Medicines & Healthcare products Regulatory Agency

MHRA

# Public Assessment Report

# National Procedures

# Mexiletine hydrochloride 50, 100 and 200 mg Hard Capsules

# (mexiletine hydrochloride)

# Product Licence Numbers: PL 39936/0011-0013

# Arriello s.r.o

# LAY SUMMARY

## Mexiletine hydrochloride 50, 100 and 200 mg Hard Capsules

## (mexiletine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Mexiletine hydrochloride 50, 100 and 200 mg Hard Capsules. It explains how these products were assessed and their authorisations 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 Mexiletine Hard Capsules in this lay summary for ease of reading.

For practical information about using Mexiletine Hard Capsules, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

**What are Mexiletine Hard Capsules and what are they used for?**
These applications are for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Mexiletine Hard Capsules are indicated for the documented irregular heartbeat which, in the judgement of the physician, is considered as life threatening.

**How do Mexiletine Hard Capsules work?**
Mexiletine Hard Capsules contain the active substance mexiletine hydrochloride. It works by blocking certain electrical signals in the heart to stabilize the heart.

**How are Mexiletine Hard Capsules used?**
The pharmaceutical form of this medicine is a capsule and the route of administration is oral (by mouth).

Patients should take this medicine exactly as a doctor or pharmacist has told them. They should check with a doctor or pharmacist if they are not sure.

A doctor may ask them to start therapy with a dose of 400 mg (2 capsules of 200 mg).

The maintenance dose is 150 mg (1 capsule of 50 mg plus 1 capsule of 100 mg) to 300 mg (1 capsule of 100 mg plus 1 capsule of 200 mg) given two to three times daily.

If necessary, dose may be adjusted in 50 or 100 mg increments. A minimum of two to three days between dose adjustments is recommended.

The dose should not exceed 1200 mg per day (6 capsules of 200 mg).

In some cases, a doctor may then decide to either increase or lower the amount patients take each day. This will depend on how they react to this medicine.

Mexiletine capsules are not recommended in children and adolescents.

**Use in patients with liver problems**

Mexiletine should be used with caution in patients with mild or moderate liver dysfunction. In those patients a minimum of two weeks between dose adjustments is recommended. Mexiletine capsules should not be used in patients with severe liver disease.

**Use in patients with kidney problems**
For patients with mild-to-moderate kidney disease, no adjustment of the starting dose is required.

Mexiletine should not be used in patients with severe kidney disease.

**Use in patients with poor metabolism (poor CYP2D6 metabolisers)**
There is a potential for increased plasma levels in CYP2D6 poor metabolisers (7% of the European population). In those patients, a minimum of one week between dose adjustments is recommended.

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

This medicine can only be obtained with a prescription.

The patient should always take the 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 Mexiletine Hard Capsules have been shown in studies?**
As the active substance, mexiletine hydrochloride, has been in clinical use for over 10 years, data were provided in the form of literature references to show that Mexiletine Hard Capsules are safe and efficacious treatment for the documented irregular heartbeat which, in the judgement of the physician, is considered as life threatening.

In addition, the applicant provided the results of a new pharmacokinetic study and comparative analyses against relevant literature data to support the bridging between the literature and the proposed products.

**What are the possible side effects of Mexiletine Hard Capsules?**
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC 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 behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for ‘MHRA Yellow Card’ online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Mexiletine Hard Capsules (which may affect more than 1 in 10 people) are abdominal (belly) pain, dyspepsia (difficulty to digest), insomnia (difficulty sleeping), dizziness and involuntary shaking (tremor).

**Why were Mexiletine Hard Capsules approved?**
It was concluded that the data provided from literature references had shown that Mexiletine Hard Capsules are effective in the treatment of documented irregular heartbeat which, in the

judgement of the physician, is considered as life threatening. Furthermore, the well-established use of the active substance mexiletine hydrochloride has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that 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 Mexiletine Hard Capsules?**

A Risk Management Plan (RMP) has been developed to ensure that Mexiletine Hard Capsules are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, 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 and reviewed continuously.

**Other information about Mexiletine Hard Capsules**

Marketing Authorisations for Mexiletine Hard Capsules were granted in the United Kingdom (UK) on 17 June 2021.

The full PAR for Mexiletine Hard Capsules follows this summary.

This summary was last updated in August 2021.

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# I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Mexiletine hydrochloride 50, 100 and 200 mg Hard Capsules (PL 39936/0011-0013) could be approved.

The products are approved for the treatment of documented ventricular arrhythmias which, in the judgement of the physician, are considered as life-threatening.

Class I antiarrhythmic drugs have not been shown to improve survival in patients with ventricular arrhythmias.

Mexiletine is a local anaesthetic, antiarrhythmic agent, structurally similar to lidocaine. Mexiletine is effective in the suppression of induced ventricular arrhythmias. Mexiletine, like lidocaine inhibits the inward sodium current, thus reducing the rate of rise of the action potential, Phase 0. Mexiletine decreases the Effective Refractory Period (ERP) in Purkinje fibers. The decrease in ERP is of lesser magnitude than the decrease in Action Potential Duration (APD), with a resulting increase in the ERP/APD ratio.

These applications were approved under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as well-established use applications. The data submitted for these applications are in the form of literature references. However, to support the bridging between the literature and the proposed products the applicant has also provided the results of a new pharmacokinetic study and comparative analyses against relevant literature data.

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.

Advice was sought from the Commission of Human Medicines (CHM) on 21-22 May 2020 from Chemistry Pharmacy and Standards Expert Advisory Group (CPS EAG) on 19 May 2020 and from Cardiovascular, Diabetes, Renal, Respiratory & Allergy (CDRRA) EAGs in May 2020 to consider quality and clinical issues. Following consideration of the applicant's responses and further data that were submitted, the approval of the marketing authorisation was recommended following further advice form CHM and CPS EAG in May 2021 .

National marketing authorisations were granted in the United Kingdom (UK) on 17 June 2021.

# II QUALITY ASPECTS

## II.1 Introduction

These products consist of capsules. Each hard capsule contains 50 mg, 100 mg or 200 mg of mexiletine hydrochloride, equivalent to 41.55 mg, 83.10 mg or 166.20 mg of mexiletine.

In addition to mexiletine hydrochloride, these products also contain the excipients maize starch; silica, colloidal anhydrous; magnesium stearate (E572) making up the capsule content.
The capsule shells are composed of titanium dioxide (E171) and gelatin, for all strengths, and in addition the 200 mg capsule shell also contains indigotine (E132).

