbott Healthcare Products Limited).

Comparable dissolution and impurity profiles are provided for these products versus the originator products.

Manufacture

A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Process validation data has been submitted for the minimum production batch size and the results are satisfactory. The applicant has committed to conduct the validation of any interim production batch sizes that may be manufactured until the full- scale commercial batches have been validated.

Finished product specifications

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

Container Closure System

The tablets are packed in:

- Polyvinylchloride/aclar blister and aluminium/aluminium blister pack containing 28 and 56 film-coated tablets.

Not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with no special storage conditions is set. This is satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling

The SmPCs, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

The Marketing Authorisation Holder has committed to submit mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Form

The MAA forms are pharmaceutically satisfactory.

Expert Report/Quality overall summary

The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

There are no objections to the approval of these products from a pharmaceutical point of view.

NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of eprosartan mesilate are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of environmental risk assessment.

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

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

BIOEQUIVALENCE

In support of these applications, the Marketing Authorisation holder has submitted a bioequivalence study:

A randomised, open label, balanced, single center, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study of Eprosartan Mesylate 600 mg tablets (Test) and TEVETEN 600 mg tablets (Reference) in healthy adult, male, human subjects under fed conditions.

The pre-dose sample was collected within 1 hour prior to drug administration. The post-dose blood samples were collected at 0.33, 0.66, 1.00, 1.33, 1.66, 2.00, 2.33, 2.66, 3.00, 3.33, 3.66, 4.00, 4.33, 4.66, 5.00, 5.33, 5.66, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00 and 36.00 hours after drug administration in each study period. The blood sampling up to 24.00 hours was done in-house. There was a washout period of 7 days between the dosings.

Ratio and 90% Confidence Intervals of Test versus Reference for Eprosartan (Linear Log Trapezoidal)

Parameter	Ratio of Means (%)	90% C.I.		Geometric mean	
		Lower Limit	Upper Limit	A	B
C_{max}	102.69%	91.96%	114.68%	2436.9533	2373.0590
AUC_{0-t}	102.10%	93.84%	111.09%	12175.797	11925.583
AUC_{0-inf}	101.91%	93.85%	110.65%	12410.600	12178.333

The results showed that the 90% confidence intervals for AUC and C_{max} fell within the acceptable range (80.00-125.00%). Bioequivalence has been shown for the test formulation (Eprosartan Mesylate 600 mg tablets) and the reference formulation (TEVETEN 600 mg tablets).

A justification with regard to the linearity of the drug substance pharmacokinetics over the dose range from 300 mg to 600 mg has been accepted. The 300 mg, 400 mg and 600 mg tablet strengths meet the biowaiver criteria as specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) hence the results and conclusions from the bioequivalence study with the 600 mg strength can be extrapolated to the 300 mg and 400 mg strengths.

EFFICACY

No new efficacy data have been submitted and none are required for these applications.

SAFETY

No new safety data have been submitted and none are required for these applications.

EXPERT REPORT

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS

These are satisfactory.

PATIENT INFORMATION LEAFLET

This is satisfactory.

LABELLING

These are satisfactory

MAA FORM

These are satisfactory.

CONCLUSIONS

There are no objections to the approval of these products from a clinical point of view.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Eprosartan 300 mg, 400 mg and 600 mg Film-coated Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of these type.

EFFICACY

With the exception of the bioequivalence study, no new data have been submitted and none are required for applications of these type.

Bioequivalence has been demonstrated between the applicant's Eprosartan Mesylate 600 mg Film-coated tablets and the reference product, TEVETEN 600 mg tablets. As the 300 mg, 400 mg and 600 mg Film-coated tablet strengths meet the biowaiver criteria as specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the results and conclusions from the bioequivalence study with the 600 mg strength can be extrapolated to the 300 mg and 400 mg strengths.

SAFETY

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with those for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labellings are in line with current guidelines.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with eprosartan mesilate is considered to have demonstrated the therapeutic value of the compound. The risk benefit assessment is, therefore, considered to be positive.

Eprosartan 300 mg, 400 m Eprosartan 300 mg, 400 mg and 600 mg Film-coated Tablets**PL 37222/0027-29****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the Marketing Authorisation applications on 29 th December 2011.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 19 th April 2012.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 30 th August 2012 and 4 th September 2013
4	The applicant responded to the MHRA's requests, providing further information to the quality section on 13 th November 2013 and 19 th September 2013
5	The applications were determined on 24 th October 2013.

Eprosartan 300 mg, 400 mg and 600 mg Film-coated Tablets

PL 37222/0027-29

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

The following table lists non-safety updates to the Marketing Authorisations (PL 37222/00027-0029) 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
23 October 2014	Type 1B	To update sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) for Eprosartan 300mg, 400mg and 600mg film-coated tablets in line with the outcome of the Article 31 Referral (EMEA/H/A-31/3170) and the QRD template. As a consequence, the Patient Information Leaflet (PIL) has also been updated.	Approved 27 November 2014

Module 2

Summary of Product Characteristics

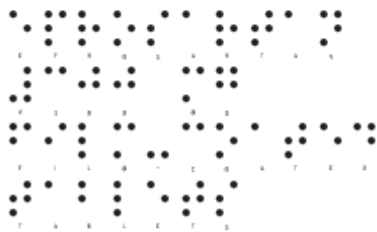
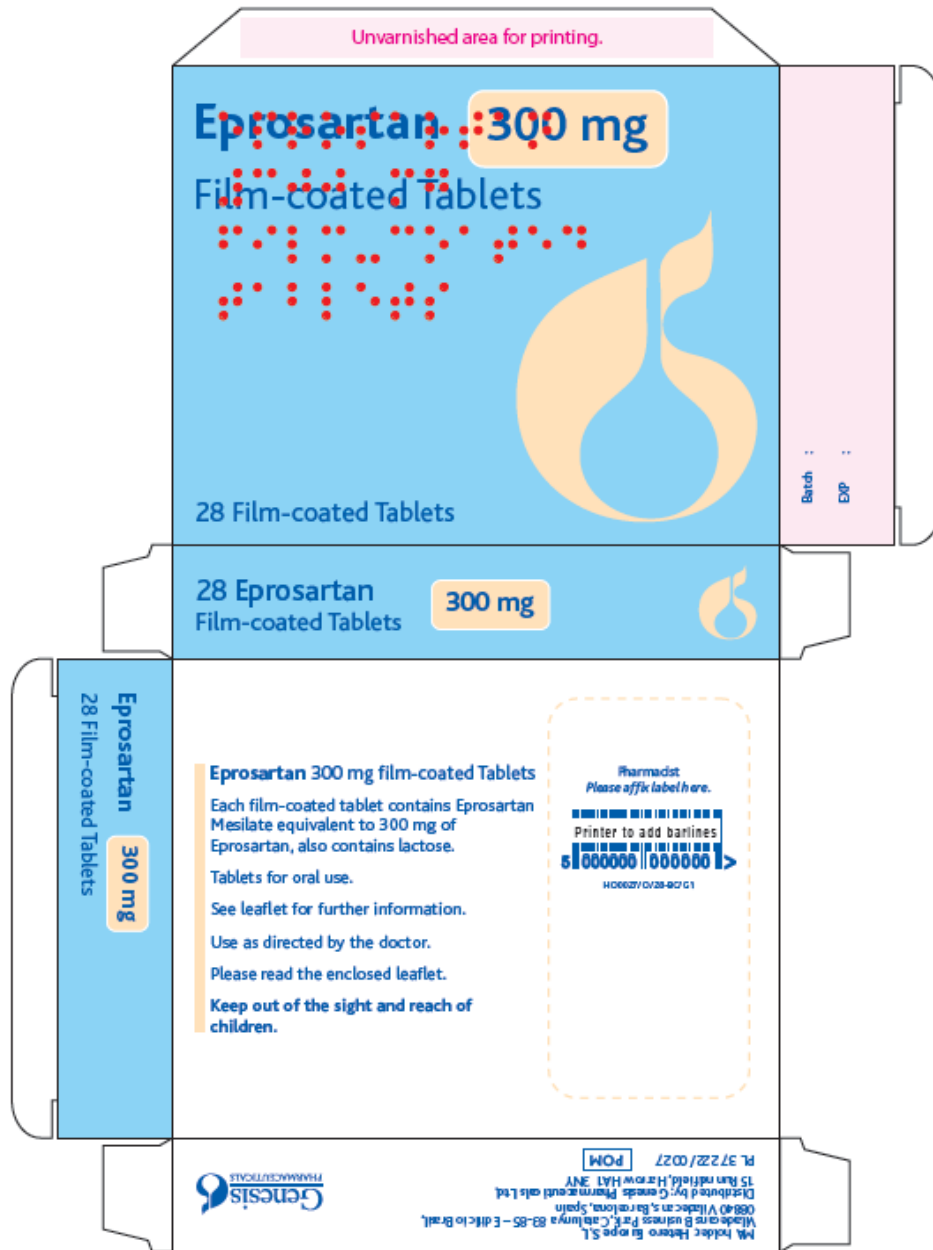
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

