Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Metoprolol Tartrate 50 mg Film-coated Tablets
Metoprolol Tartrate 100 mg Film-coated Tablets

metoprolol tartrate

PL 28278/0038-0039

Ipca Laboratories UK Ltd

LAY SUMMARY

Metoprolol Tartrate 50 mg Film-coated Tablets
Metoprolol Tartrate 100 mg Film-coated Tablets
metoprolol tartrate

This is a summary of the Public Assessment Report (PAR) for Metoprolol Tartrate 50 and 100 mg Film-coated Tablets. It explains how these products 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 these products.

These products will be referred to as Metoprolol Tartrate tablets in this lay summary for ease of reading.

For practical information about using Metoprolol Tartrate tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Metoprolol Tartrate tablets and what are they used for?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, a reference medicines already authorised, called Lopresor® 50mg and 100mg Tablets.

Metoprolol tartrate belongs to a group of medicines called beta blockers. It is used to treat:
- high blood pressure
- angina pectoris (pain in the chest caused by blockages in the arteries to the heart)
- irregular heart rhythm (arrhythmia)
- the symptoms caused by an overactive thyroid gland (thyrotoxicosis)

It is used to **prevent**:
- heart damage and death due to heart attacks
- migraine

How are Metoprolol Tartrate tablets used?
The pharmaceutical form of these medicines is tablets, and the route of administration is by mouth (oral).

Recommended dose:
Recommended dose should not exceed 400 mg/day in any of below mentioned conditions.

High blood pressure: Initially 100 mg metoprolol tartrate daily. The dose may be increased to 200mg daily in single or divided doses.

Angina: 50 to 100 mg metoprolol tartrate two or three times daily.

Irregular heart beats: 50mg metoprolol tartrate two or three times daily. The dose may be increased to 300mg daily in divided doses.

Heart attack: 50mg metoprolol tartrate every six hours. The usual maintenance dose is 200mg daily in divided doses. The medicine should be taken for at least 3 months.

Prevention of migraine: 100 to 200 mg metoprolol tartrate daily in divided doses (in the

morning and evening).

Overactive thyroid gland (thyrotoxicosis): 50mg metoprolol tartrate four times daily.

Use in children of these medicines are not recommended.

Patients with impaired kidney or liver function: In such cases the dose should be adjusted. The patient should follow their doctor's advice.

Taking these medicines: the tablet should be swallowed whole. The score line is only there to help break the tablet in cases where a patient finds difficulty in swallowing it whole.

For further information on how Metoprolol Tartrate tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

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

What benefits of Metoprolol Tartrate tablets have been shown in studies?
Because Metoprolol Tartrate tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Metoprolol Tartrate tablets?
For the full list of all side effects reported with this medicine/these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Metoprolol Tartrate tablets are generic medicines and are bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicines.

Why were Metoprolol Tartrate tablets approved?
It was concluded that, Metoprolol Tartrate tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Metoprolol Tartrate tablets?

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Metoprolol Tartrate tablets The RMP details the important risks of Metoprolol Tartrate tablets, how these risks can be minimised, any uncertainties about Metoprolol Tartrate tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Metoprolol Tartrate tablets:

Summary of safety concerns	
Important Identified Risks	• Metabolic and endocrine disorders • Cardiovascular disorders • Withdrawal reactions • Increased sensitivity to allergens and severity of allergic reactions
Important Potential Risks	• Use during pregnancy and breastfeeding
Missing Information	• None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Metoprolol Tartrate tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Metoprolol Tartrate tablets

Marketing authorisations for Metoprolol Tartrate tablets were granted in the United Kingdom (UK) on 16 June 2022.

The full PAR for Metoprolol Tartrate tablets follows this summary.

This summary was last updated in August 2022.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Metoprolol Tartrate 50 mg and 100mg Film-coated Tablets (PL 28278/0038-0039) could be approved.

These products are approved in adults for the management of:

- Hypertension.
- Angina pectoris.
- Cardiac arrhythmias (in particular supraventricular tachycardias).
- As an adjunctive treatment of thyrotoxicosis.
- Early intervention of metoprolol in acute myocardial infarction reduces infarct size and the incidence of ventricular fibrillation. Pain relief may also decrease the need for opiate analgesics.
- long-term prophylaxis after recovery from acute myocardial infarction.
- Prophylaxis of migraine.

Metoprolol has been shown to reduce mortality when administered to patients with acute myocardial infarction

Mechanism of action

Metoprolol is a cardioselective beta-adrenergic blocking agent. It has a relatively greater blocking effect on beta1 receptors (i.e. those mediating adrenergic stimulation of heart rate and contractility and release of the fatty acids from fat stores) than on beta2 receptors which are chiefly involved in broncho and vasodilation.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Lopresor® 50mg and 100mg Tablets that have been licensed for a suitable time, in line with the legal requirements.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations for Metoprolol Tartrate tablets were granted in the United Kingdom (UK) on 16 June 2022.

II QUALITY ASPECTS

II.1 Introduction

The active substance is metoprolol tartrate. Each film-coated tablet contains 50 mg or 100 mg of metoprolol tartrate.

The other ingredients are:

50mg tablet

Tablet core: lactose monohydrate, cellulose microcrystalline, sodium starch glycolate type A, silica, colloidal anhydrous, croscarmellose sodium, starch, pregelatinised, and magnesium stearate.

Tablet coating: hypromellose 15cps, titanium dioxide, talc, macrogol 400, and ferric oxide red.

100mg tablet

Tablet core: lactose monohydrate, cellulose, microcrystalline, sodium starch glycolate type A, silica, colloidal anhydrous, croscarmellose sodium, starch, pregelatinised, and magnesium stearate.