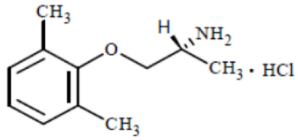
The finished products are packaged in polyvinylchloride (PVC)/polyvinyldichloride (PVDC)/aluminium blisters. Each blister contains 10 or 14 capsules. The pack sizes are 30, 50, 56, 84, 100 and 200 hard capsules.

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 to be in contact with food.

## II.2 ACTIVE SUBSTANCE

**rINN: Mexiletine hydrochloride**
Chemical Name: (2RS)-1-(2,6-Dimethylphenoxy)propan-2-amine hydrochloride
Molecular Formula: $C_{11}H_{18}ClNO$
Chemical Structure:




Molecular Weight: 215.7 g/mol
Appearance: White or almost white, crystalline powder.
Solubility: Freely soluble in water and in methanol, sparingly soluble in methylene chloride

Mexiletine hydrochloride 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 PRODUCT

**Pharmaceutical development**
A satisfactory account of the pharmaceutical development has been provided.

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.

With the exception of gelatin, no excipients of animal or human origin are used in the final products.

Confirmation has also been given that the magnesium stearate used in the capsules is of vegetable origin.

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 product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**
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 27 months, with the storage condition 'Store below 30 C' is approved.

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
These applications were submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended, as well-established use applications. No new non-clinical studies were submitted, as the data submitted for these applications are in the form of literature references. The literature review provided is satisfactory.

### III.2 Pharmacology
The non-clinical data from the published literature submitted demonstrated the pharmacodynamic effects of mexiletine both in vitro and in vivo in non-clinical models. The literature review is satisfactory

### III.3 Pharmacokinetics
No new pharmacology data were provided and none were required for these applications.

### III.4 Toxicology
No new pharmacology data were provided and none were required for these applications.

### III.5 Ecotoxicity/Environmental Risk Assessment

An Environmental Risk Assessment (ERA) has been provided. The results of the ERA show that there is no risk of increased environmental exposure with the use of these products.

### III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of mexiletine hydrochloride are well known. As mexiletine hydrochloride is a well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The grant of marketing authorisations is recommended.

## IV CLINICAL ASPECTS

### IV.1 Introduction

Mexiletine has been licensed and used worldwide for many decades. It is a well-known agent, appears in medical literature and relevant clinical guidelines. Also a number of recent publications indicate a continuing scientific interest in its use. In support of the applications, a large number of references together with a Clinical Overview discussing the relevant data on the clinical pharmacology, efficacy and safety of mexiletine were submitted. With the exception of the data from pharmacokinetic bridging study and comparative analyses against relevant literature data, no new clinical studies were made available, as the data submitted for these applications are in the form of literature references. The literature review provided is satisfactory. The study was conducted in-line with current Good Clinical Practice (GCP).

### IV. 2 Pharmacokinetics

Mexiletine is extensively metabolised and formation of its metabolites is mainly mediated by CYP enzymes, particularly CYP2D6. As expected, CYP2D6 genetic polymorphism can affect mexiletine pharmacokinetic (PK), with poor metabolisers showing reduced clearance, and higher exposure to the drug compared to extensive metabolisers. Parameters affecting also other CYP (such as smoking, a CYP1A2 inducing factor) can also impact on mexiletine PK. Elimination of mexiletine is reduced in patients with cirrhosis. Renal impairment generally does not appear to have a significant effect, although the effect of severe renal impairment is unclear. Age is not an important parameter. Weight appears to influence mexiletine PK.

**Bridging data**

In order to support the application, the applicant performed a single-arm pharmacokinetic bridging study to investigate the bioavailability of the test product Mexiletine 200 mg capsules and the results were compared with available literature data for other mexiletine products.

The data from the PK study indicated an exposure within the range collected from literature. Other parameters that were also taken into account in the evaluation of the submitted data included the fact that these are immediate release products, mexiletine bioavailability is high and it appears to be highly soluble. In such case formulation differences between products are not expected to play a prominent role. Overall, taking into account the available data and the different parameters, it was concluded that the proposed mexiletine formulations can reasonably be expected to perform in a similar manner as the products used in the literature. Any potential small differences are unlikely to be clinically important given the anticipated use of these medicines in practice.

It was also accepted that the conclusions about the bridging data generated with the proposed 200 mg capsules could be extrapolated to the lower strengths (50 mg and 100 mg).

## IV.3 Pharmacodynamics

The pharmacodynamic properties of mexiletine have been extensively studied. It is classified as a Class 1B antiarrhythmic and its electrophysiologic properties are similar to those of lidocaine. It blocks sodium channels in cardiac myocytes. In patients with normal conduction system, mexiletine appears to have a minimal effect on cardiac impulse generation and propagation. However, this may not be the case in patients with pre-existing conduction defects; depression of the sinus rate, prolongation of sinus node recovery time, decreased conduction velocity and increased effective refractory period of the intraventricular conduction system have been observed. Haemodynamic studies suggest that oral administration of mexiletine, depending on dose, may have a small negative effect on cardiac output (may increase systemic vascular resistance, but no significant negative inotropic effect). Blood pressure and heart rate are not normally affected.

## IV.4 Clinical efficacy

The Efficacy review was based on a large number of published studies which generally support the antiarrhythmic properties of mexiletine in different settings. Despite some limitations in the available evidence, it is accepted that there is sufficient evidence to support the efficacy of mexiletine in preventing premature ventricular contractions (PVCs) and suppressing ventricular arrythmias in different conditions. Yet the impact on long term clinical outcomes is uncertain, and the summary of product characteristics (SmPC) includes a warning that treatment with mexiletine may not prolong life. This is related to the findings of the Cardiac Arrhythmia Suppression Trial [CAST] published in 1989, which showed that suppression of PVCs in post myocardial infarction patients resulted in excessive mortality compared to placebo; although in that study class 1C antiarrhythmics were tested, the warning, extrapolating the findings to the whole class I members, was also included in the originator Mexitil SmPC.

As is the case with other old similar medicines, mexiletine has been surpassed by other antiarrhythmic therapies (medicinal and interventional) but it appears it is still in use in different conditions to suppress ventricular arrhythmias. Mexiletine is mentioned in guidelines among the recommended therapies for the prevention of serious ventricular arrhythmias in certain patients with long QT syndromes.

Overall, the data provided supported the efficacy and safety of mexiletine in the treatment of ventricular arrhythmias and is an effective antiarrhythmic agent which may be useful in the management of certain patients.