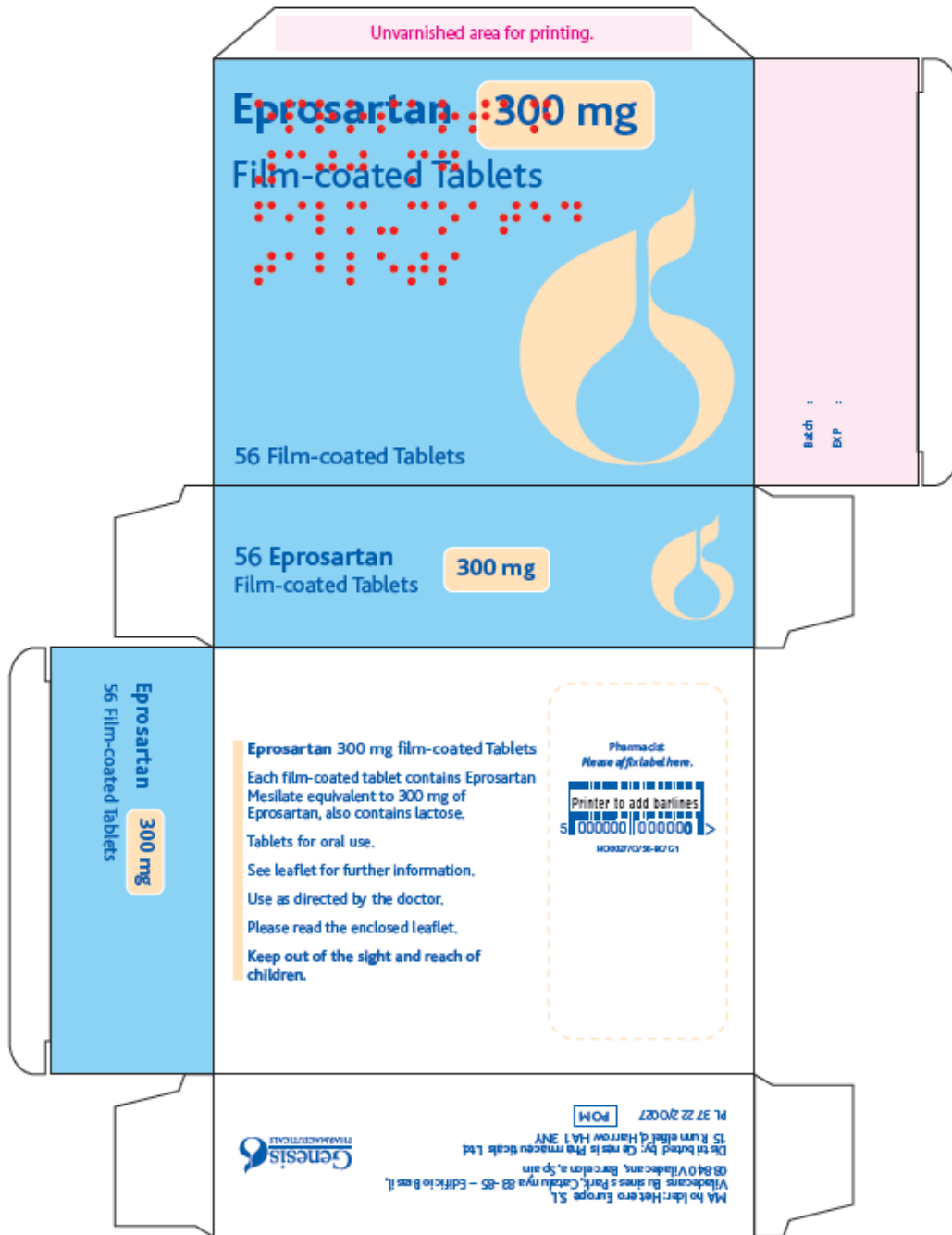
Module 3

Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING





Braille reads:
Eprosartan
#300 mg
film-coated
tablets



Eprosartan 300 mg film-coated tablets

Hetero Europe S.L.

Eprosartan 300 mg film-coated tablets

Hetero Europe S.L.

