Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Ontozry 12.5 mg tablets
Ontozry 25 mg film-coated tablets
Ontozry 50 mg film-coated tablets
Ontozry 100 mg film-coated tablets
Ontozry 150 mg film-coated tablets
Ontozry 200 mg film-coated tablets
Treatment initiation pack(Ontozry 12.5 mg tablets and Ontozry 25 mg film-coated tablets)

(cenobamate)

PLGB 53287/0001 - 0007

Arvelle Therapeutics Netherlands B.V.

LAY SUMMARY

Ontozry 12.5 mg tablets, 25, 50, 100, 150, 200 mg film-coated tablets and 12.5 mg/25 mg treatment initiation pack (cenobamate)

This is a summary of the Public Assessment Report (PAR) for Ontozry 12.5 mg tablets, 25, 50, 100, 150, 200mg film-coated tablets and 12.5 mg/25 mg treatment initiation pack. 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 Ontozry in this lay summary for ease of reading.

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

These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 26 March 2021 (EMEA/H/C/005377/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

These applications are full-dossier applications. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that these medicines are suitable for treating the specified indications.

Ontozry is used to treat epilepsy, a condition where someone has seizures or fits because of abnormal activity in the brain. Ontozry is used in combination with other antiepileptic medicines in adult patients with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic products, to treat a type of epilepsy that has focal-onset seizures with or without secondary generalisation. Focal-onset seizures are those caused by abnormal brain activity starting in a part of the brain on one side, and secondary generalisation means that that the abnormal activity is spreading to both sides of the brain. These medicines can be used only in adults.

How does Ontozry work?

Epilepsy is caused by abnormal electrical activity in the brain. The exact way in which Ontorzy works is unclear but it affects the activity of channels that allow electrical impulses to be transmitted between nerve cells. This may prevent abnormal electrical activity in the brain, reducing the chance of an epileptic fit.

How is Ontozry used?

The pharmaceutical forms of these medicines are tablet and film-coated tablet and the route of administration is oral (via the mouth). Swallow the tablets whole with a glass of water. Do not break the tablets in half because the tablets are not suitable for splitting into two equal halves.

The patient will take Ontozry with other medicines to treat epilepsy.

Recommended dosage
The patient will start Ontozry with a daily dose of one 12.5 mg tablet for the first 2 weeks, followed by one 25 mg tablet once a day for the next 2 weeks. Then their dose will be gradually adjusted every 2 weeks until they reach the dose that works best. The patient's doctor will work out the right daily dose for them and may need to adjust it over time.

The recommended daily dose is between 200 mg and 400 mg once daily.

Method of use
Take the recommended dose once a day at around the same time. Ontozry can be taken at any time either during the day or in the evening, with food or between meals.

For further information on how Ontozry is 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 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 of Ontozry have been shown in studies?
In a main study involving 437 patients Ontorzy was more effective than placebo (a dummy treatment) at lowering the number of seizures in patients with uncontrolled partial seizures despite past treatment. Around 40% of patients who took a 100 mg daily dose of Ontorzy during 3 months of treatment and 64% of those who took a 400 mg daily dose had at least a 50% drop in the frequency of their seizures. This compares with 26% of patients taking placebo.

What are the possible side effects of Ontozry?
For the full list of all side effects reported with 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 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 Ontorzy (which may affect more than 1 in 10 people) are:
- feeling sleepy (somnolence), sedated or very tired (fatigue)
- feeling dizzy
- spinning sensation (vertigo)
- having problems with coordination of movements, having problems walking or keeping your balance (ataxia, gait disturbance,
abnormal coordination)
- headache

Why was Ontozry approved?

It was concluded that Ontozry has been shown to be effective for the treatment of epilepsy, when used in combination with other antiepileptic medicines in adult patients who have not been adequately controlled despite treatment with at least 2 anti-epileptic products, to treat a type of epilepsy that has focal-onset seizures with or without secondary generalisation.

Furthermore, the side effects observed with use of these products are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that these medicines can be approved for use.

What measures are being taken to ensure the safe and effective use of Ontozry?

A Risk Management Plan (RMP) has been developed to ensure that Ontozry is 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.

These medicinal products are black triangle products which are denoted by the symbol ▼. This means they are subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Ontozry

Marketing authorisations were granted in Great Britain on 04 June 2021.

The full PAR for Ontozry follows this summary.

This summary was last updated in July 2021.

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 Ontozry 12.5 mg tablets, 25, 50, 100, 150, 200 mg film-coated tablets and 12.5 mg/25 mg treatment initiation pack (PLGB 53287/0001 - 0007) could be approved.

Ontozry is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic medicinal products.

Cenobamate is a small molecule with a dual mechanism of action. It is a positive allosteric modulator of subtypes of the γ-aminobutyric acid ($GABA_A$) ion channel, that does not bind to the benzodiazepine binding site. Cenobamate has also been shown to reduce repetitive neuronal firing by enhancing the inactivation of sodium channels and by inhibiting the persistent component of the sodium current. The precise mechanism of action by which cenobamate exercises its therapeutic effects in patients with focal-onset seizures is unknown.

These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 26 March 2021 (EMEA/H/C/005377/0000), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

These applications were approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) P/0120/2020.

At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

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 were granted on 04 June 2021.

II. ASSESSOR'S COMMENTS ON THE PRODUCT INFORMATION SUMMARIES OF PRODUCT CHARACTERITICS (SmPCs)

The SmPCs are in line with current guidelines and are satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with current guidelines and is satisfactory.

LABEL
The labelling is in line with current guidelines and is satisfactory.

QUALITY ASPECTS
MHRA considered that the quality data submitted for these applications is satisfactory.

The grant of marketing authorisations is recommended.

III. NON-CLINICAL ASPECTS
MHRA considered that the non-clinical data submitted for these applications is satisfactory.

The grant of marketing authorisations are recommended.

IV. CLINICAL ASPECTS
MHRA considered that the clinical data submitted for these applications is satisfactory.

The grant of marketing authorisations is recommended.

V. 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 shall perform the required pharmacovigilance activities and interventions detailed in the submitted RMP and any other agreed subsequent updates of the RMP. This is acceptable.