## IV.5 Clinical safety

In general, the safety profile of mexiletine is well established. A variety of adverse effects (AEs) affecting different organ systems have been reported including cardiovascular, central nervous system as well as gastrointestinal, musculoskeletal, dermatologic AEs.

The submitted literature covers most key areas and the proposed product information appears to reflect the available safety data.

### 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

Mexiletine has been licensed and used for the treatment of ventricular arrhythmias for many decades. It is a well-known agent, appears in medical literature and relevant clinical guidelines, and there is a continuing scientific interest in its use. The relevant requirements according to Regulation 54 of The Human Medicines Regulation 2012 for confirming a well-established use in the UK are met.

The findings, taking also into account the PK characteristics of mexiletine and its expected clinical use, support that the proposed mexiletine formulations can be expected to perform in a similar manner as the products used in the literature.

In terms of the efficacy and safety data, the applicant submitted a review of a large number of published studies which generally supported the antiarrhythmic properties of the drug in different settings. The applicant has also provided recent published literature to support the efficacy and safety of mexiletine in the treatment of ventricular arrhythmias and reinforce the view that this is an effective antiarrhythmic agent which may be useful in the management of certain patients.

## 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.

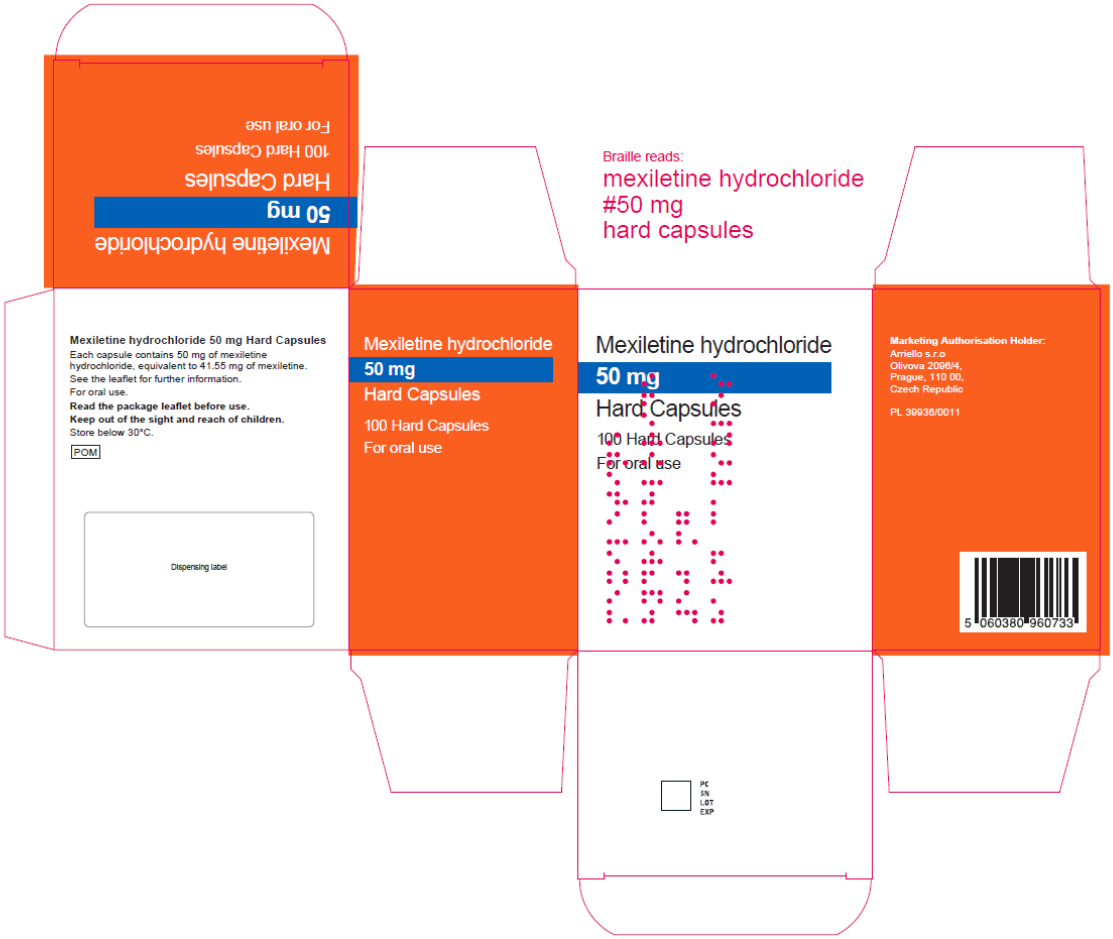
## VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the label at the time of licensing are provide below.