Eprosartan 300 mg film-coated tablets

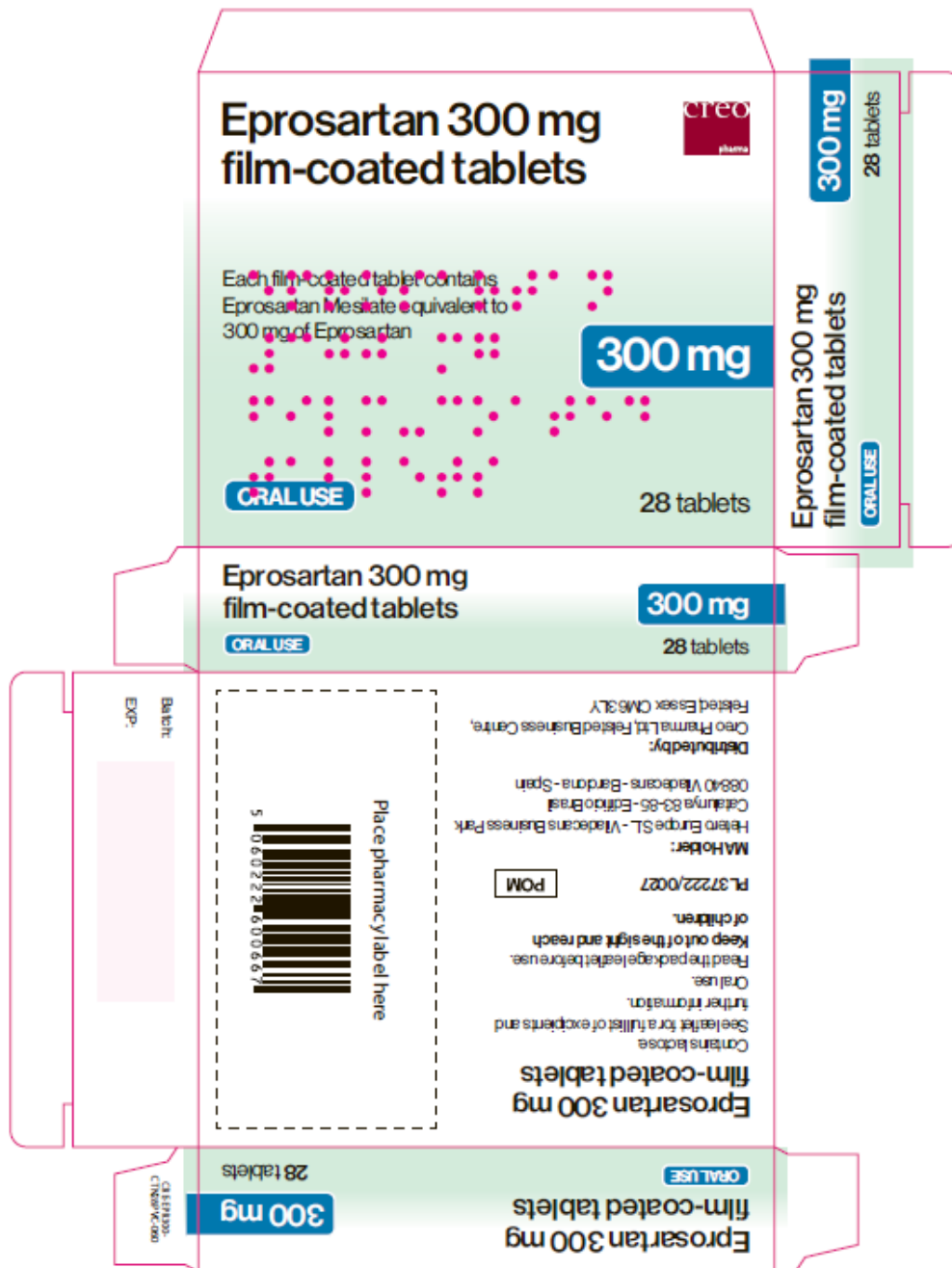
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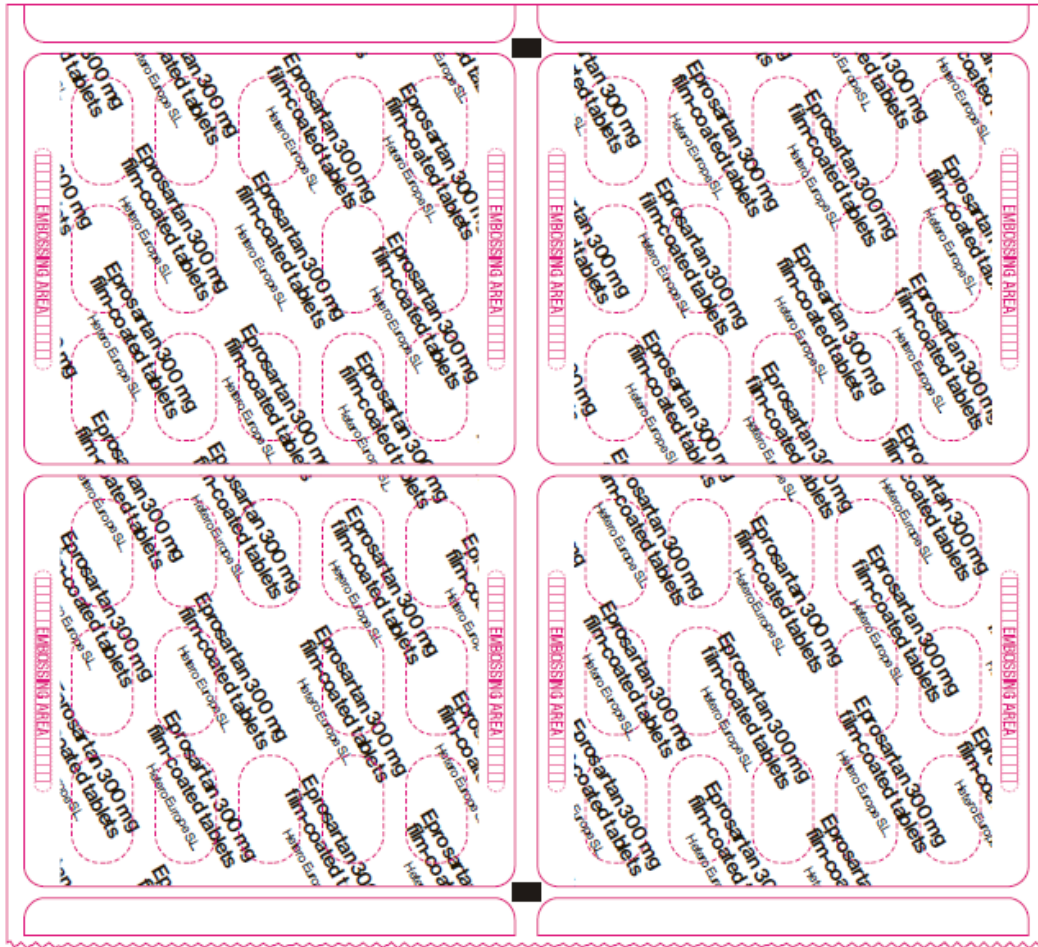
Eprosartan 300 mg film-coated tablets

Hetero Europe S.L.

Eprosartan 300 mg film-coated tablets

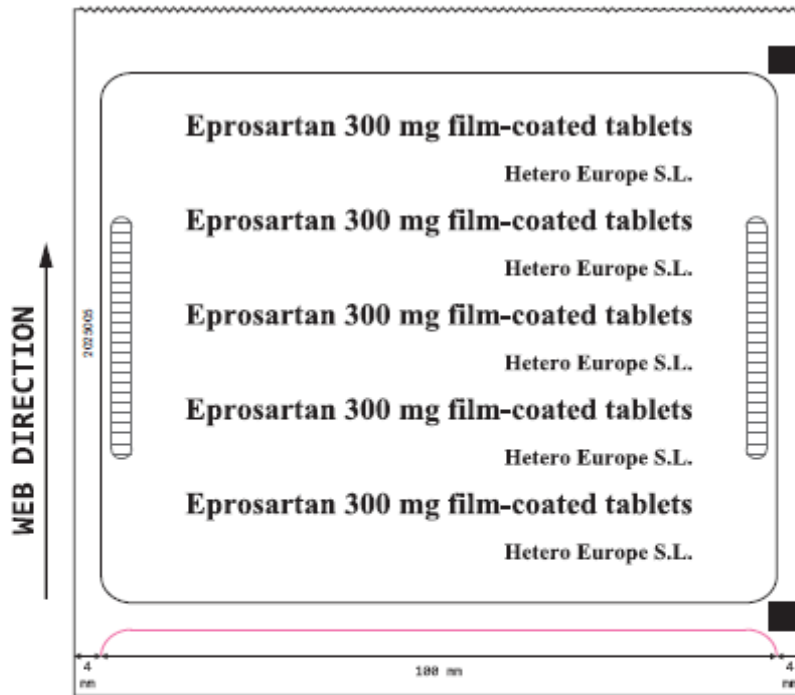
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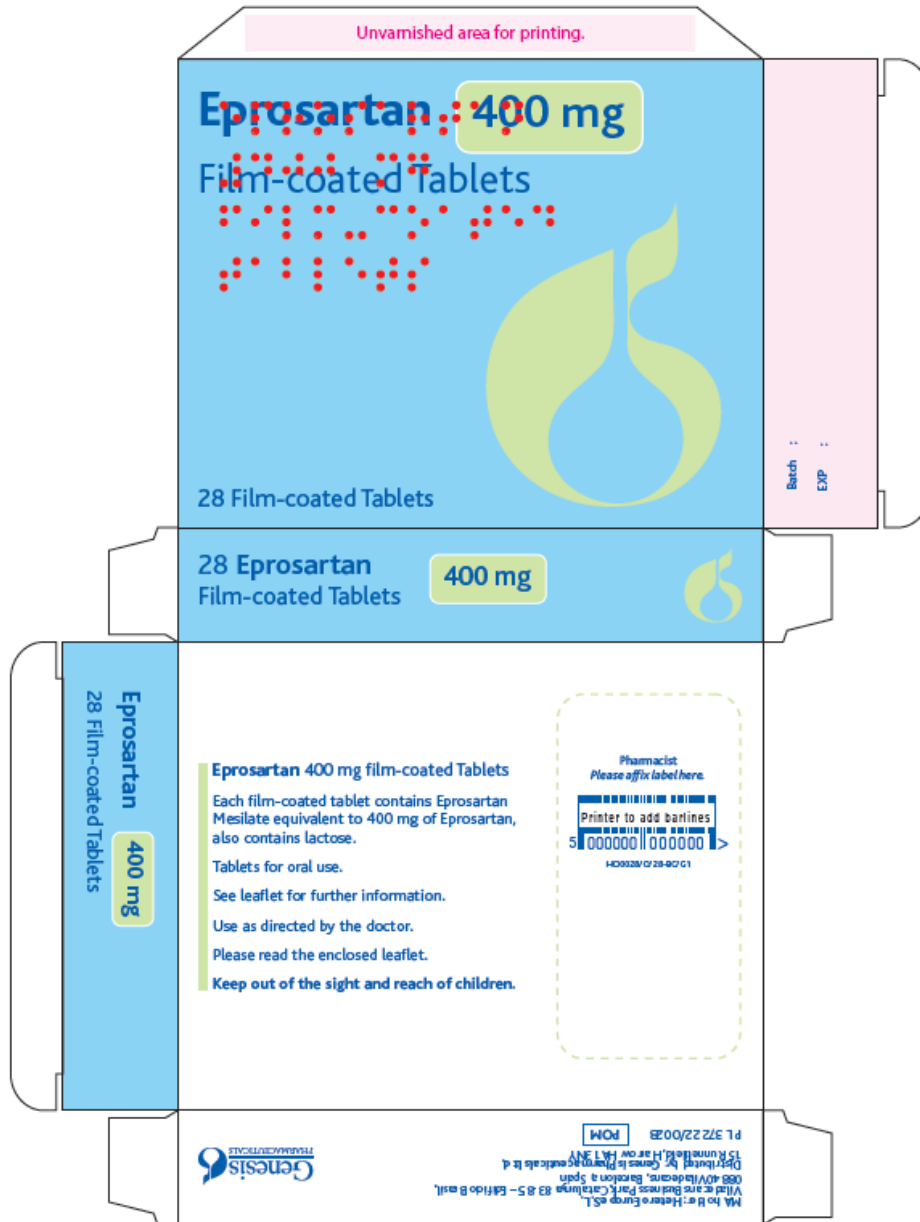