VI. 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.

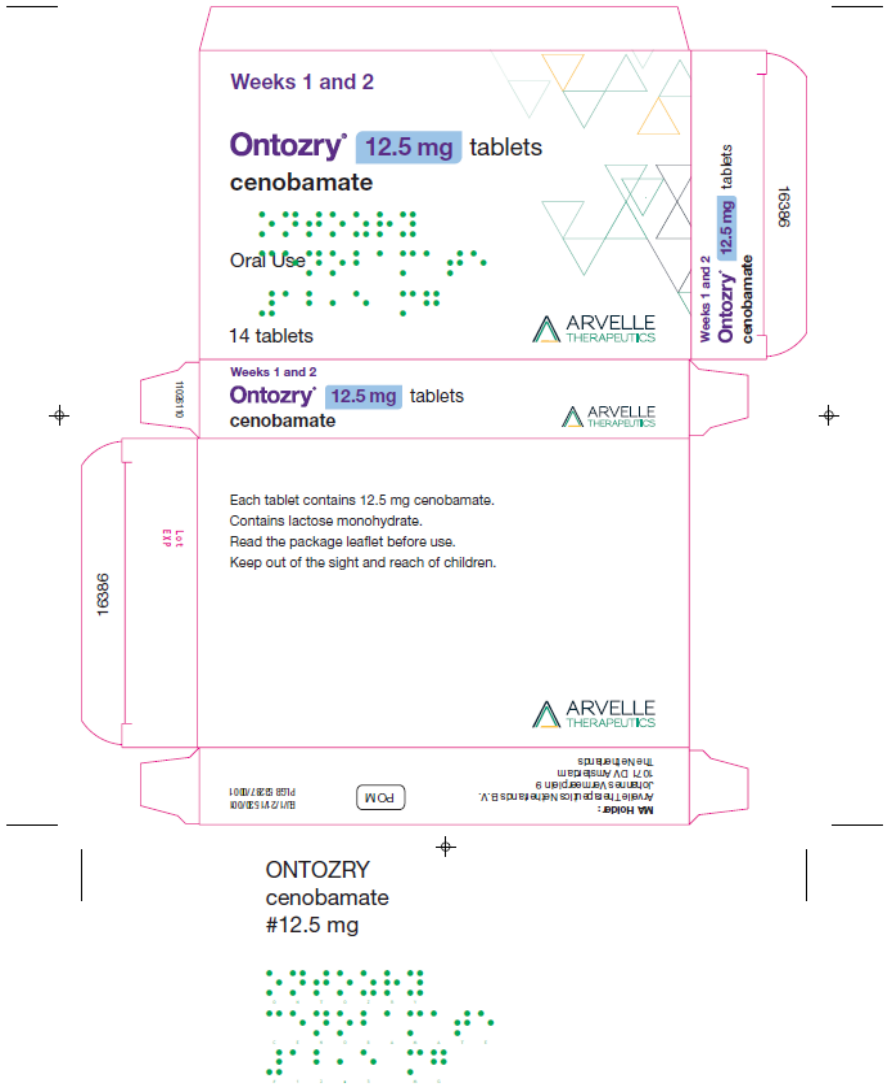
VII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory.

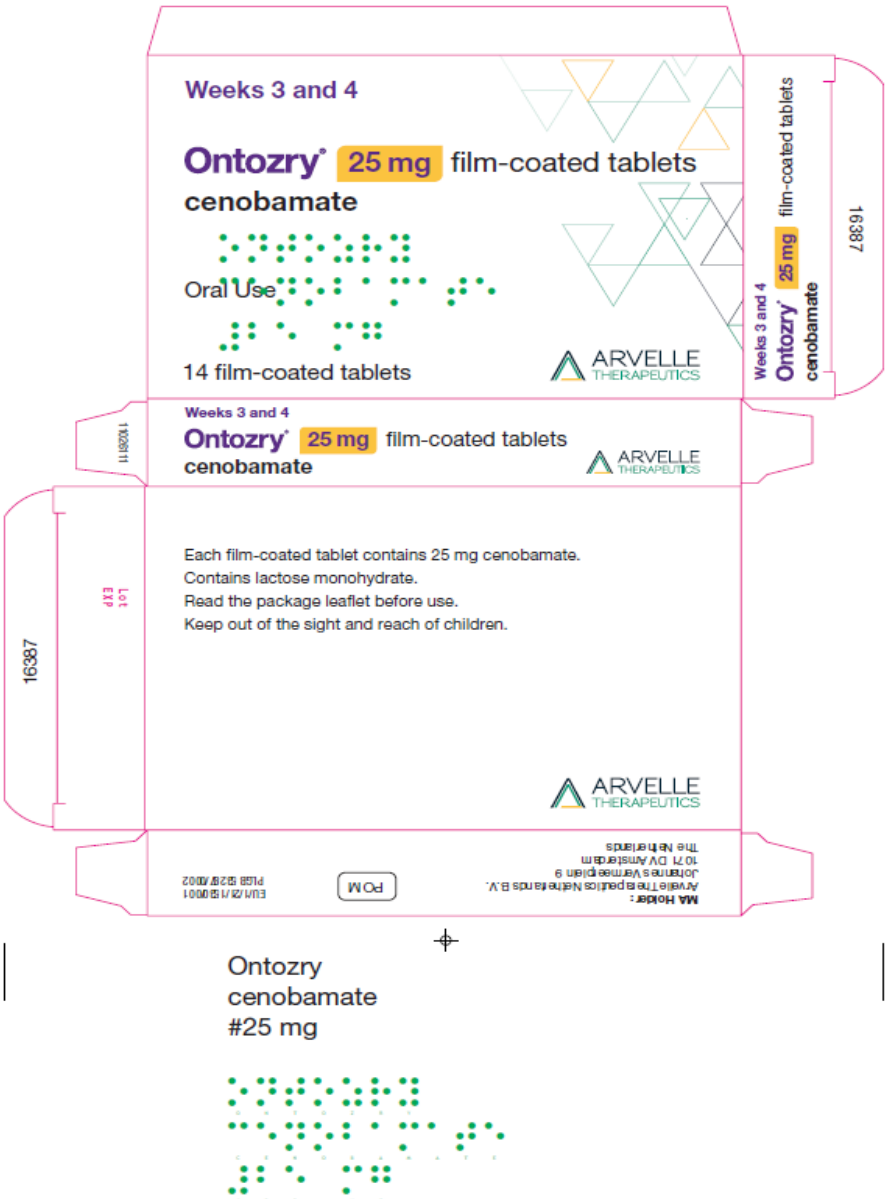
In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