Mexiletine hydrochloride
50 mg
Hard Capsules
100 Hard Capsules
For oral use
Braille reads:
mexiletine hydrochloride
#50 mg
hard capsules
Mexiletine hydrochloride 50 mg Hard Capsules
Each capsule contains 50 mg of mexiletine hydrochloride, equivalent to 41.55 mg of mexiletine.
See the leaflet for further information.
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 30°C.
POM
Dispensing label
Mexiletine hydrochloride
50 mg
Hard Capsules
100 Hard Capsules
For oral use
Mexiletine hydrochloride
50 mg
Hard Capsules
100 Hard Capsules
For oral use
PC
SN
LOT
EXP
Marketing Authorisation Holder:
Arriello s.r.o
Olivova 2096/4,
Prague, 110 00,
Czech Republic
PL 39936/0011
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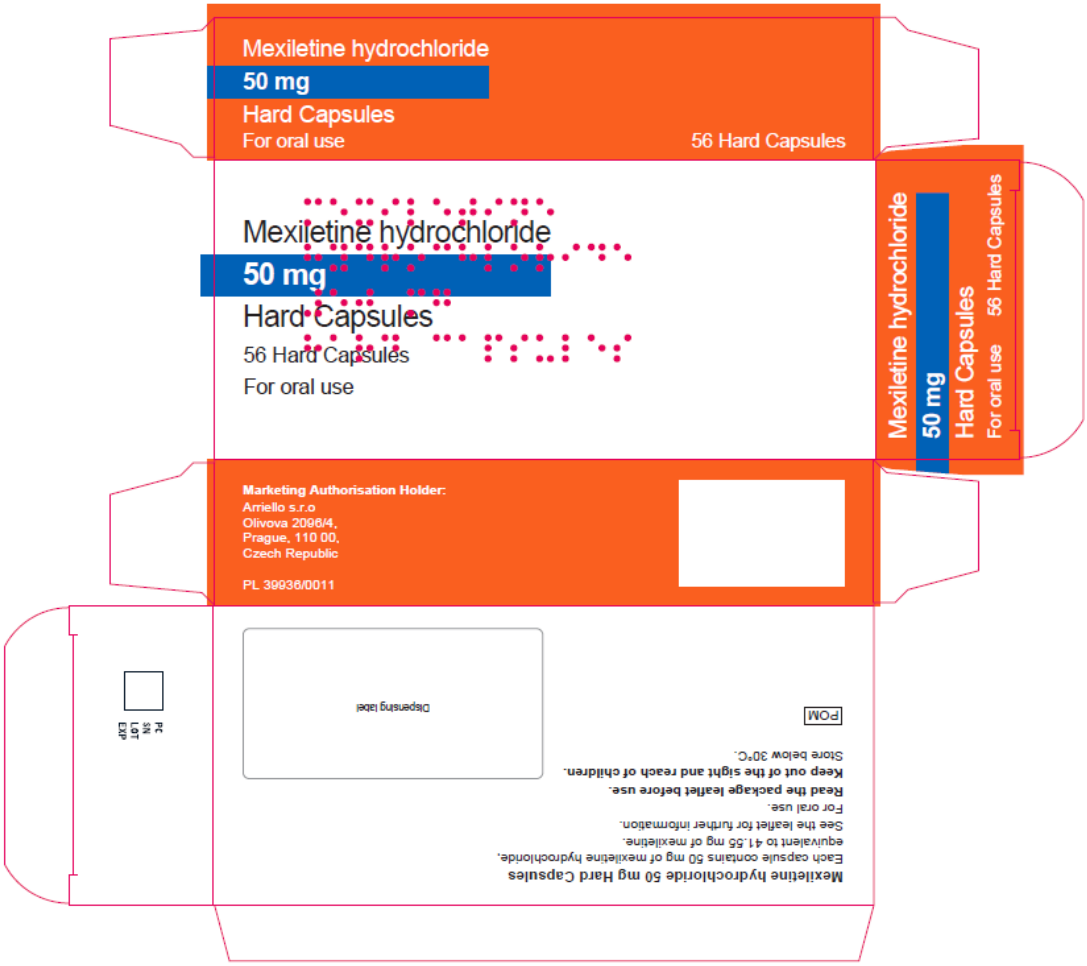
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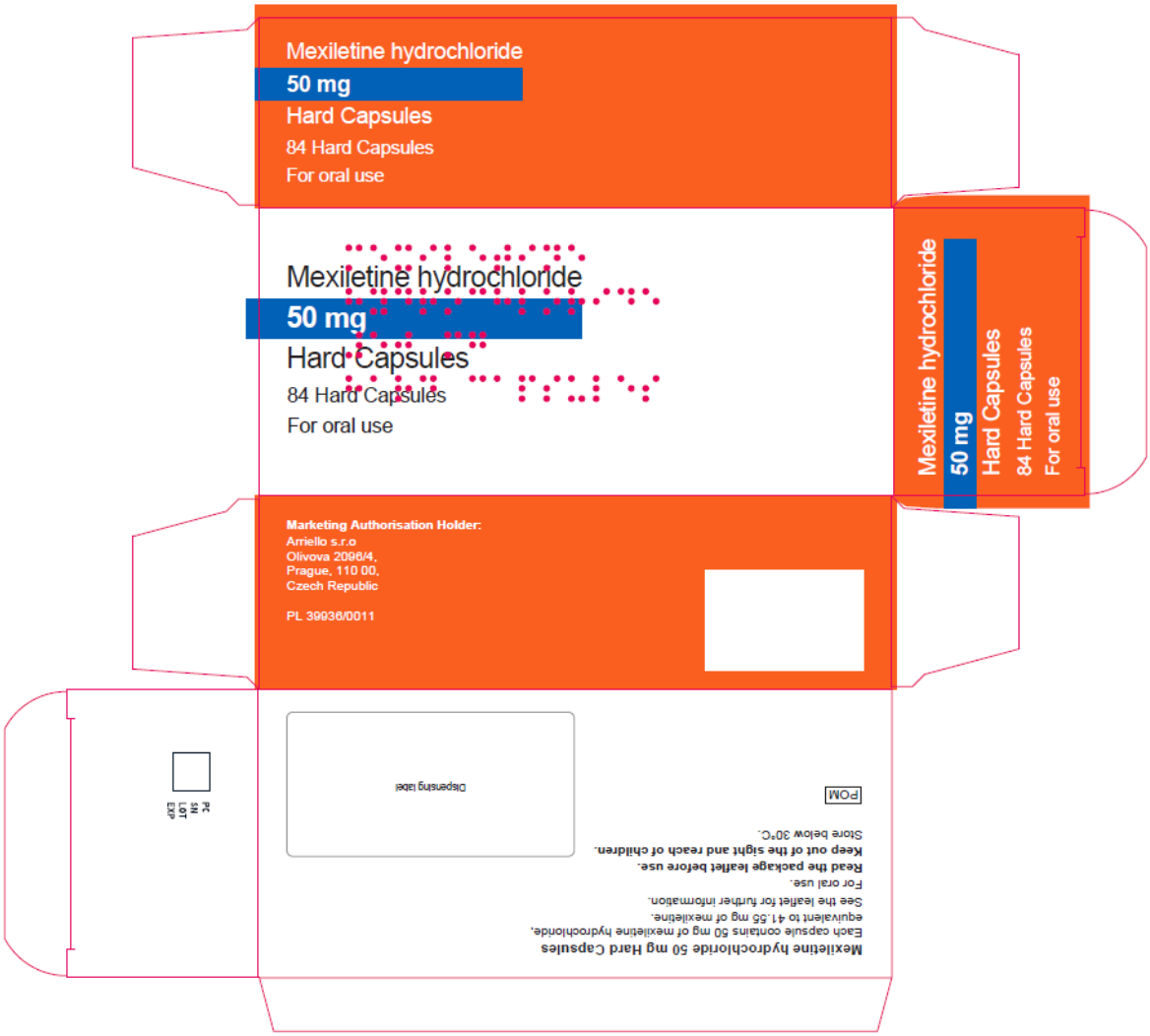
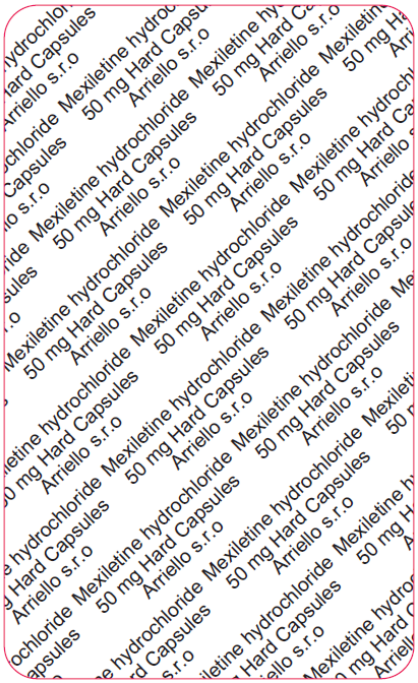
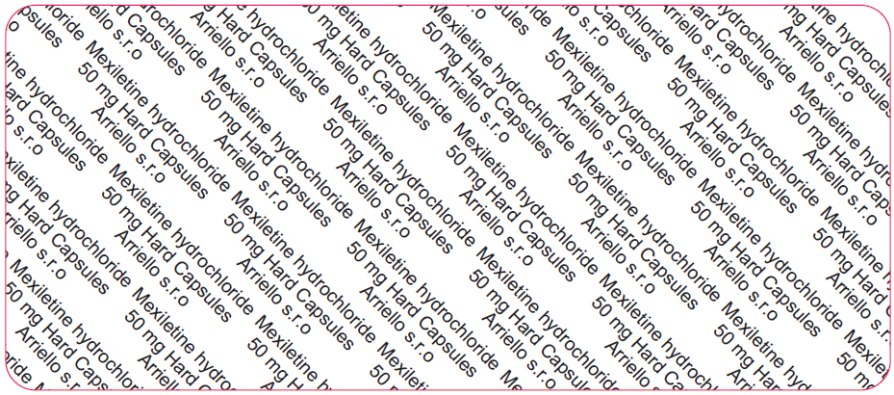
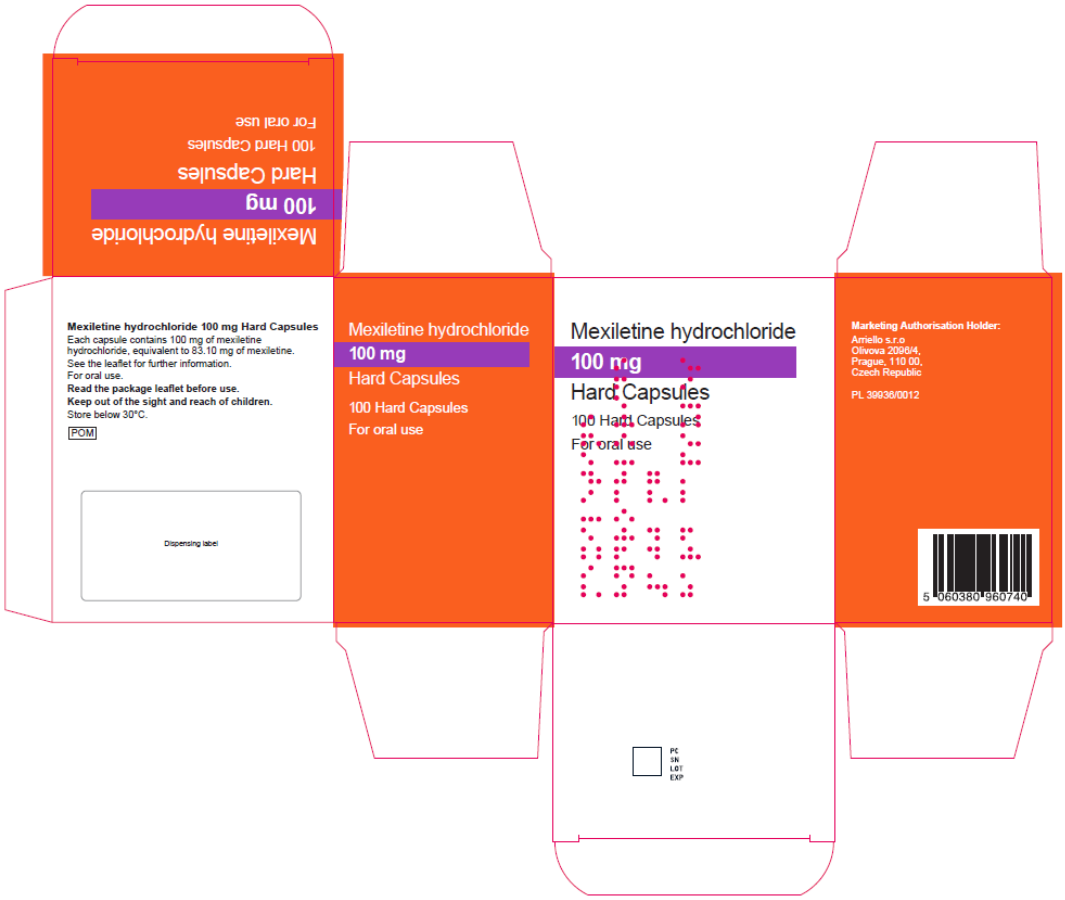