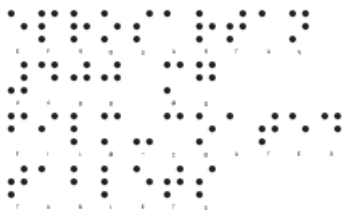


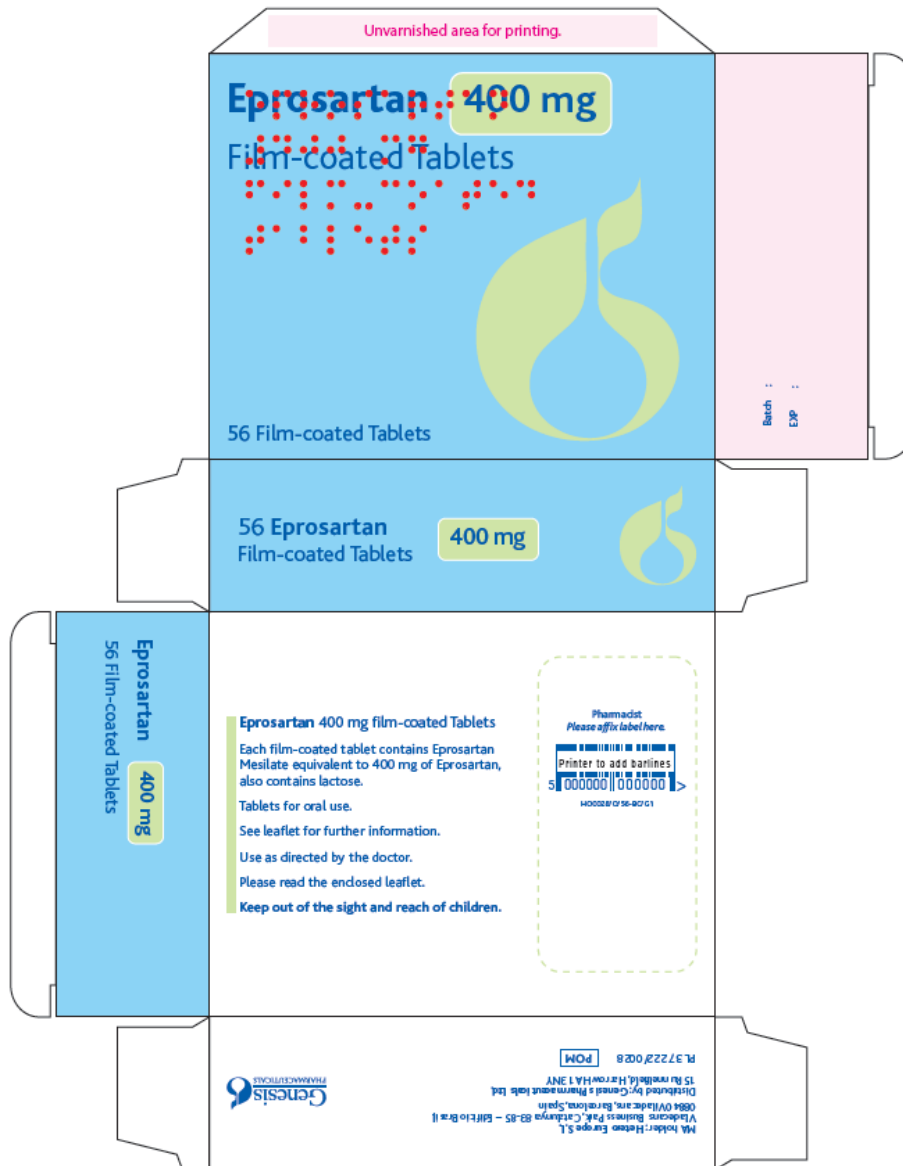


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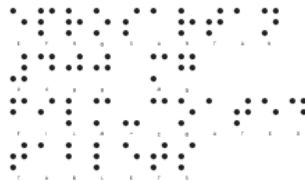


Braille reads:
 Eprosartan
 #400 mg
 film-coated
 tablets





Braille reads:
Eprosartan
#400 mg
film-coated
tablets



Eprosartan 400 mg film-coated tablets

Hetero Europe S.L.

Eprosartan 400 mg film-coated tablets

Hetero Europe S.L.