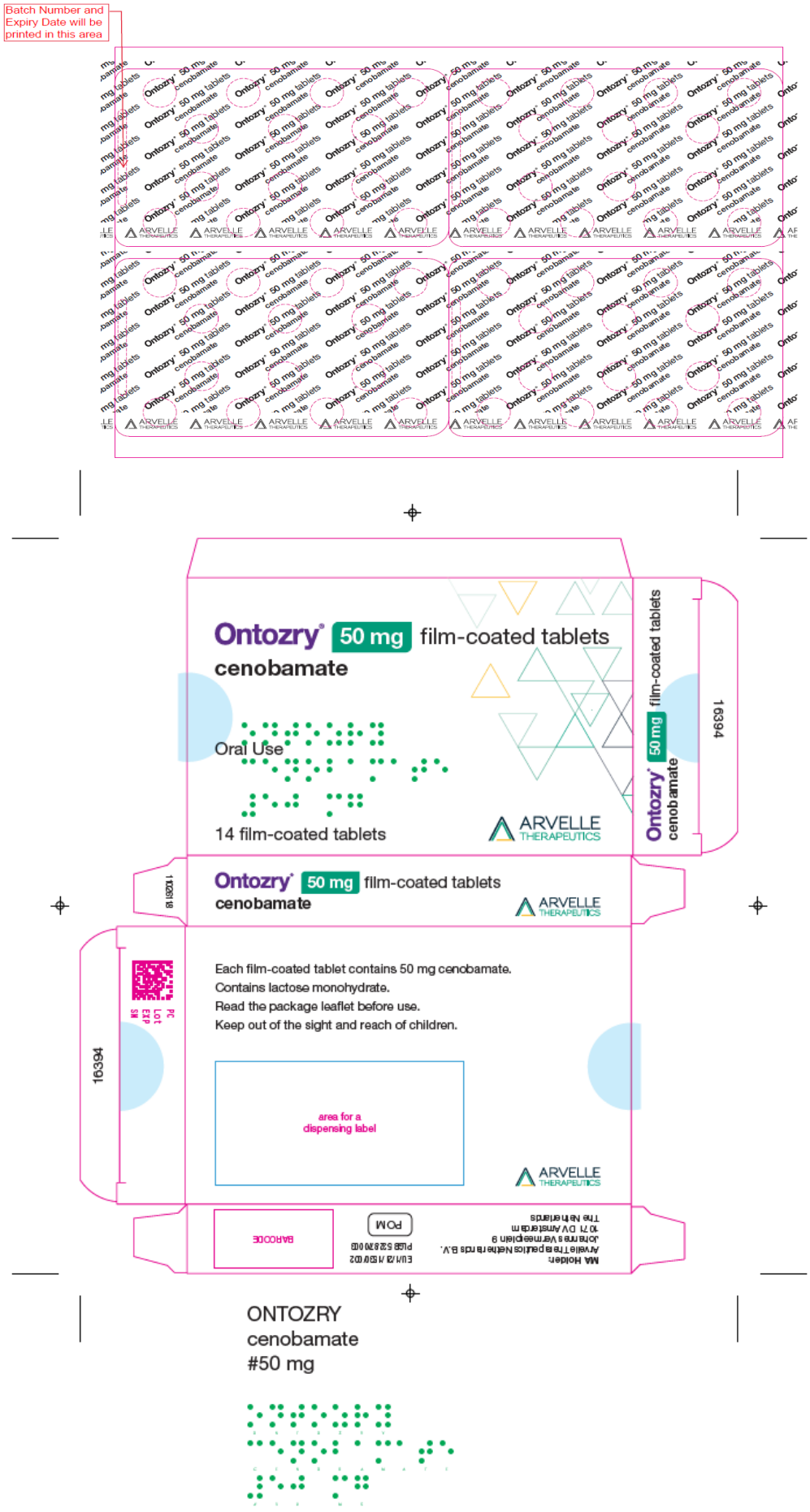
Representative copies of the labels at the time of UK licensing are provided below.