Tablet coating: hypromellose 15 cps, titanium dioxide, talc, and macrogol 400

The finished products are packaged in clear colourless PVC/aluminium blister strips of 10 and 14 tablets, in packs of 10, 14, 28, 30, 50, 56, 84, or 100 Tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

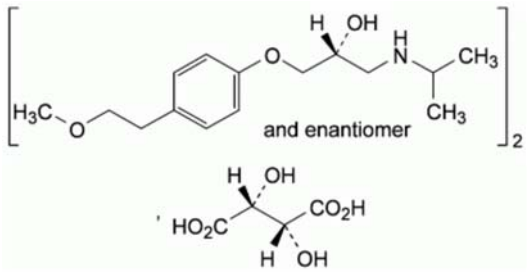
II.2 ACTIVE SUBSTANCE

rINN: Metoprolol Tartrate

Chemical Name: Bis [(2*RS*)-1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]2-propanol] (2*R*,3*R*)-2,3-dihydroxybutanedioate

Molecular Formula: $C_{34}H_{56}N_2O_{12}$

Chemical Structure:



Molecular Weight: 685

Appearance: White or almost white crystalline powder or colourless crystals

Solubility: Very soluble in water, freely soluble in alcohol.

Metoprolol tartrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final products.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

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

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with the storage conditions, ‘Store below 25°C. Store in the original package in order to protect from light’, is acceptable.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of metoprolol tartrate are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology

No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic version of an already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed products.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of metoprolol tartrate are well-known. With the exception of data from a bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

This was a randomised, open label, two-sequence, two-treatment, two-period, single dose, crossover design study. The tablets were administered with the study drug (a single oral dose) in fasting condition.

After an overnight fast, subjects were administered with a single (100mg) dose of the test or reference product. Blood samples were taken pre-dose and up to 48 hours post dose, with a washout period of 9 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Parameters	Geometric Mean*		% Ratio	90 % Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
$AUC_{0\text{-}inf}$	1119.28	1081.58	103.49	98.92	108.26
$AUC_{0\text{-}t}$	1073.88	1039.59	103.30	98.51	108.32

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test

product and the reference product.

As the additional strengths (50 mg) of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 100mg product strength can be extrapolated to the other strength.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

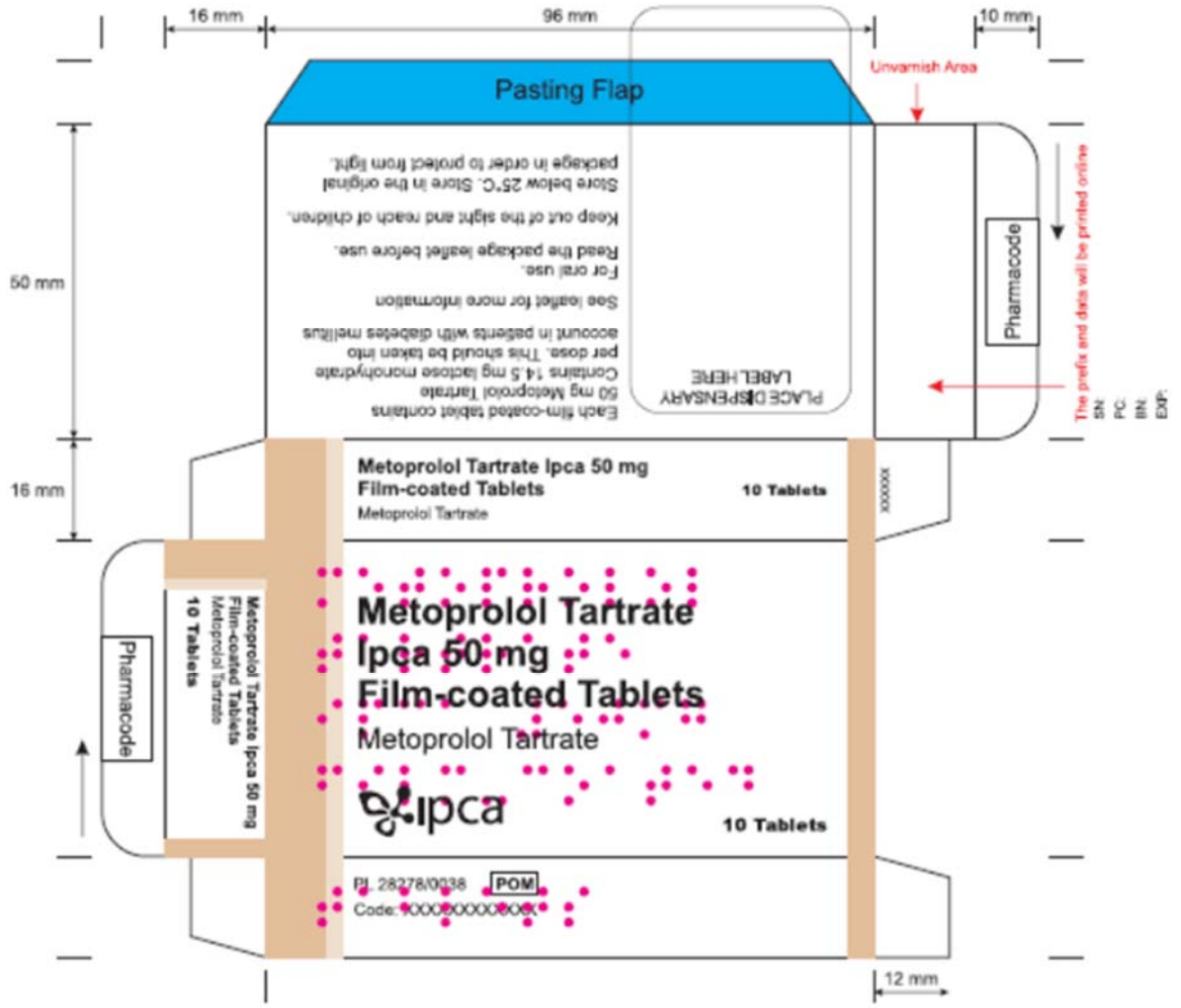
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