Blister 10 capsules



Blister 14 capsules




Mexiletine hydrochloride
100 mg
Hard Capsules
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For oral use
Mexiletine hydrochloride 100 mg Hard Capsules
Each capsule contains 100 mg of mexiletine hydrochloride, equivalent to 83.10 mg of mexiletine.
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100 mg
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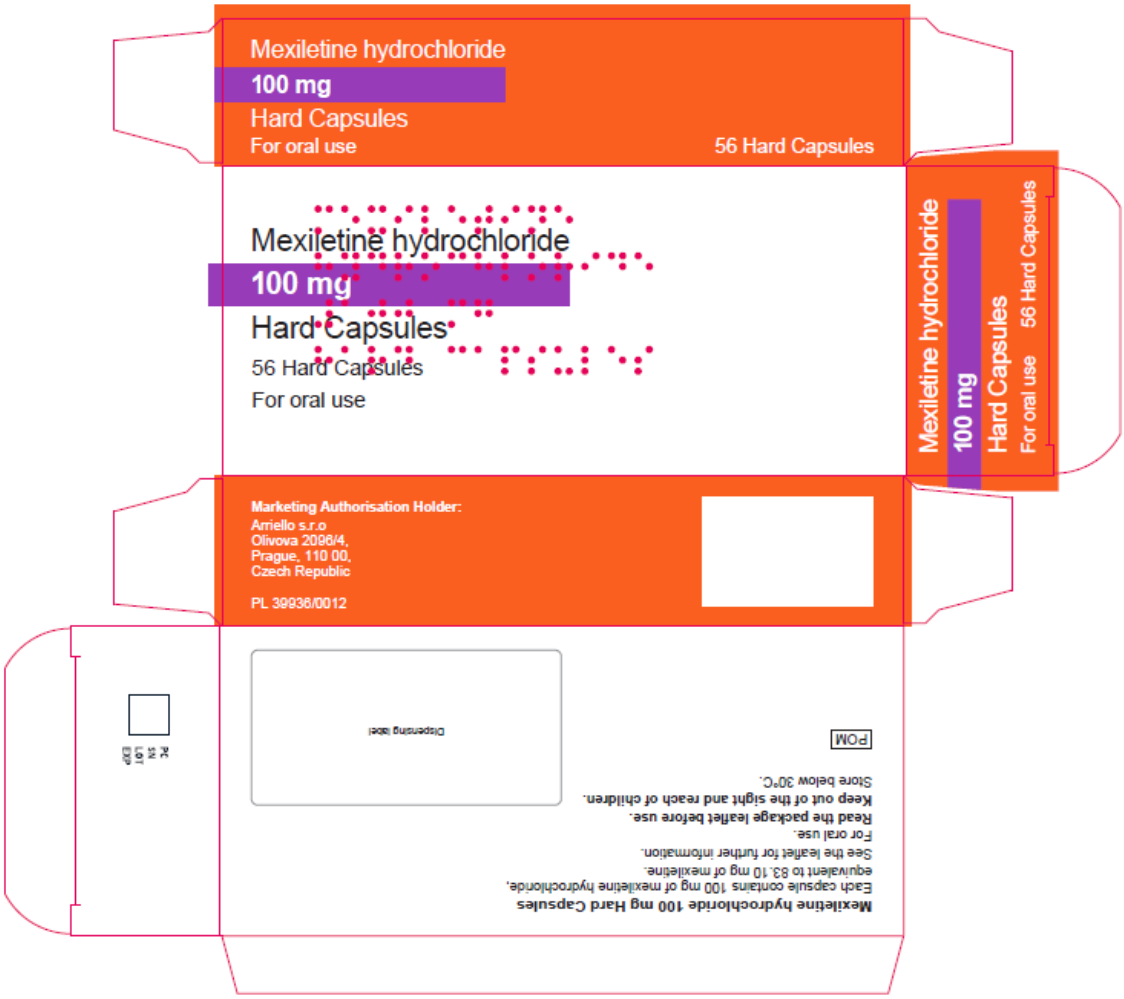
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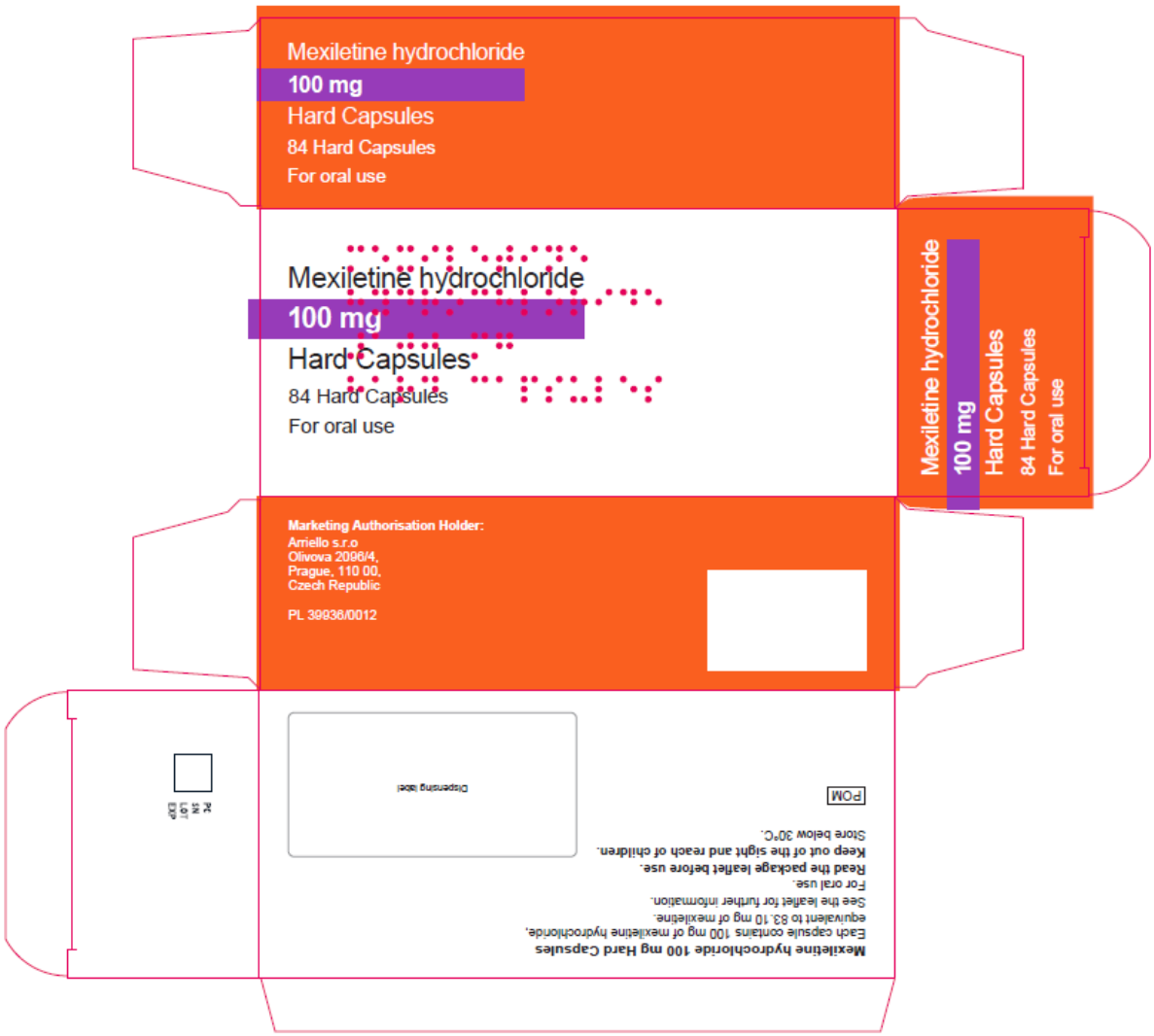
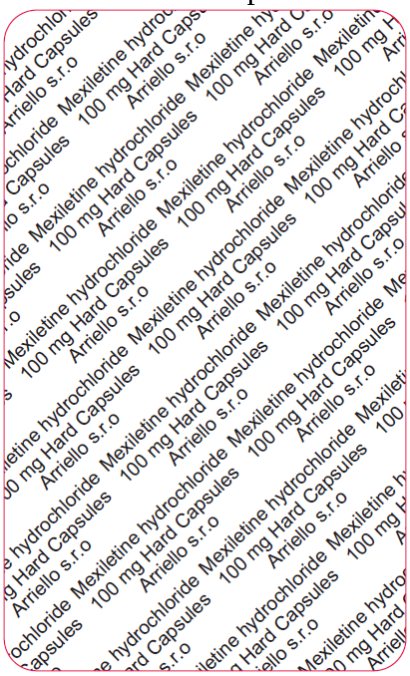
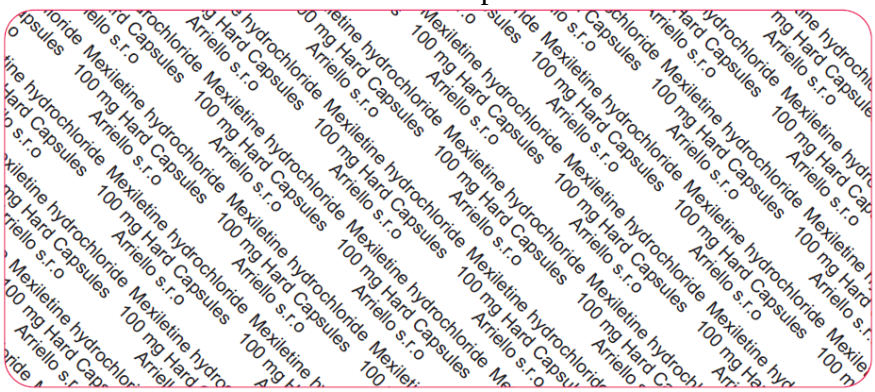
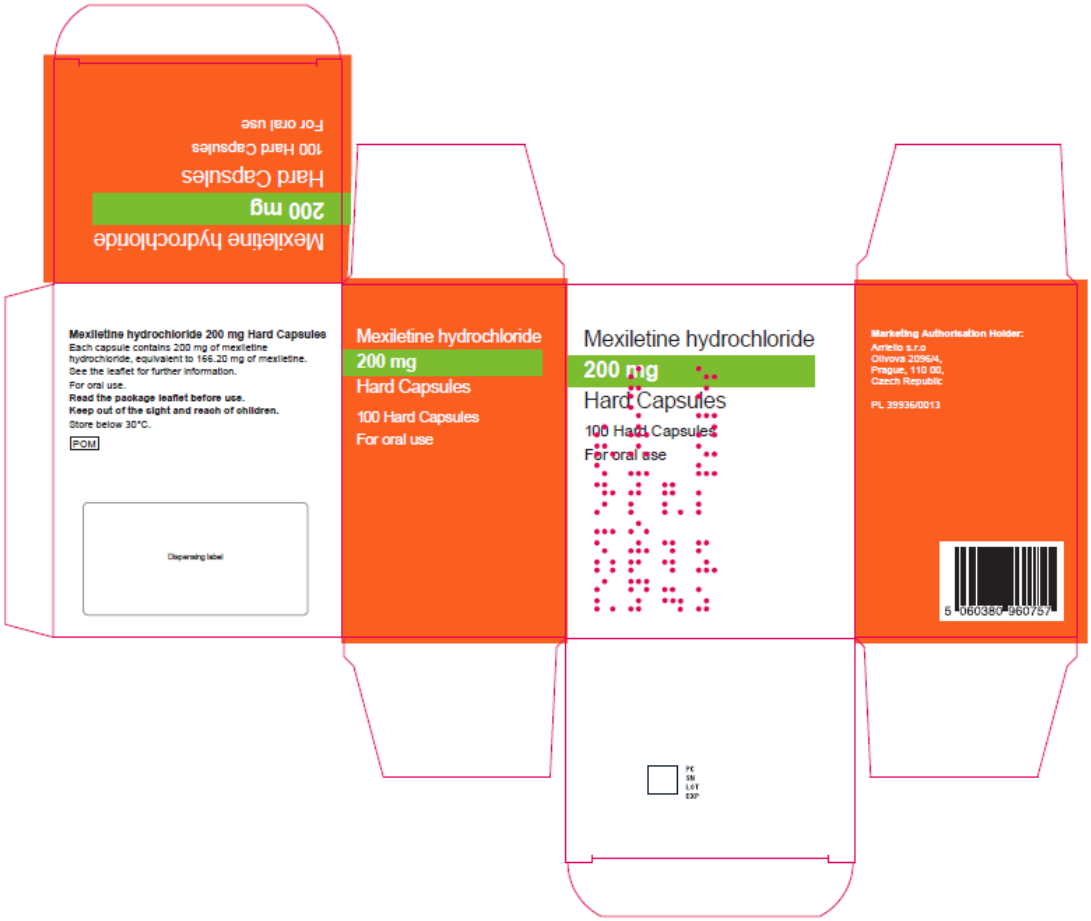