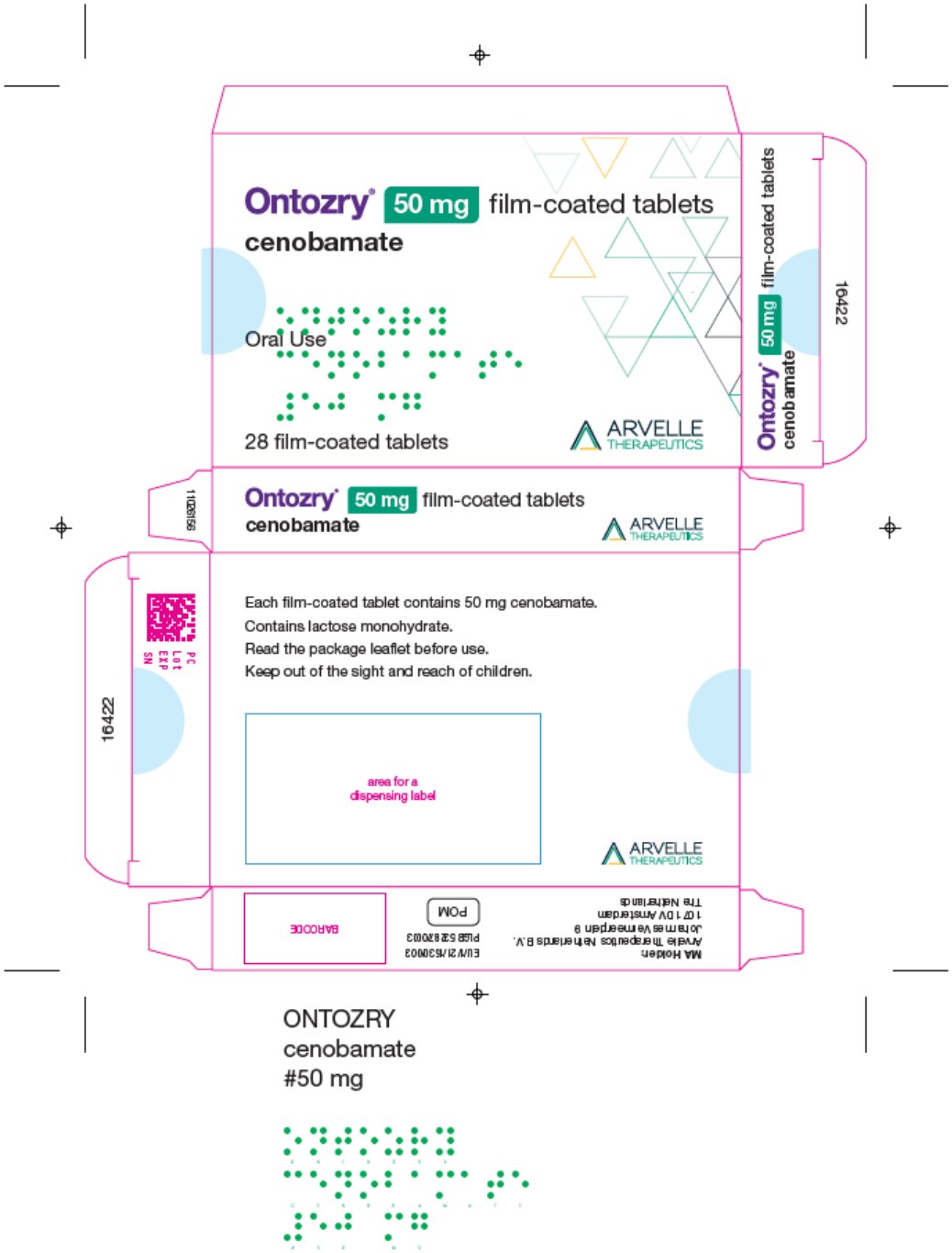

Batch Number and Expiry Date will be printed in this area


Weeks 1 and 2
Ontozry® 12.5 mg tablets
cenobamate
Oral Use
14 tablets
ARVELLE THERAPEUTICS
Weeks 1 and 2 Ontozry® 12.5 mg tablets cenobamate
16386
Weeks 1 and 2
Ontozry® 12.5 mg tablets
cenobamate
ARVELLE THERAPEUTICS
Each tablet contains 12.5 mg cenobamate.
Contains lactose monohydrate.
Read the package leaflet before use.
Keep out of the sight and reach of children.
ARVELLE THERAPEUTICS
16386
Lot EXP
POM
ONTOZRY
cenobamate
#12.5 mg