Eprosartan 400 mg film-coated tablets

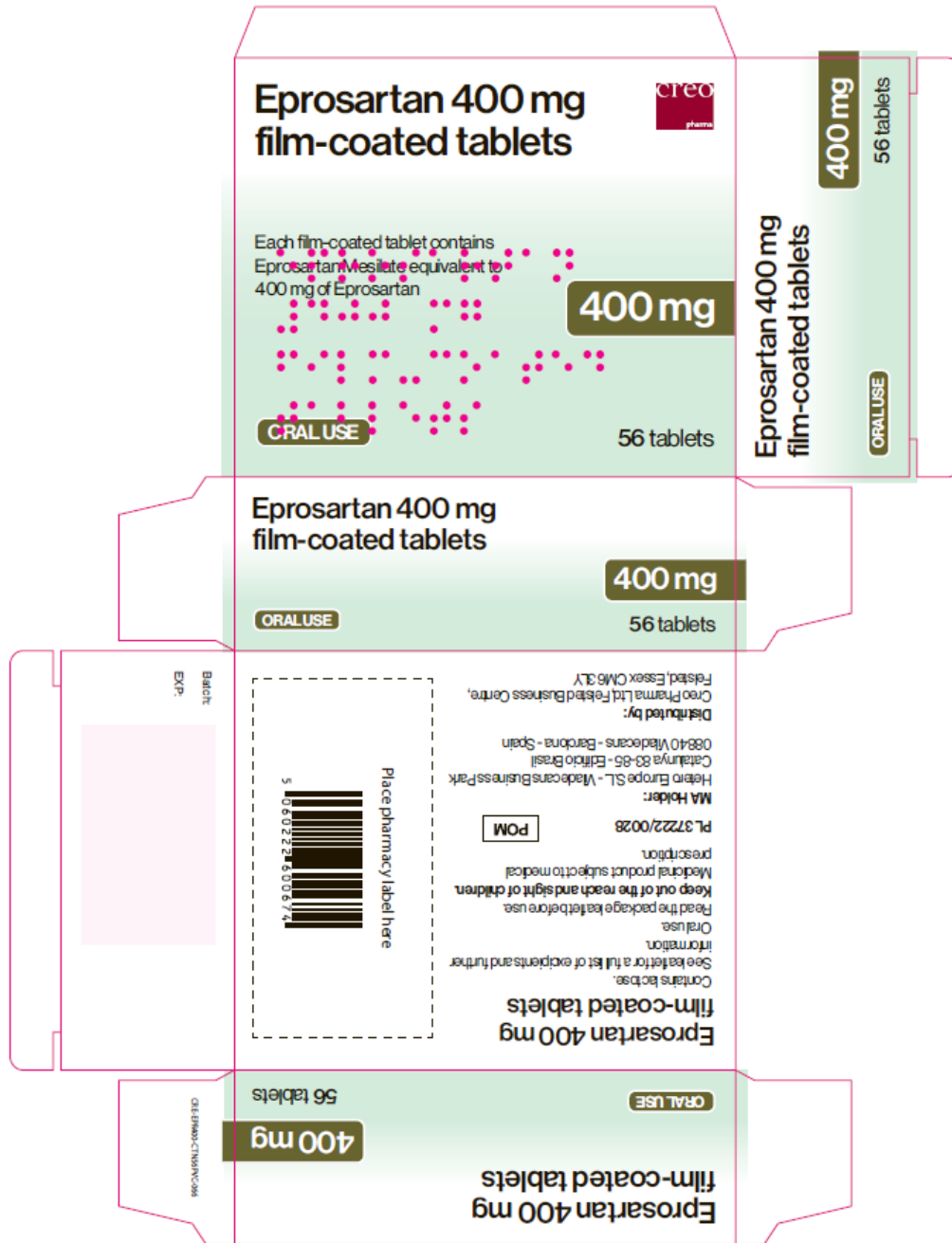
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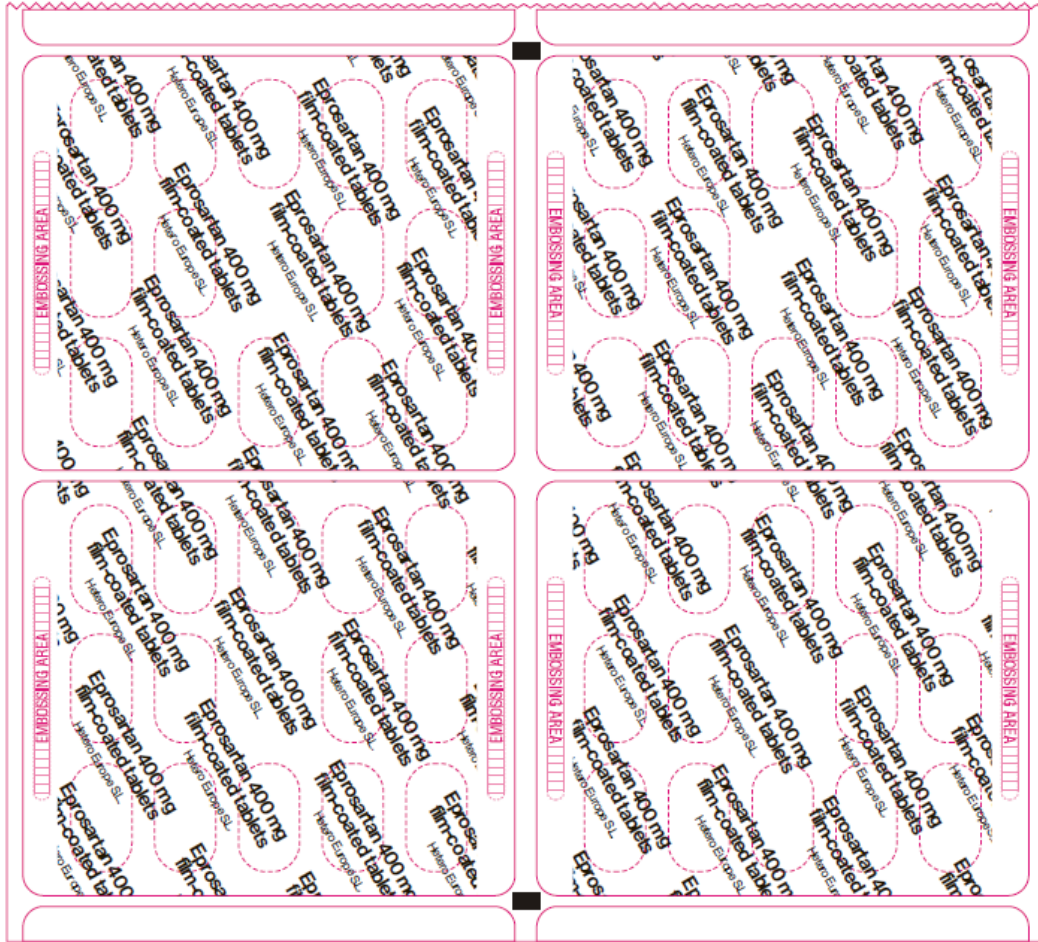
Eprosartan 400 mg film-coated tablets

Hetero Europe S.L.