Blister 10 capsules



Blister 14 capsules

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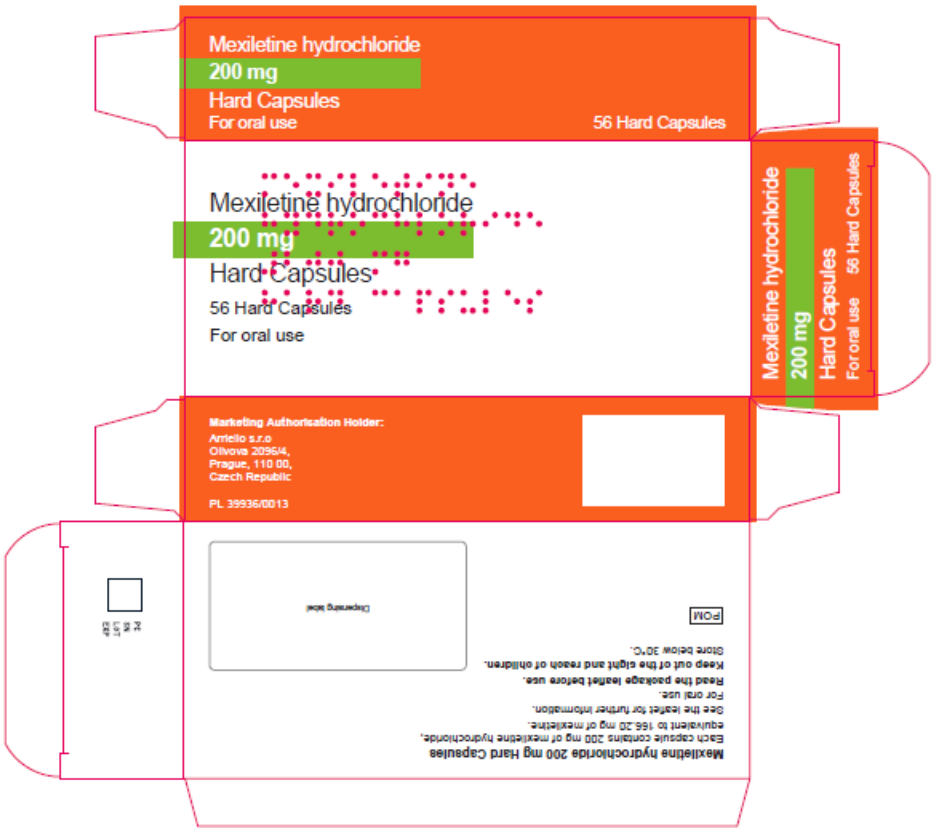
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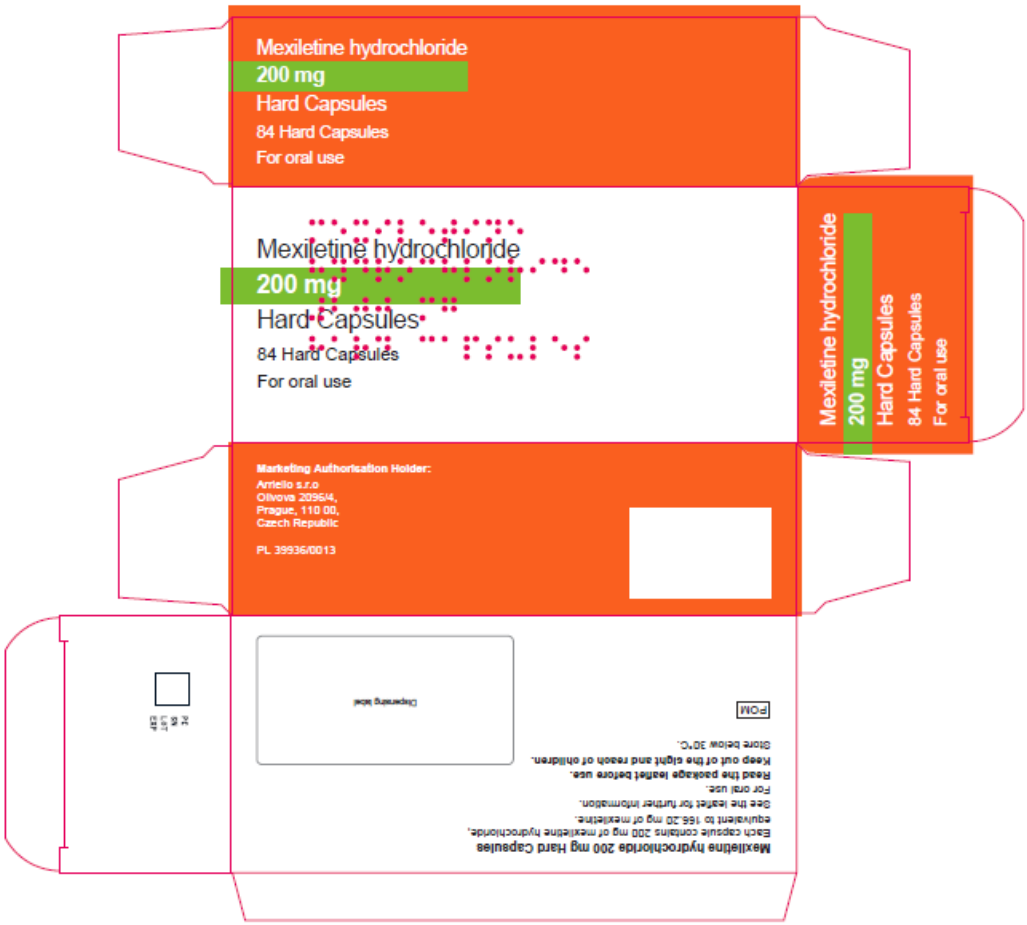
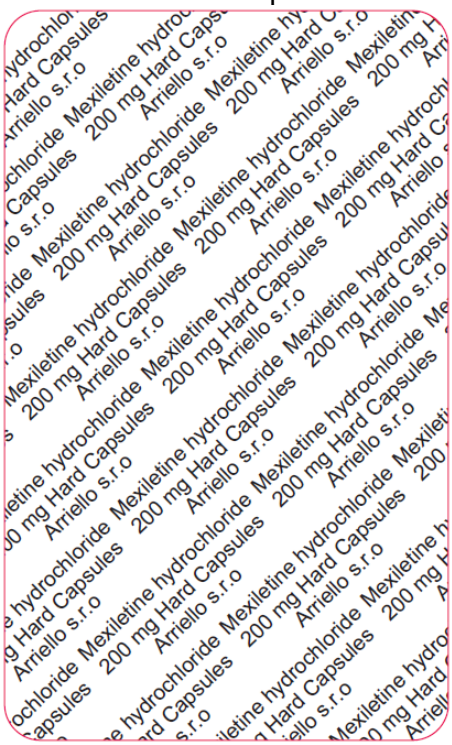
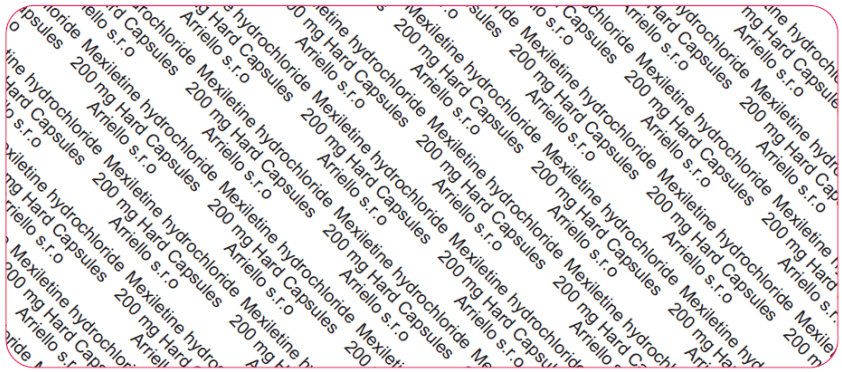
Dispensing label
POM




Blister 10 capsules




Blister 14 capsules



## 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** |
|---|---|---|---|---|---|
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