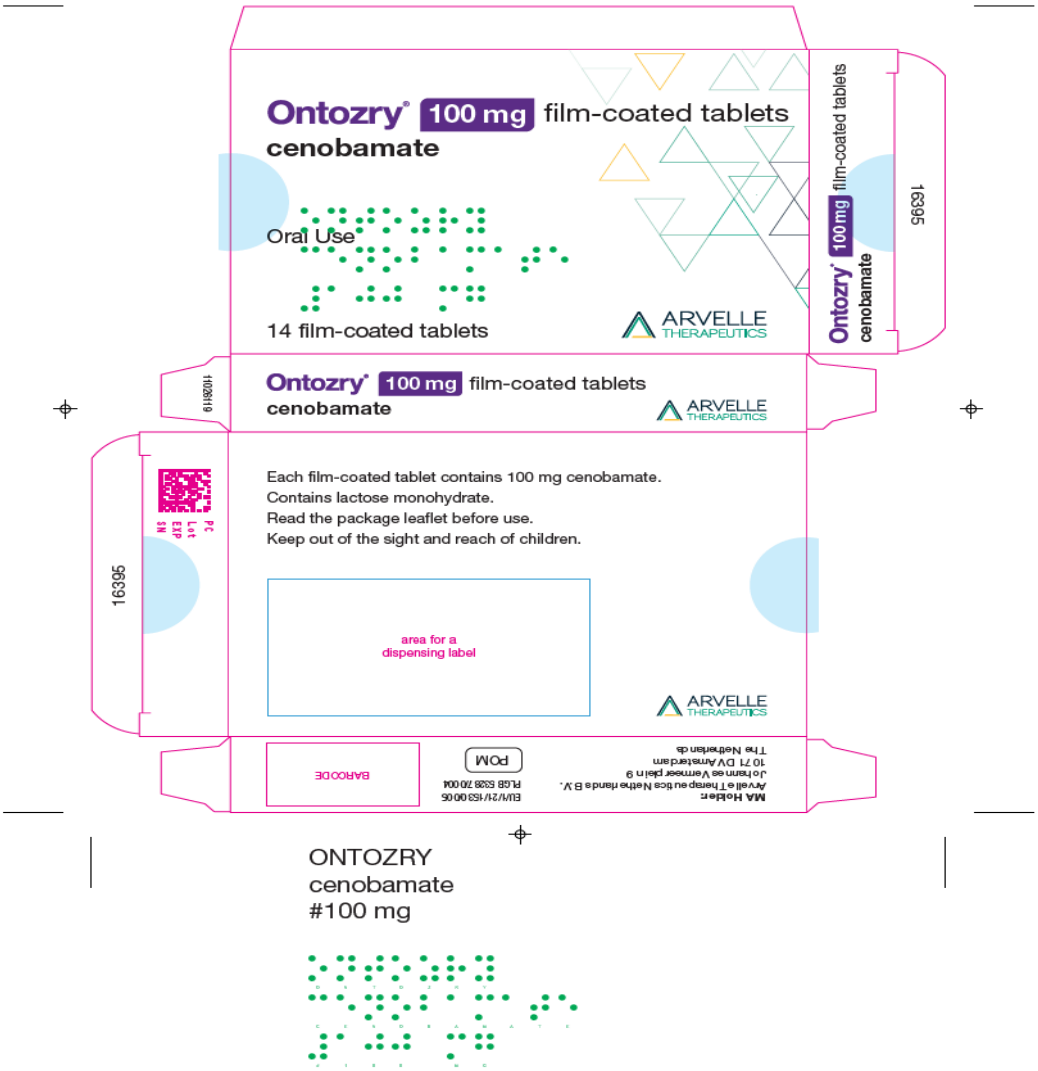

Batch Number and Expiry Date will be printed in this area

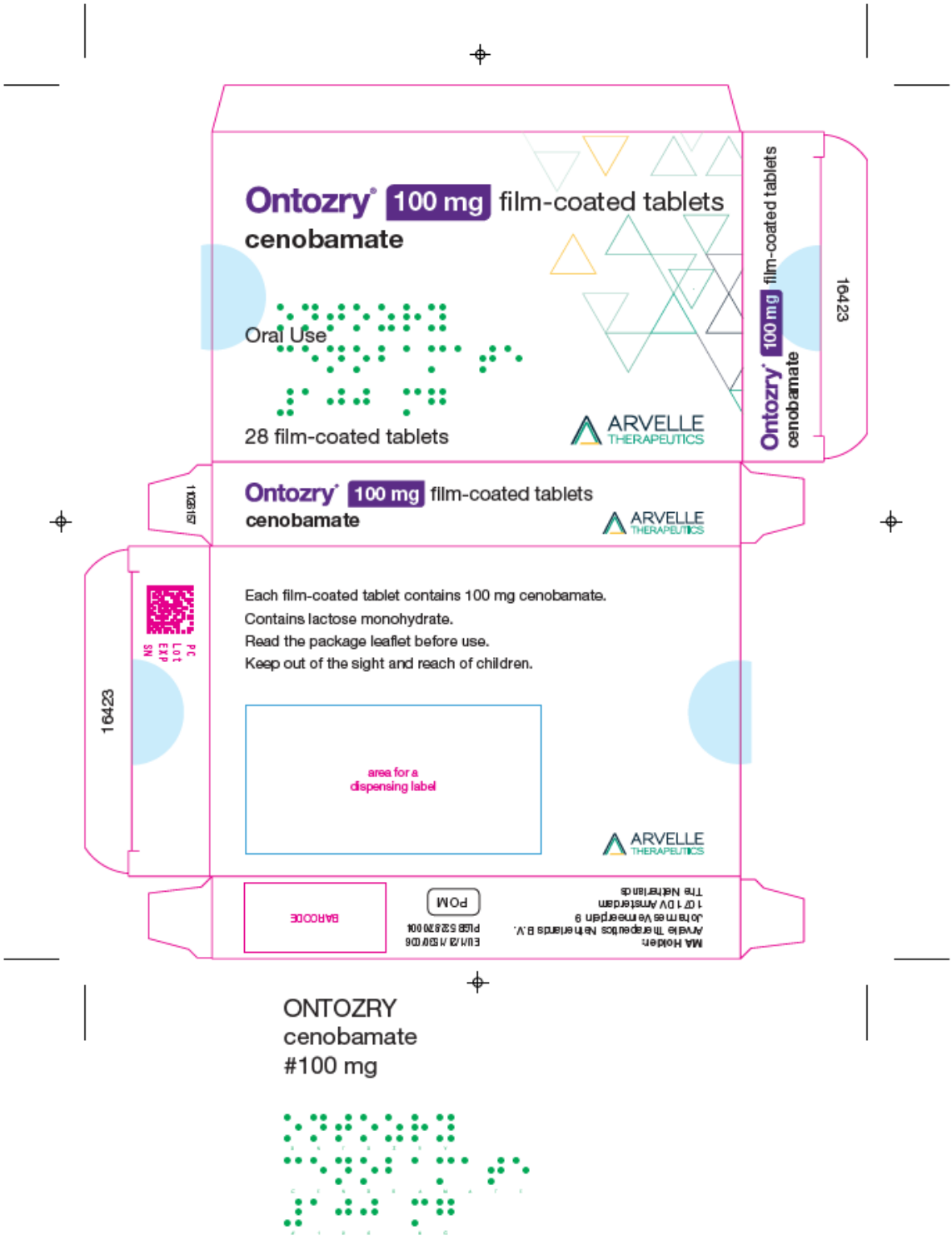

Weeks 3 and 4
Ontozry® 25 mg film-coated tablets
cenobamate
Oral Use
14 film-coated tablets
ARVELLE THERAPEUTICS
Weeks 3 and 4
Ontozry® 25 mg film-coated tablets
cenobamate
16387
Weeks 3 and 4
Ontozry® 25 mg film-coated tablets
cenobamate
ARVELLE THERAPEUTICS
Each film-coated tablet contains 25 mg cenobamate.
Contains lactose monohydrate.
Read the package leaflet before use.
Keep out of the sight and reach of children.
16387
ARVELLE THERAPEUTICS
PoM
Ontozry
cenobamate
#25 mg


Batch Number and Expiry Date will be printed in this area
Ontozry 50 mg film-coated tablets
cenobamate
Oral Use
14 film-coated tablets
ARVELLE THERAPEUTICS
Ontozry 50 mg film-coated tablets
cenobamate
16394
Each film-coated tablet contains 50 mg cenobamate.
Contains lactose monohydrate.
Read the package leaflet before use.
Keep out of the sight and reach of children.
area for a dispensing label
BARCODE
POM
ONTOZRY
cenobamate
#50 mg