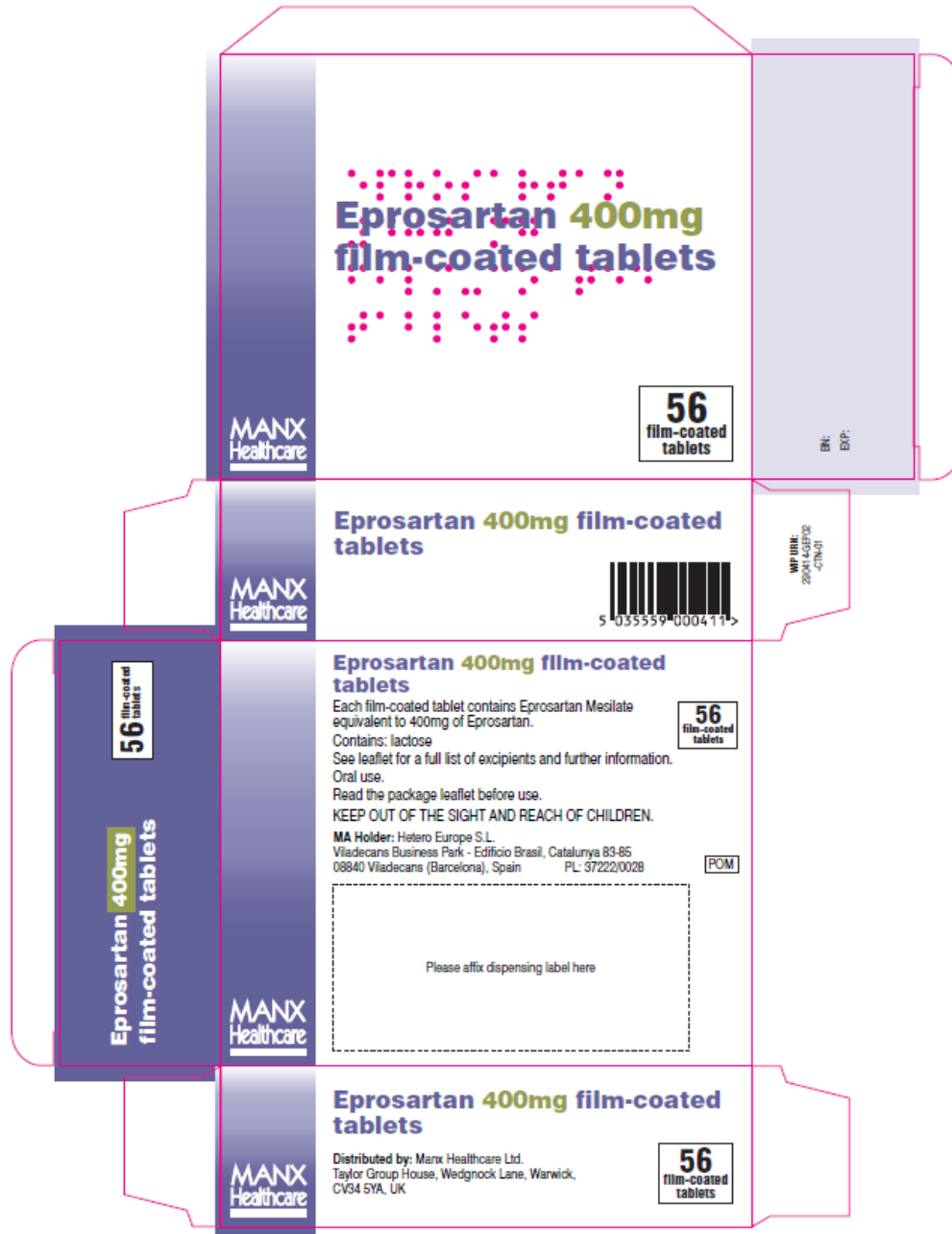
Eprosartan 400 mg film-coated tablets

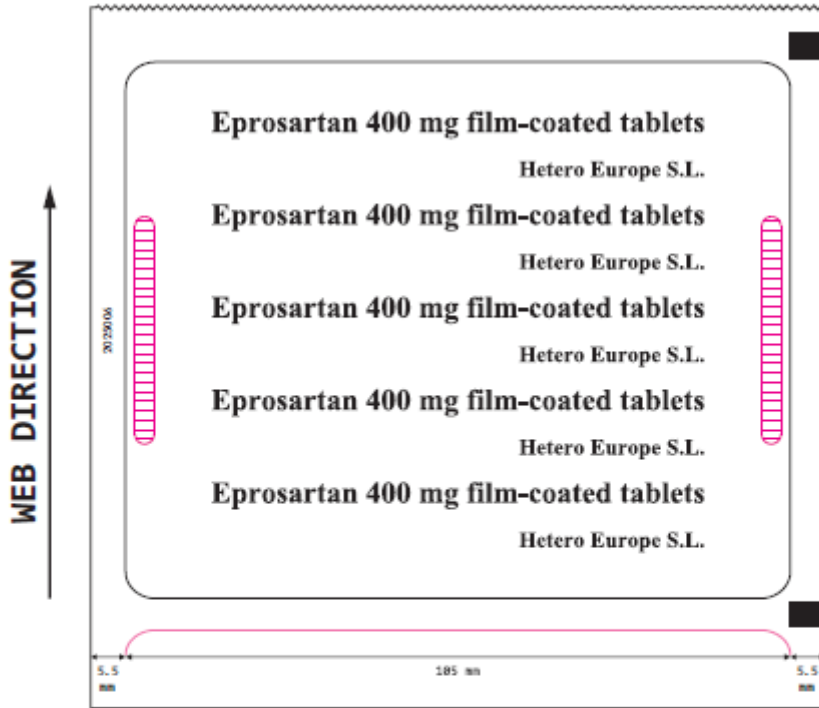
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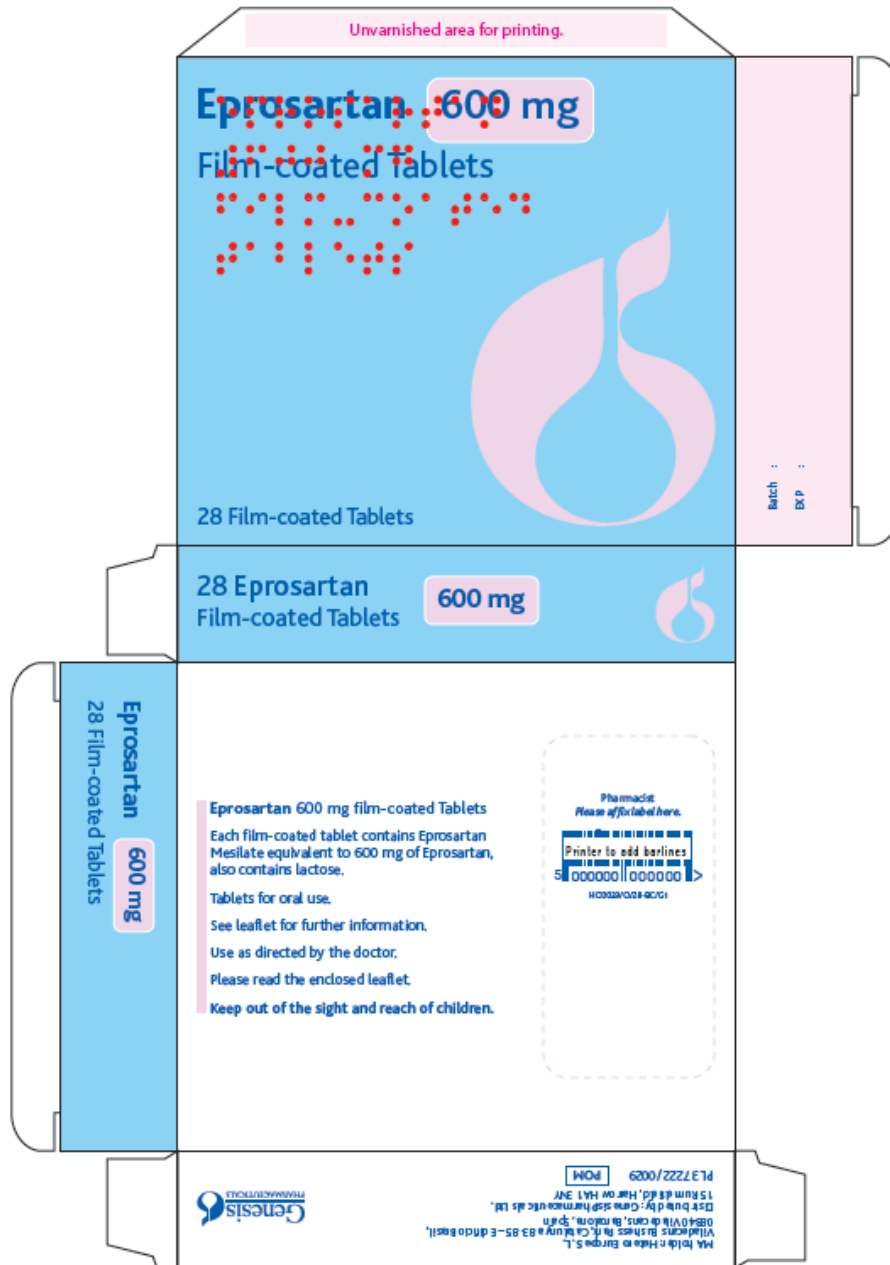