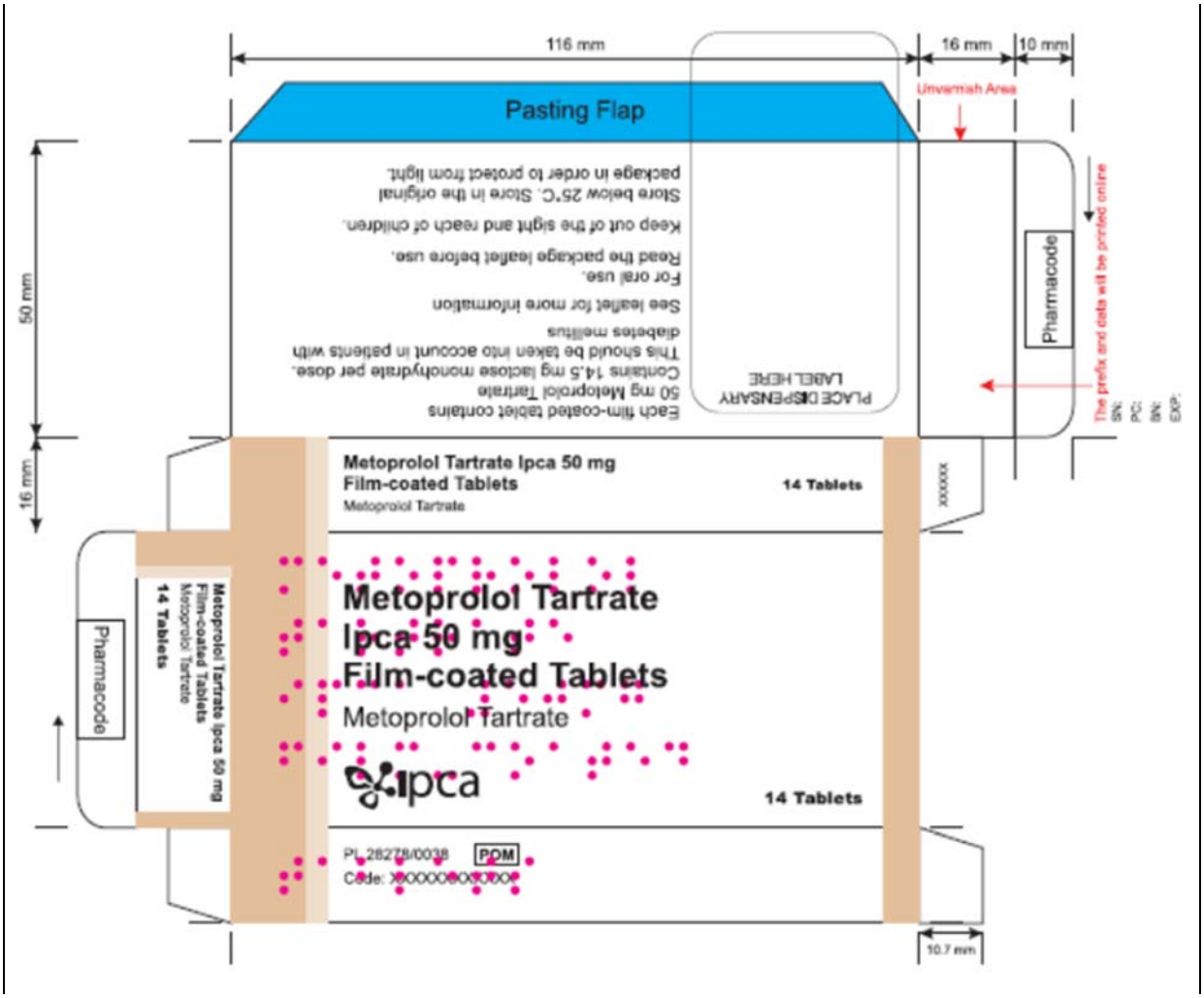
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with metoprolol tartrate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.