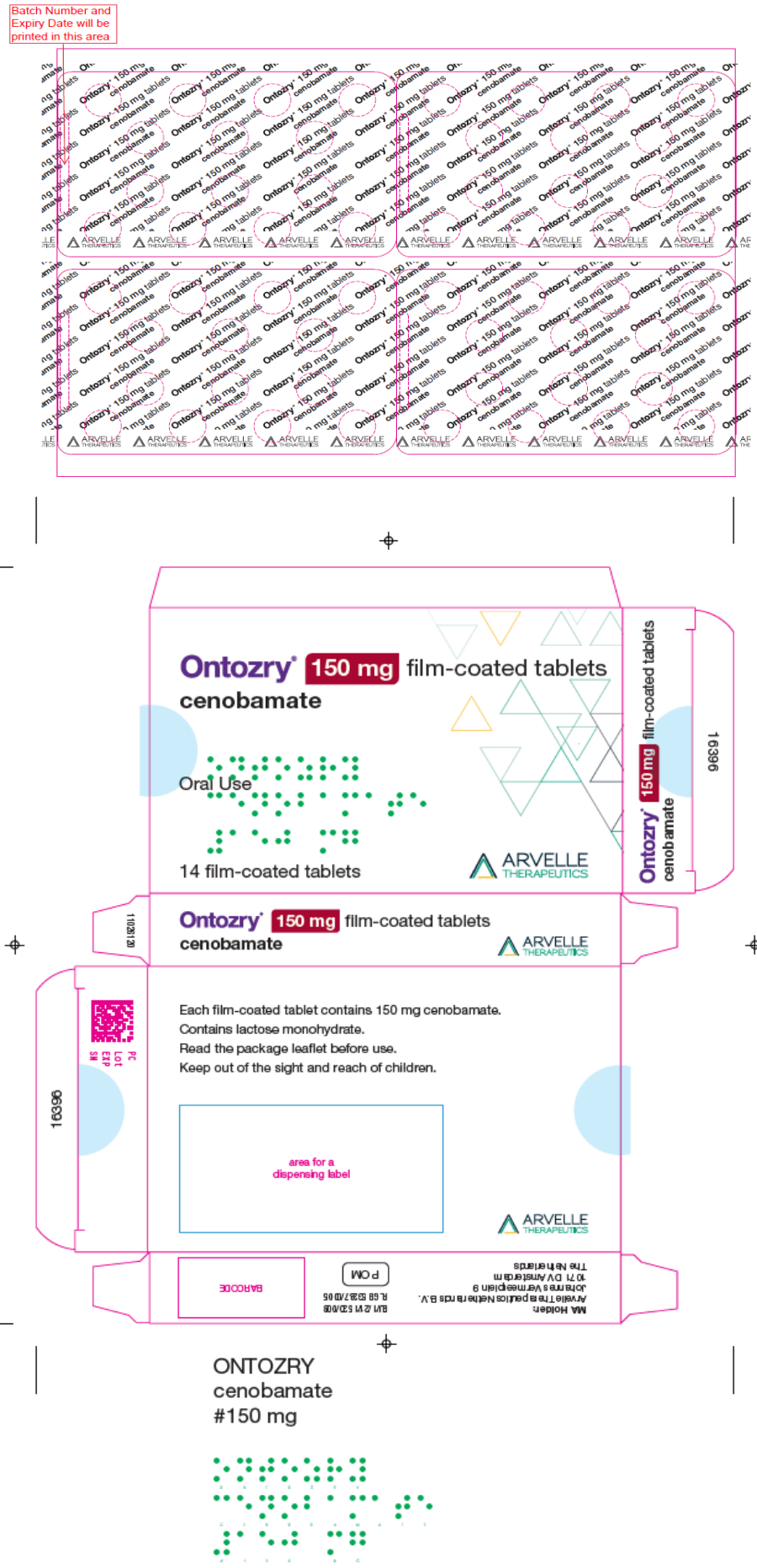

Ontozry® 50 mg film-coated tablets
cenobamate
Oral Use
28 film-coated tablets
ARVELLE THERAPEUTICS
Ontozry® 50 mg film-coated tablets
cenobamate
16422
Ontozry® 50 mg film-coated tablets
cenobamate
ARVELLE THERAPEUTICS
Each film-coated tablet contains 50 mg cenobamate.
Contains lactose monohydrate.
Read the package leaflet before use.
Keep out of the sight and reach of children.
area for a dispensing label
ARVELLE THERAPEUTICS
16422
BARCODE
POM
MA Holder:
Arvelle Therapeutics Netherlands B.V.
Joan Muyskenweg 9
1 07 1 DV Amsterdam
The Netherlands
ONTOZRY
cenobamate
#50 mg

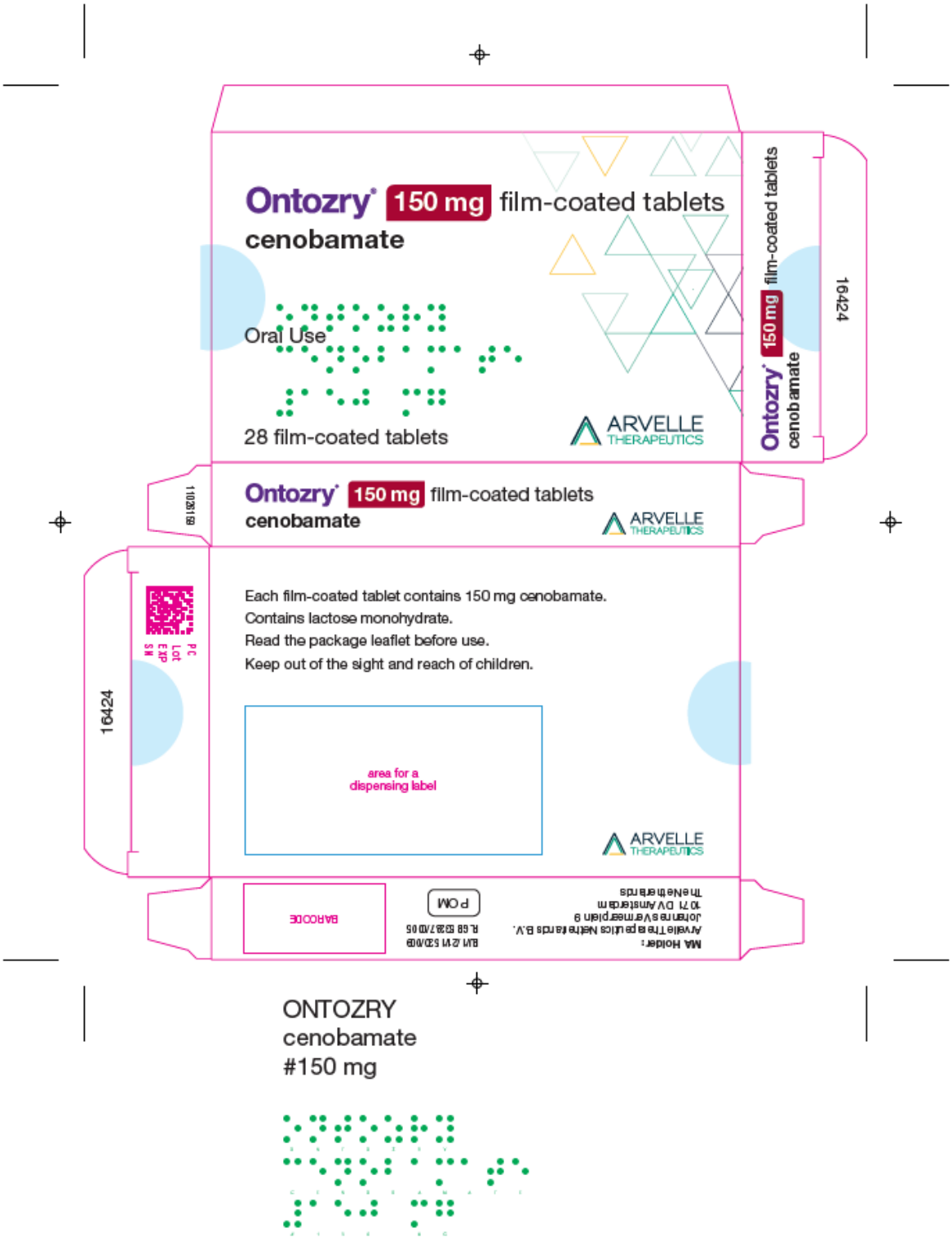

Batch Number and Expiry Date will be printed in this area
Ontozry 100 mg tablets
cenobamate
ARVELLE THERAPEUTICS


Ontozry 100 mg film-coated tablets
cenobamate
Oral Use
14 film-coated tablets
ARVELLE THERAPEUTICS
Ontozry 100 mg film-coated tablets
cenobamate
16395
Ontozry 100 mg film-coated tablets
cenobamate
ARVELLE THERAPEUTICS
Each film-coated tablet contains 100 mg cenobamate.
Contains lactose monohydrate.
Read the package leaflet before use.
Keep out of the sight and reach of children.
area for a dispensing label
16395
BARCODE
POM
ONTOZRY
cenobamate
#100 mg