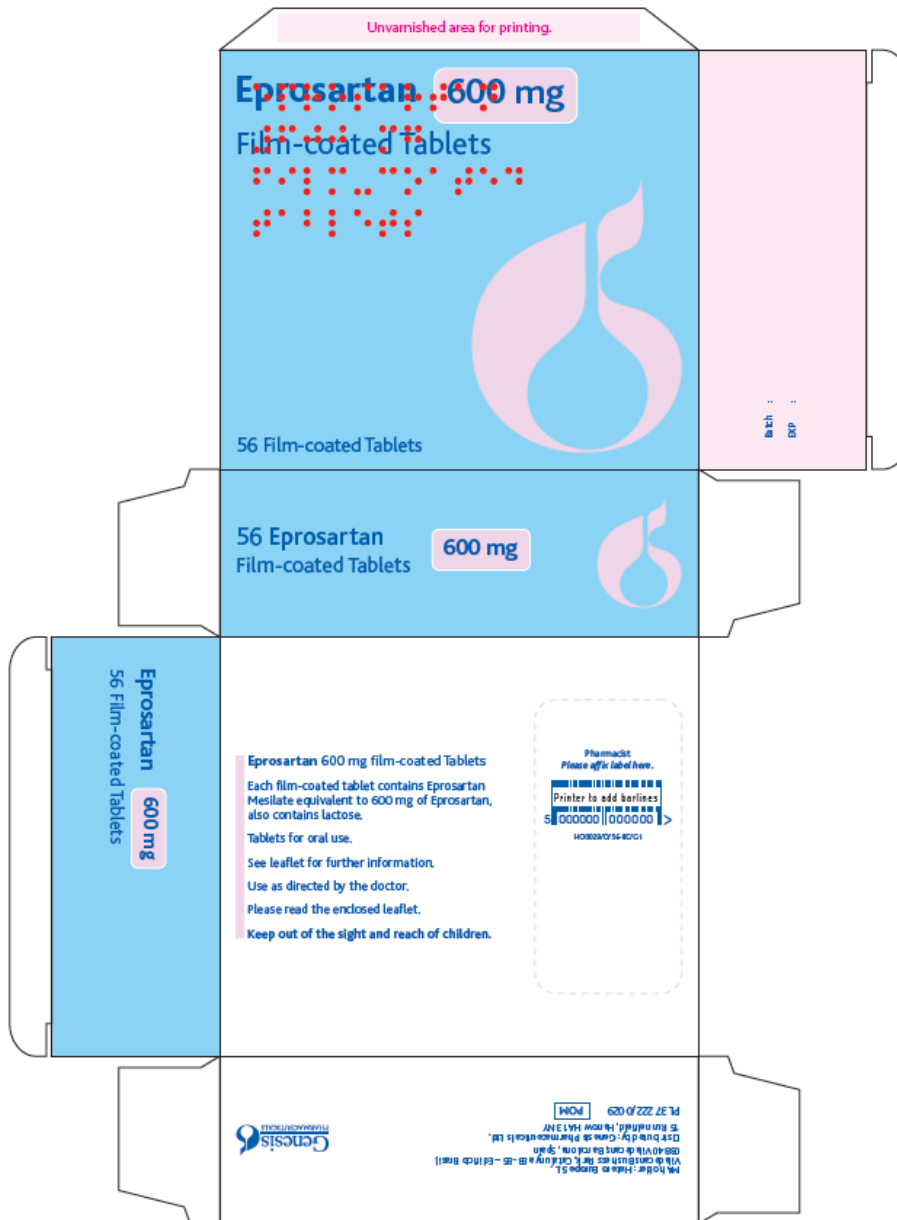


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 Total Length Over 10 Repeats = 900^{mm}₁₀
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 Colours: Black
 Layout No: PGB083131877



Braille reads:
Eprosartan
#600 mg
film-coated
tablets





Braille reads:
Eprosartan
#400 mg
film-coated
tablets



Eprosartan 600 mg film-coated tablets

Hetero Europe S.L.

Eprosartan 600 mg film-coated tablets

Hetero Europe S.L.

Eprosartan 600 mg film-coated tablets

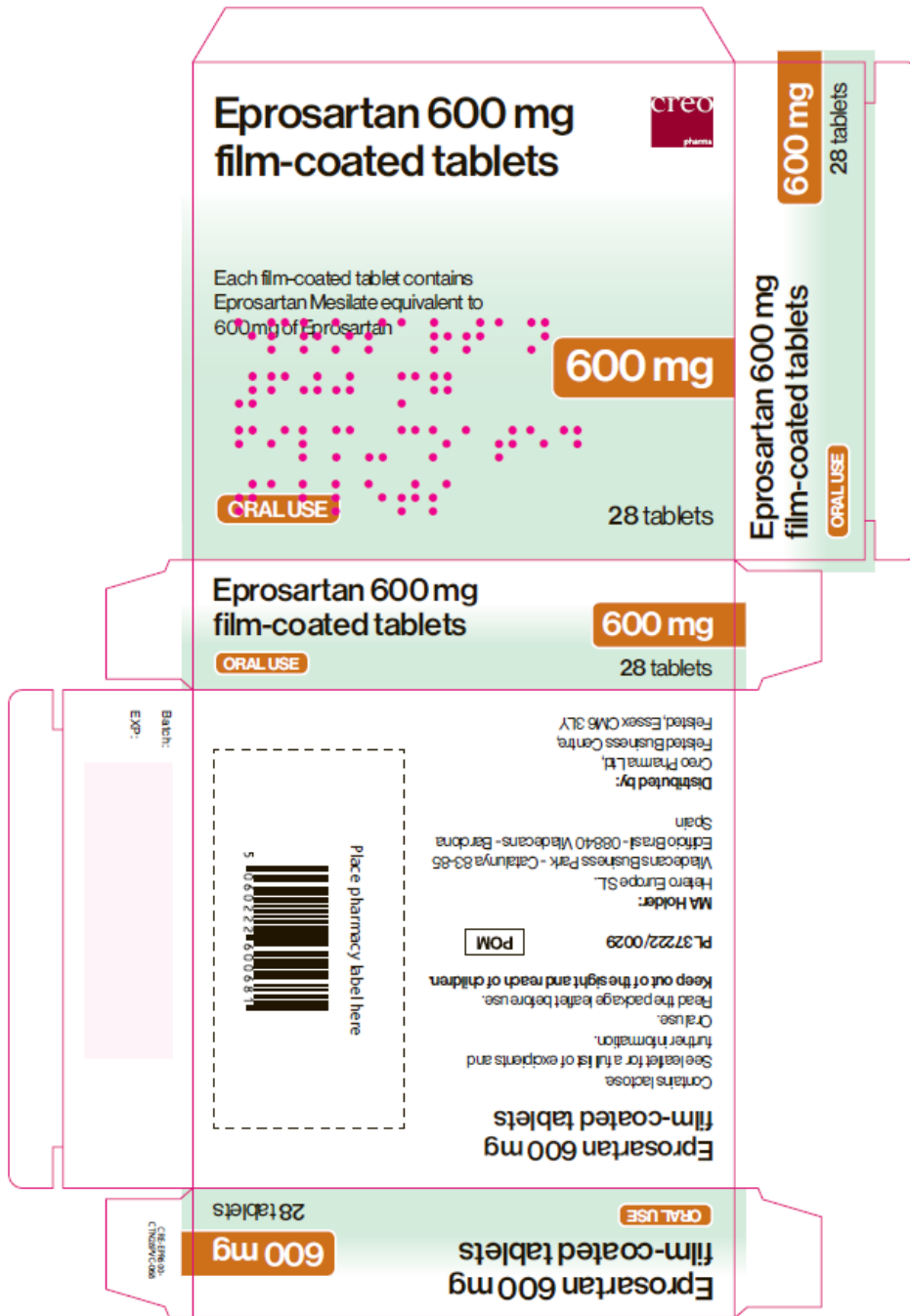
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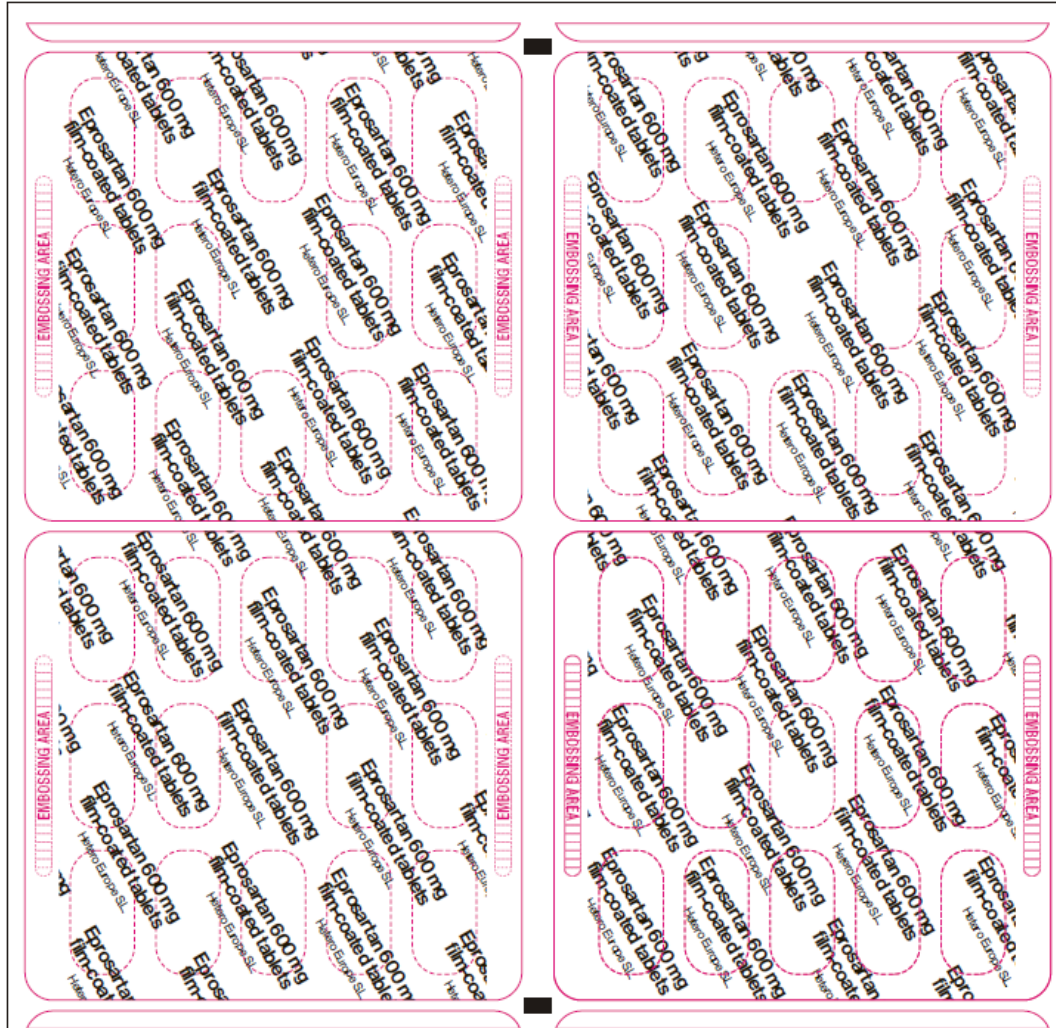
Eprosartan 600 mg film-coated tablets

Hetero Europe S.L.