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16 mm
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Pasting Flap
Unvarnish Area
50 mm
16 mm
Each film-coated tablet contains
50 mg Metoprolol Tartrate
Contains 14.5 mg lactose monohydrate per dose.
This should be taken into account in patients with
diabetes mellitus
See leaflet for more information
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C. Store in the original
package in order to protect from light.
PLACE DISPENSARY
LABEL HERE
Pharmacode
The prefix and data will be printed online
SN:
PC:
BN:
EXP:
Metoprolol Tartrate Ipca 50 mg
Film-coated Tablets
Metoprolol Tartrate
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Pharmacode
Metoprolol Tartrate Ipca 50 mg
Film-coated Tablets
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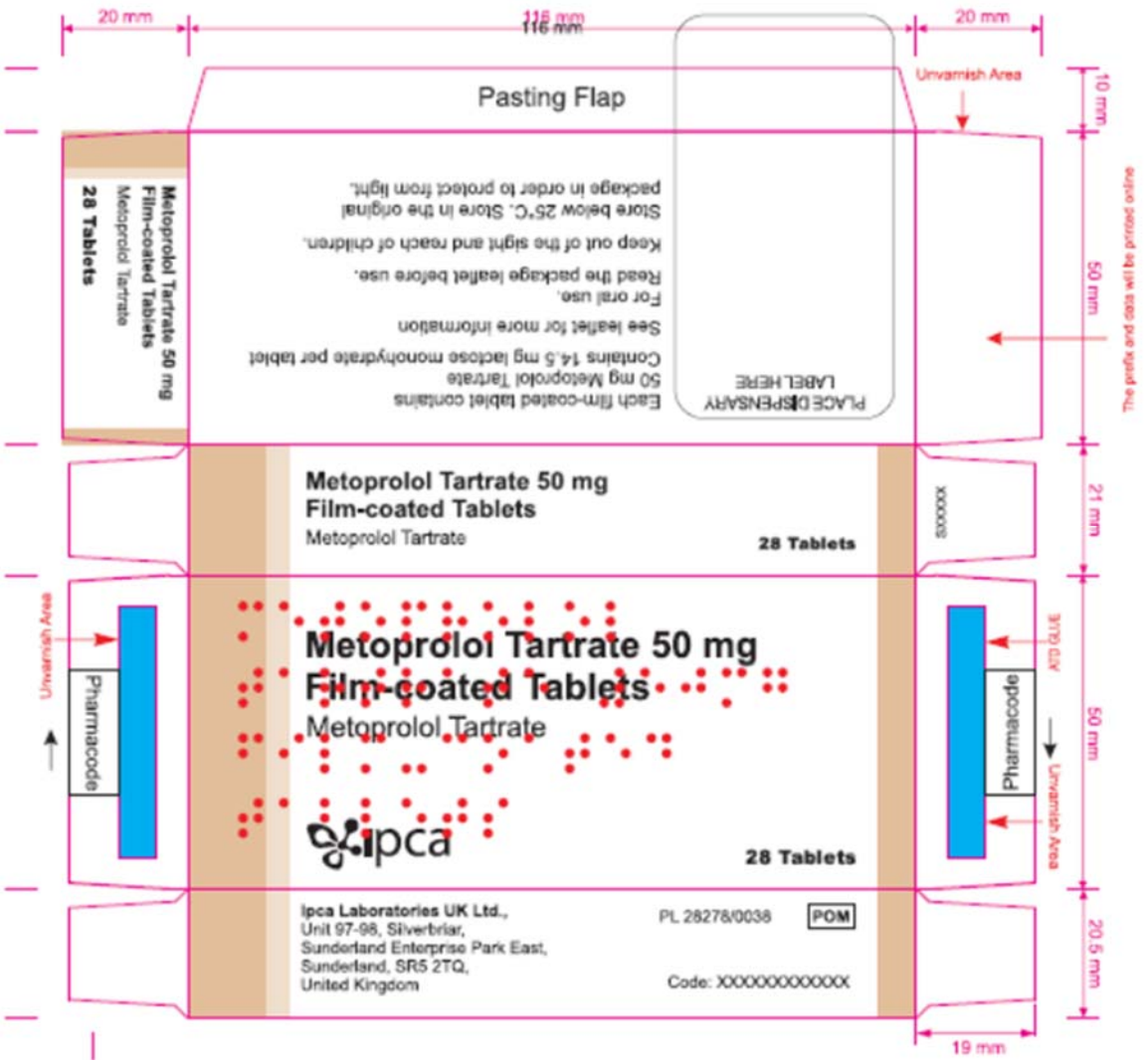
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Metoprolol Tartrate 50 mg
Film-coated Tablets
Metoprolol Tartrate
28 Tablets
Each film-coated tablet contains
50 mg Metoprolol Tartrate
Contains 14.5 mg lactose monohydrate per tablet
See leaflet for more information
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C. Store in the original