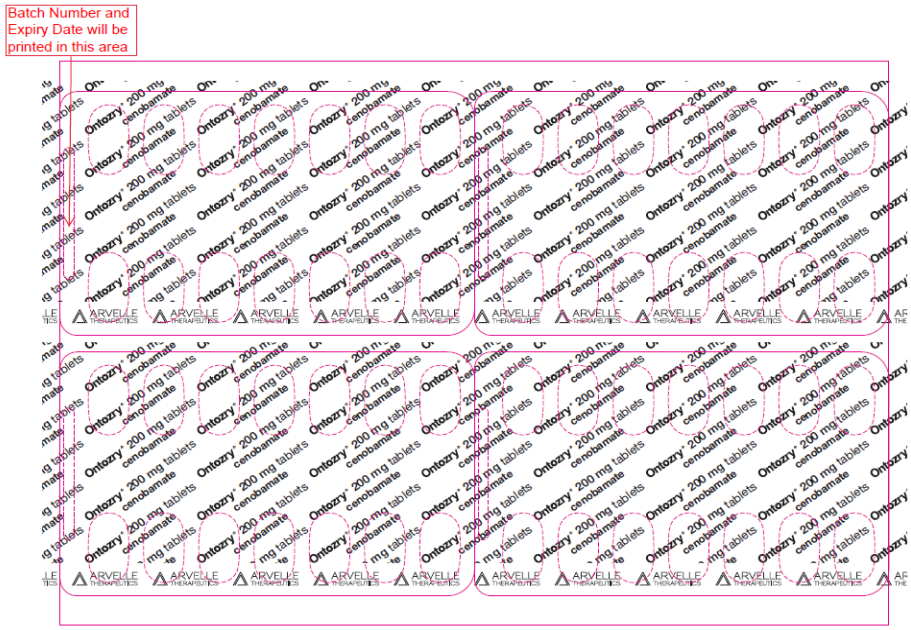


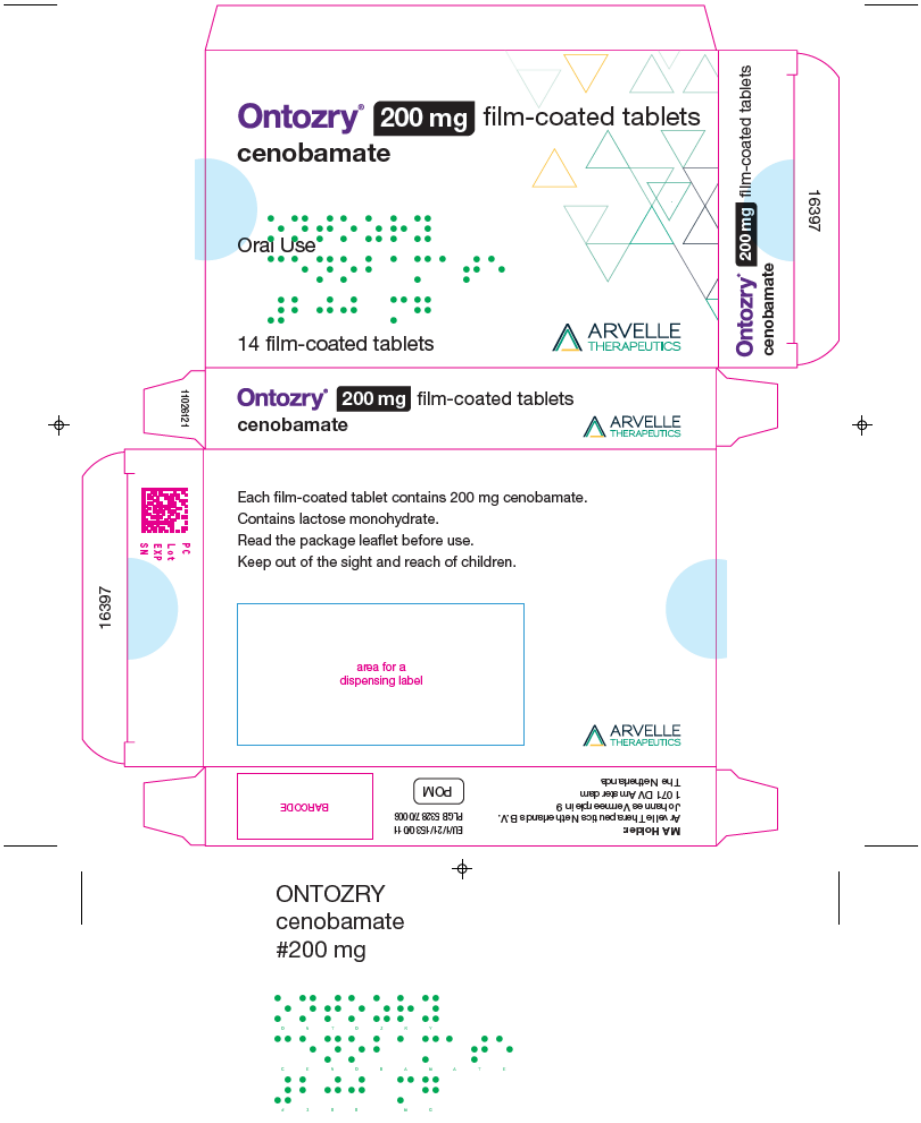
ONTOZRY
cenobamate
#100 mg


Batch Number and Expiry Date will be printed in this area
Ontozry 150 mg film-coated tablets
cenobamate
Oral Use
14 film-coated tablets
ARVELLE THERAPEUTICS
16396
Each film-coated tablet contains 150 mg cenobamate.
Contains lactose monohydrate.
Read the package leaflet before use.
Keep out of the sight and reach of children.
area for a dispensing label
BARCODE
PCM
ONTOZRY
cenobamate
#150 mg