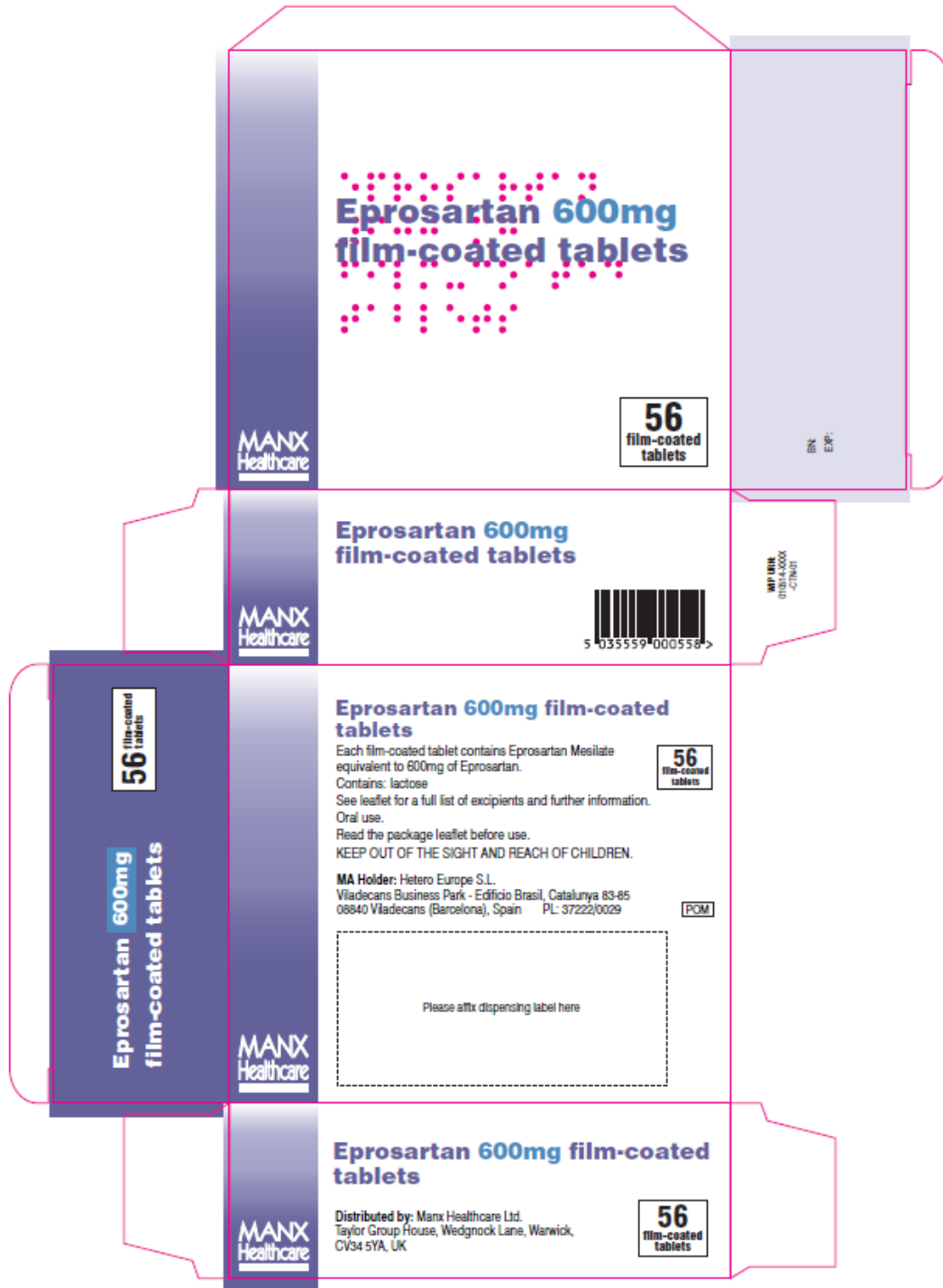
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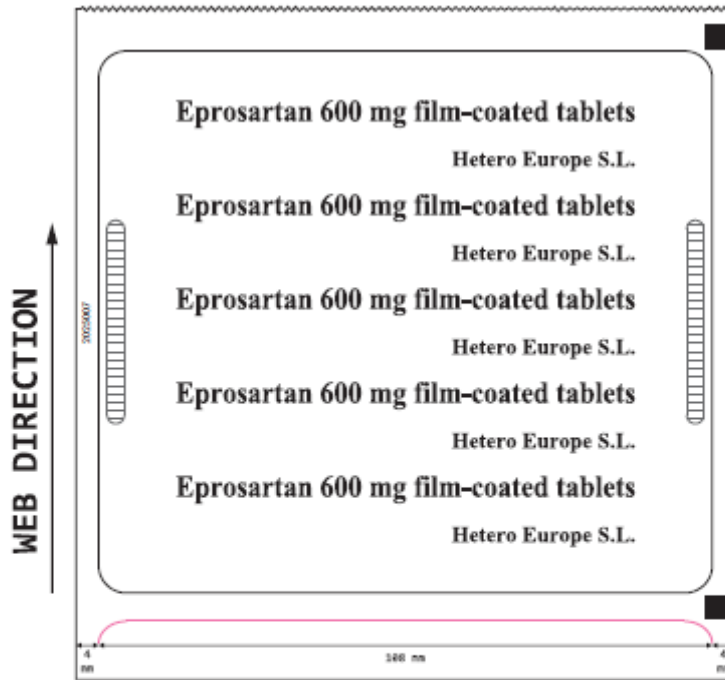
Hetero Europe S.L.











Foil Width: 116 (4+108+4)mm
Blister Size: 108 x 96 mm
Printing Repeat Length: 101^{mm}
Total Length Over 10 Repeats = 1010^{mm}
Spec: Printed on 25 microns Aluminium foil with 7 GSM HSL coating
Colours: ■ Black
Layout No: PGB083131878

ANNEX 1

Our Reference:	PL 37222/0027-0006 PL 37222/0028-0006 PL 37222/0029-0006
Product:	Eprosartan 300mg film-coated tablets Eprosartan 400mg film-coated tablets Eprosartan 600mg film-coated tablets
Marketing Authorisation Holder:	Hetero Europe S.L.
Active Ingredient(s):	Eprosartan mesilate
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type IB
Submission Complexity:	Standard
EU Procedure Number (if applicable):	
Reason:	To update sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) for Eprosartan 300mg, 400mg and 600mg film-coated tablets in line with the outcome of the Article 31 Referral (EMEA/H/A-31/3170) and the QRD template. As a consequence, the Patient Information Leaflet (PIL) has also been updated.
Supporting Evidence	Revised SmPC fragments and PIL.
Evaluation	The proposed changes to the SmPCs and PIL are in line with the outcome of the Article 31 Referral (EMEA/H/A-31/3170) and current QRD requirements. The updated SmPC fragments and PIL have been incorporated into the Marketing Authorisations.
Conclusion	The proposed changes to the SmPCs and PIL are acceptable.
Decision	Approved on 27 November 2014.