package in order to protect from light.
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Metoprolol Tartrate 50 mg
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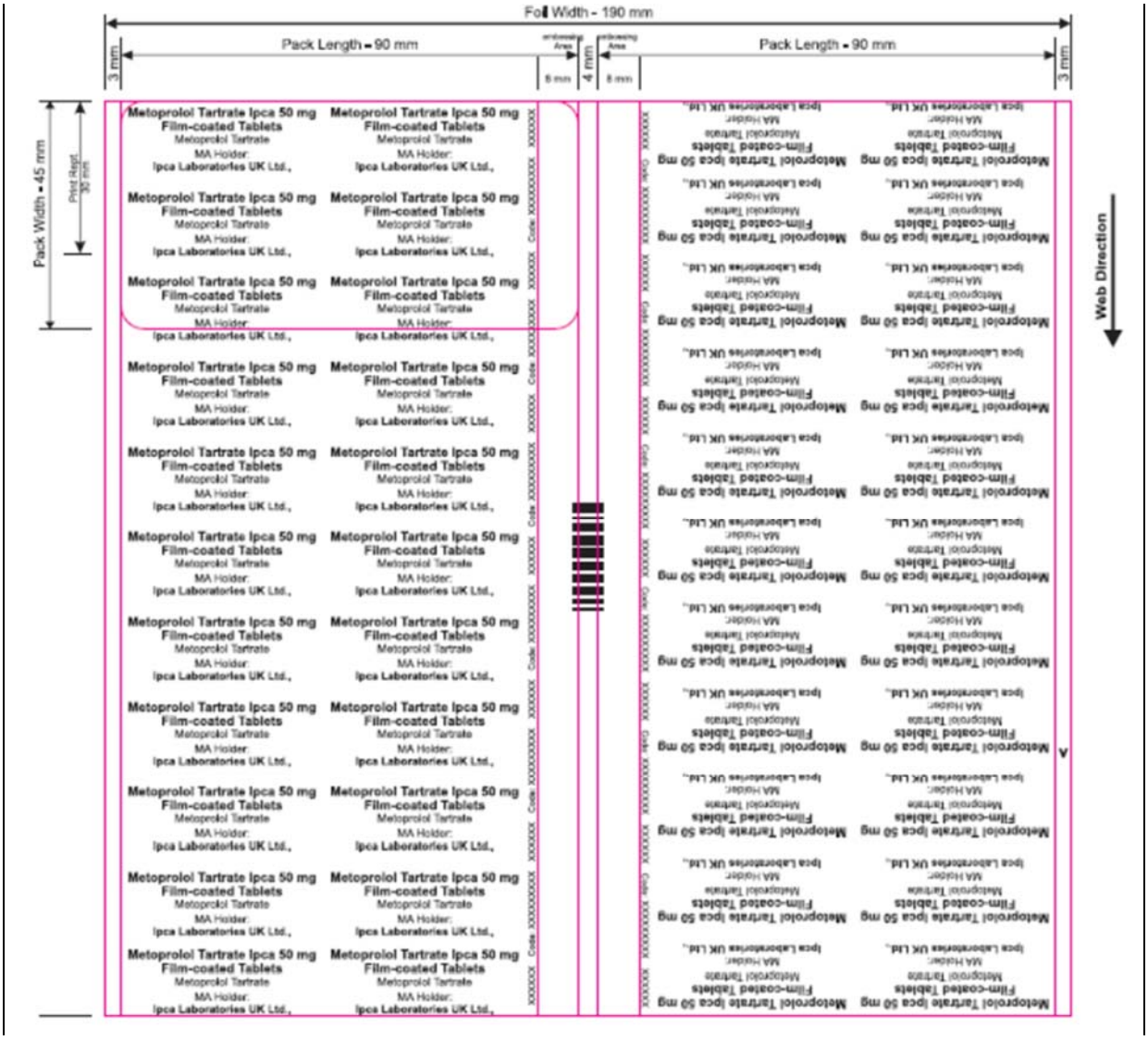
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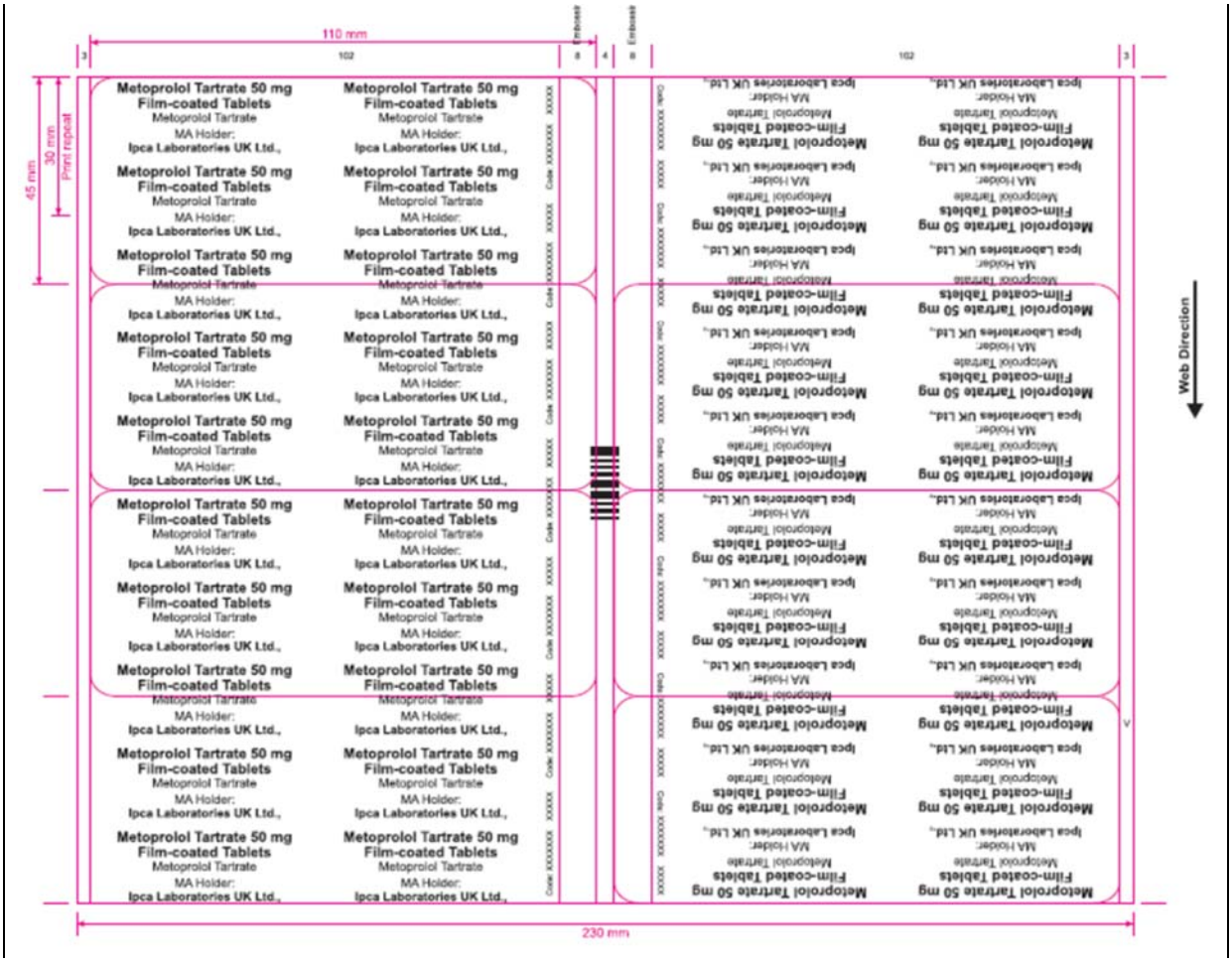
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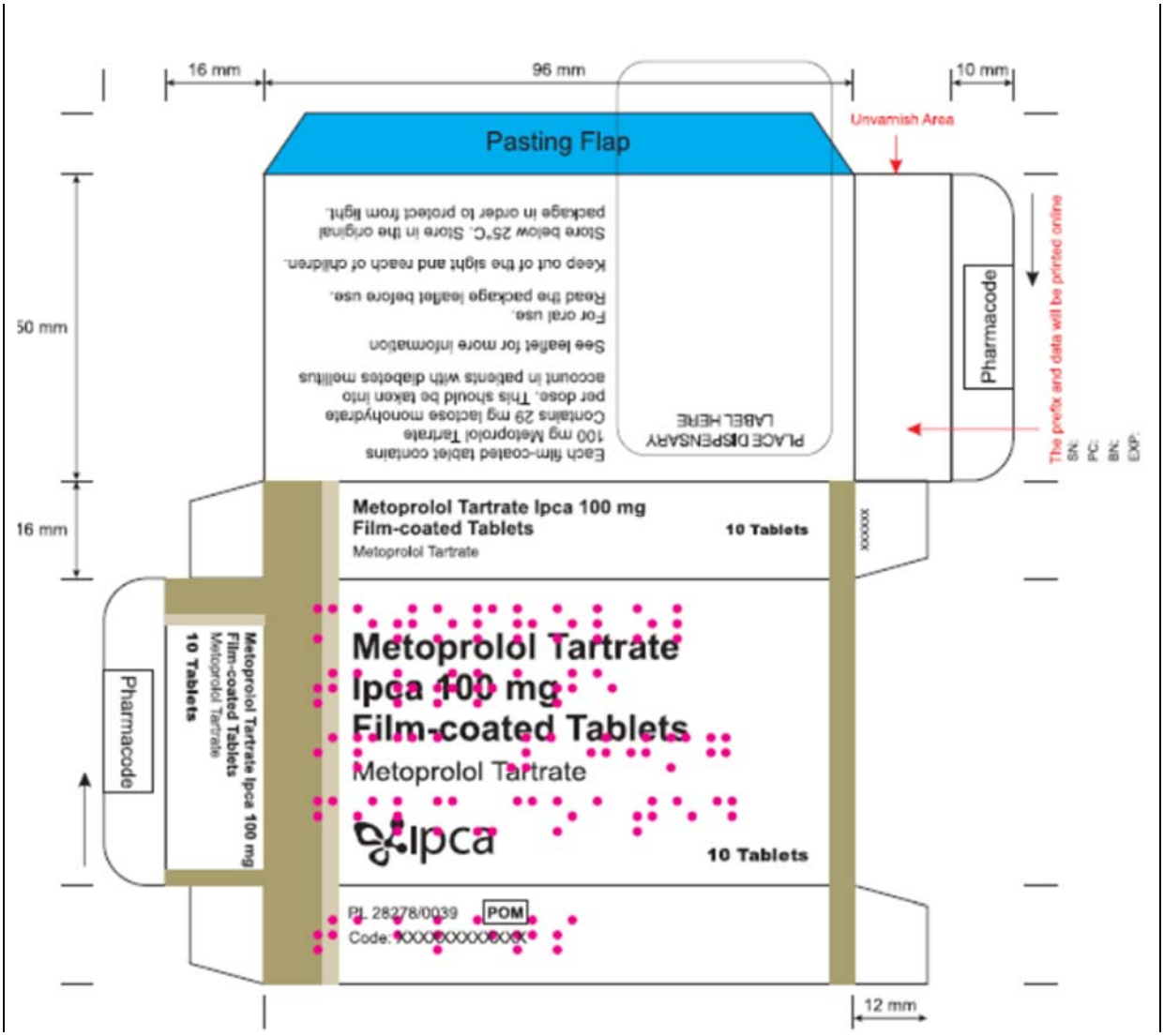
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PLACE DISPENSARY LABEL HERE
Each film-coated tablet contains 100 mg Metoprolol Tartrate
Contains 29 mg lactose monohydrate per dose. This should be taken into account in patients with diabetes mellitus
See leaflet for more information
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C. Store in the original package in order to protect from light.
Metoprolol Tartrate Ipca 100 mg Film-coated Tablets
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Metoprolol Tartrate
10 Tablets
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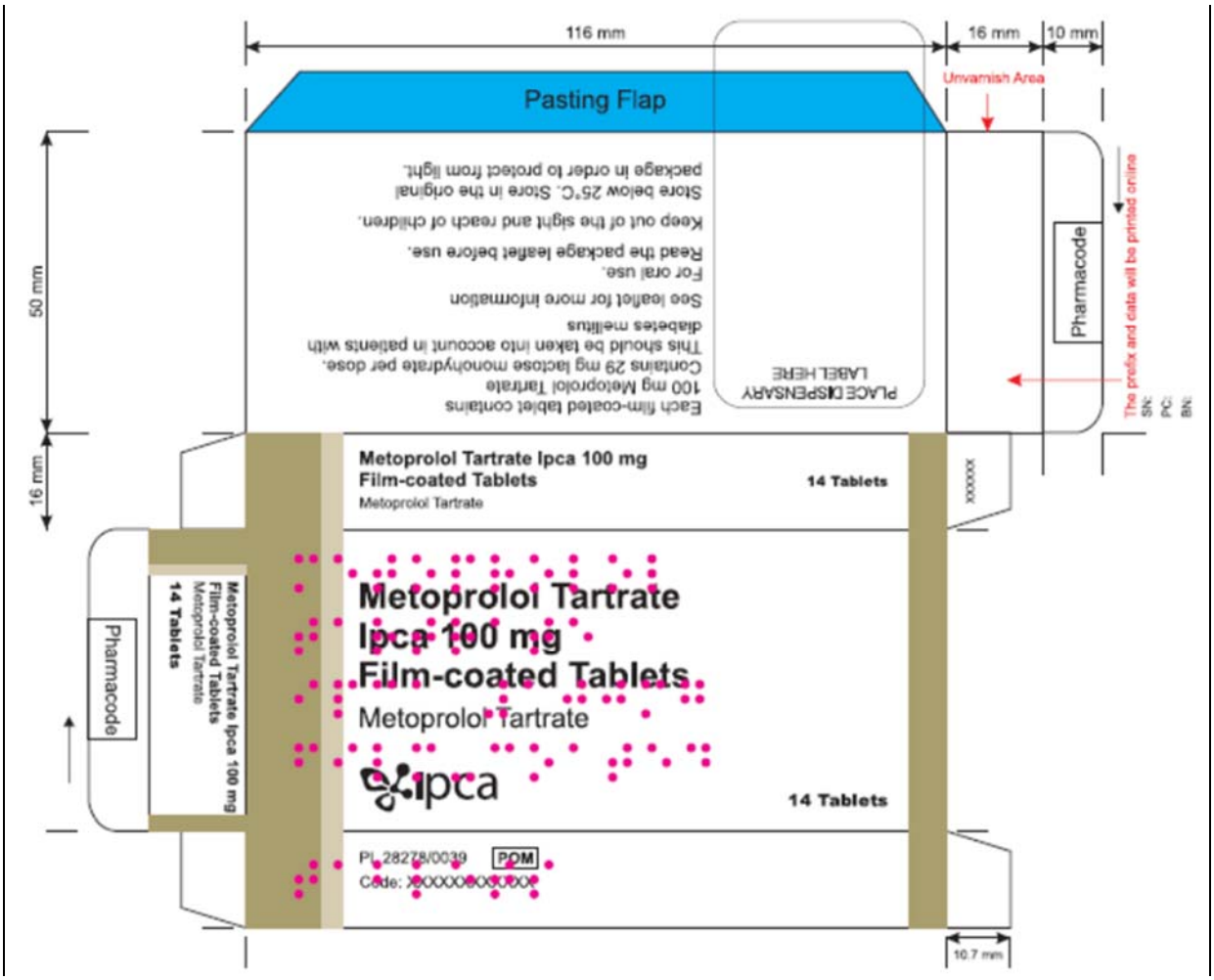
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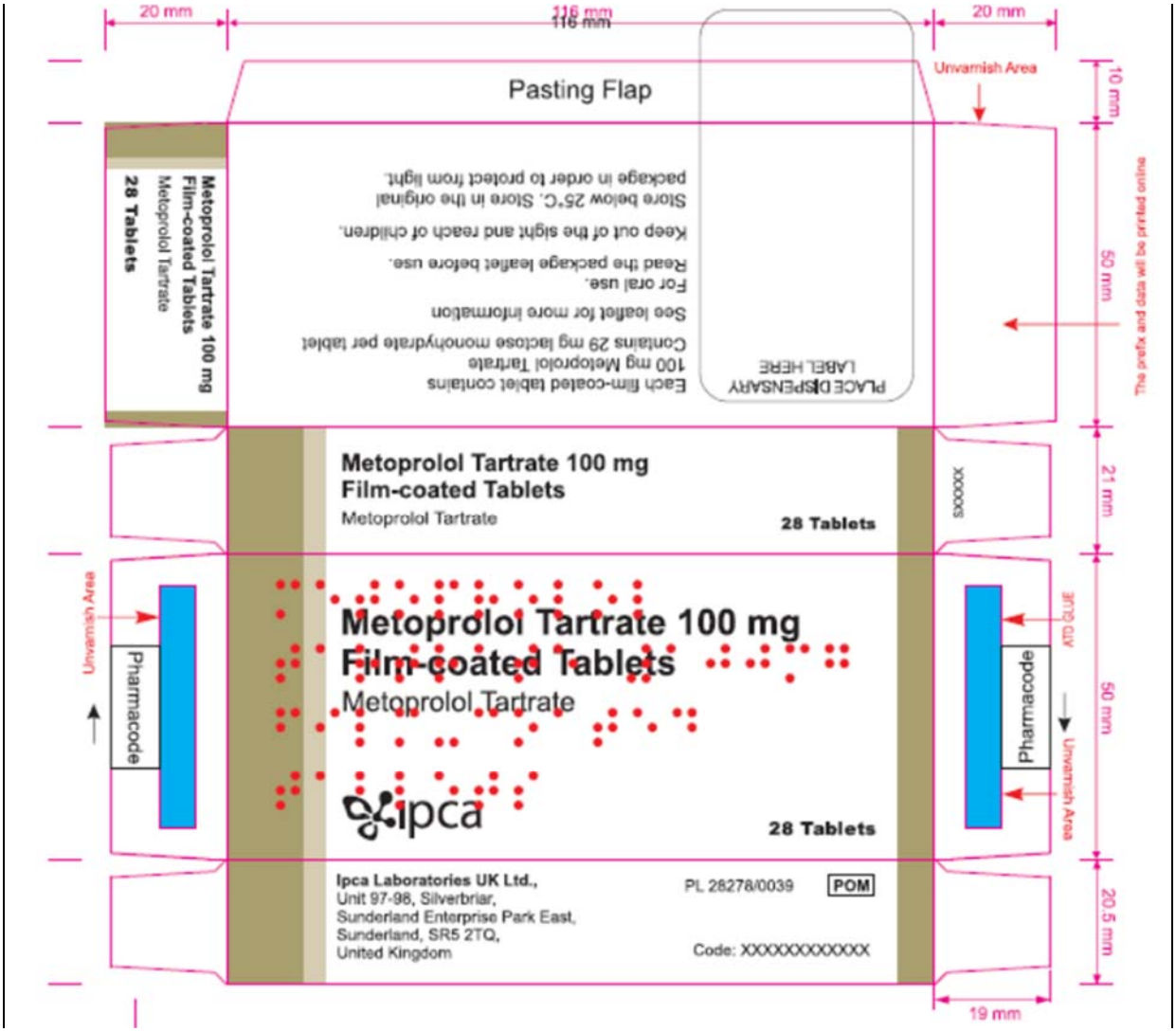
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Pharmacode
Metoprolol Tartrate 100 mg
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28 Tablets
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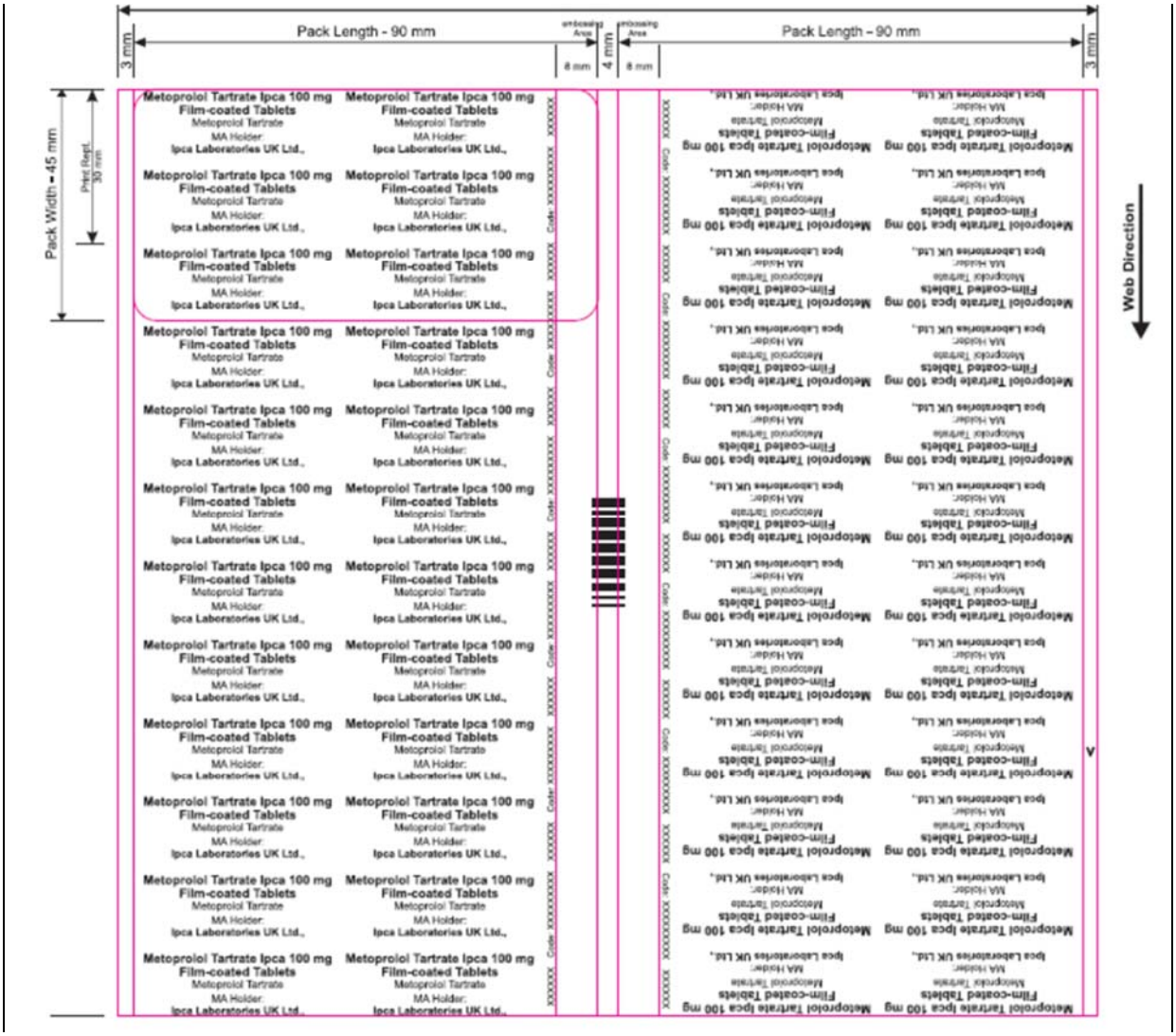
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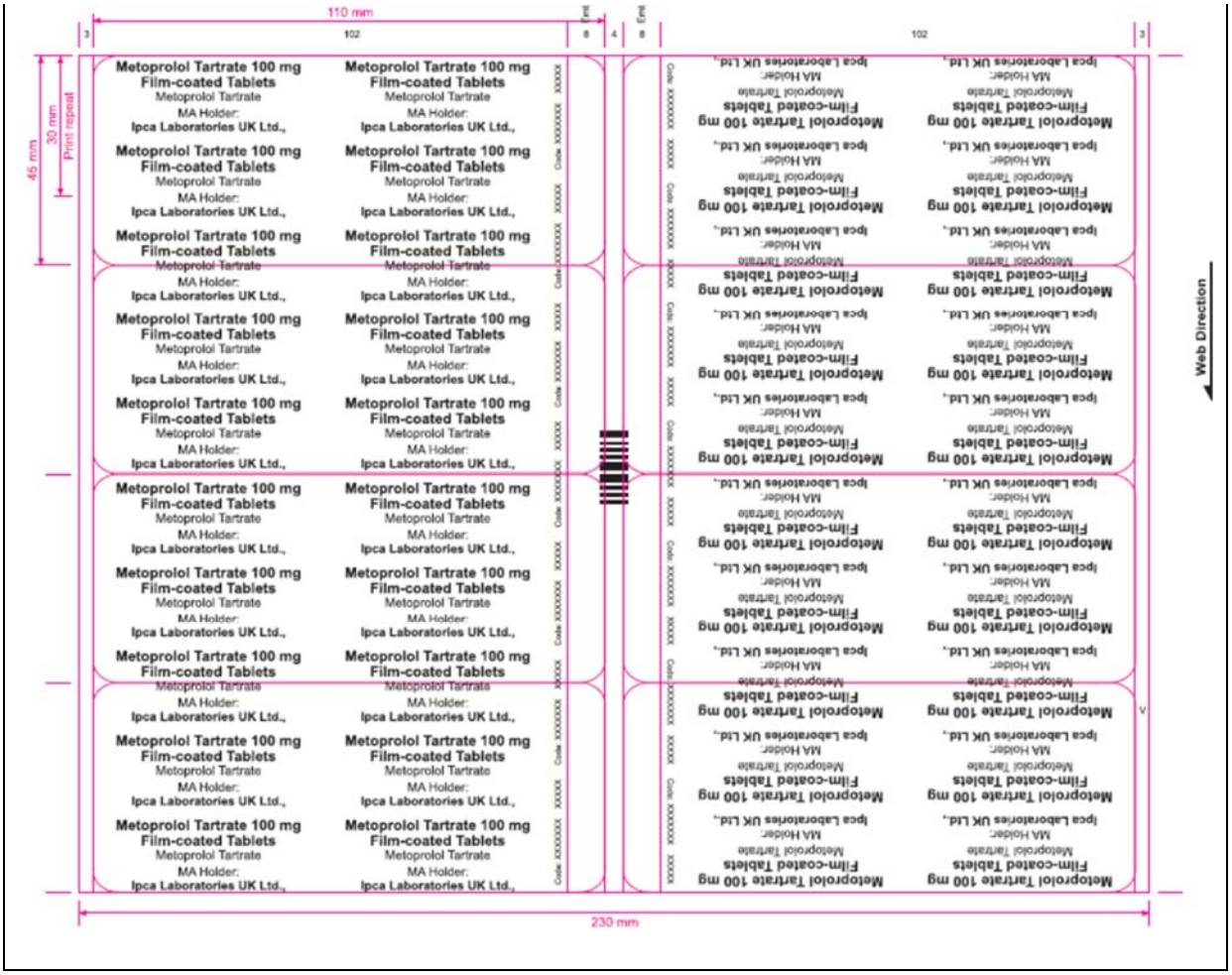
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Metoprolol Tartrate 100 mg
Film-coated Tablets
Metoprolol Tartrate
MA Holder:
Ipca Laboratories UK Ltd.,
Web Direction
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TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N