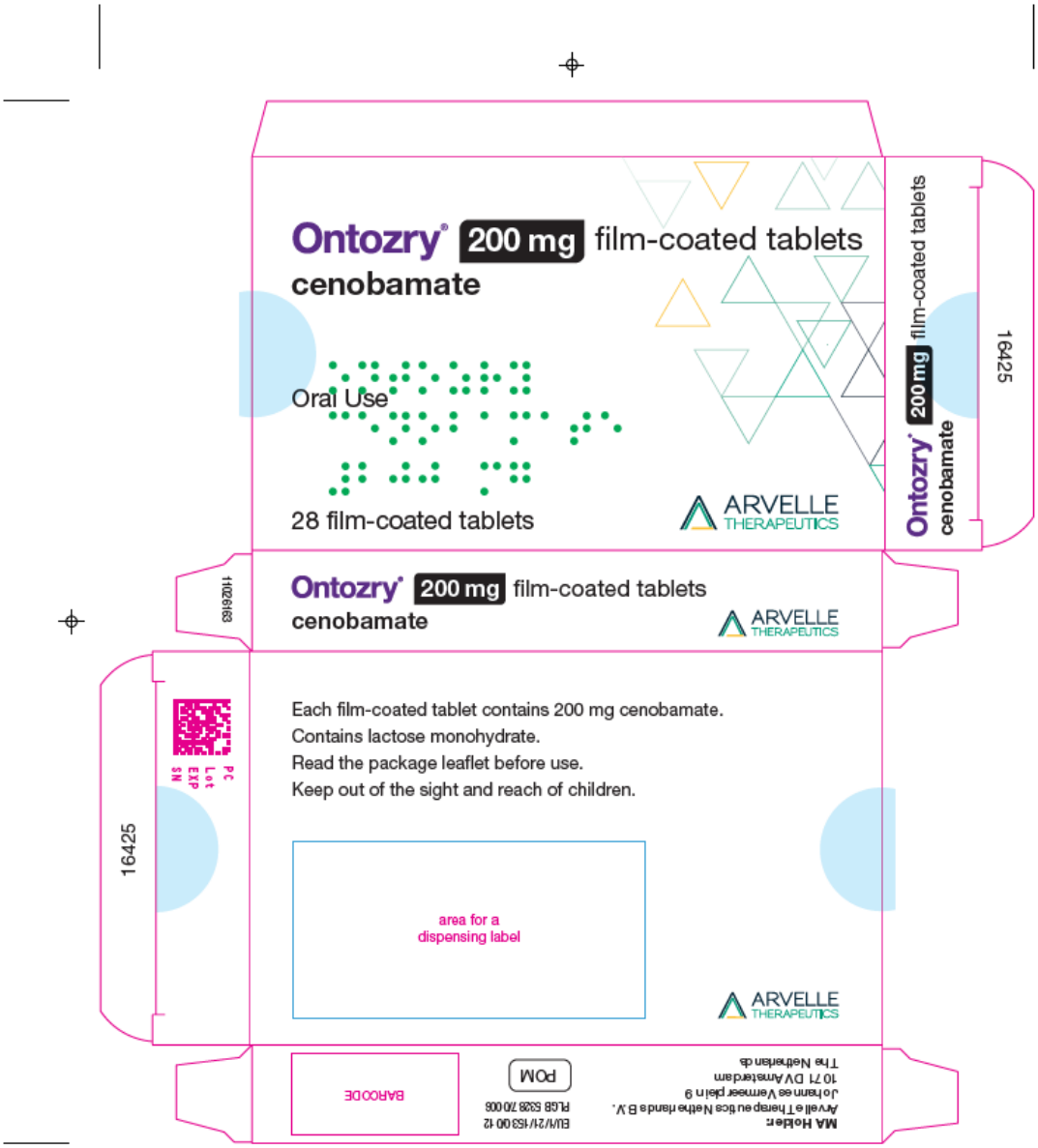


ONTOZRY
cenobamate
#150 mg

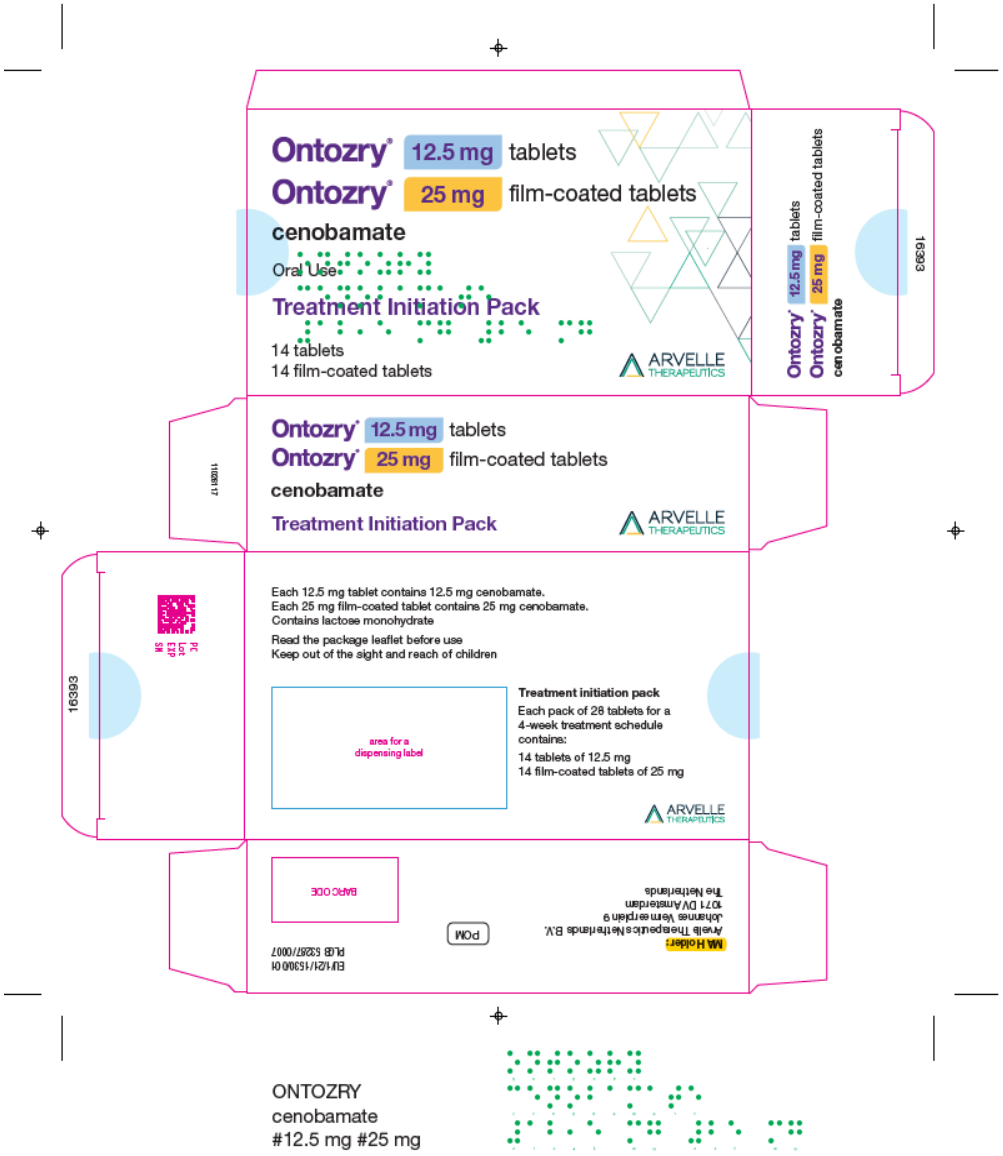




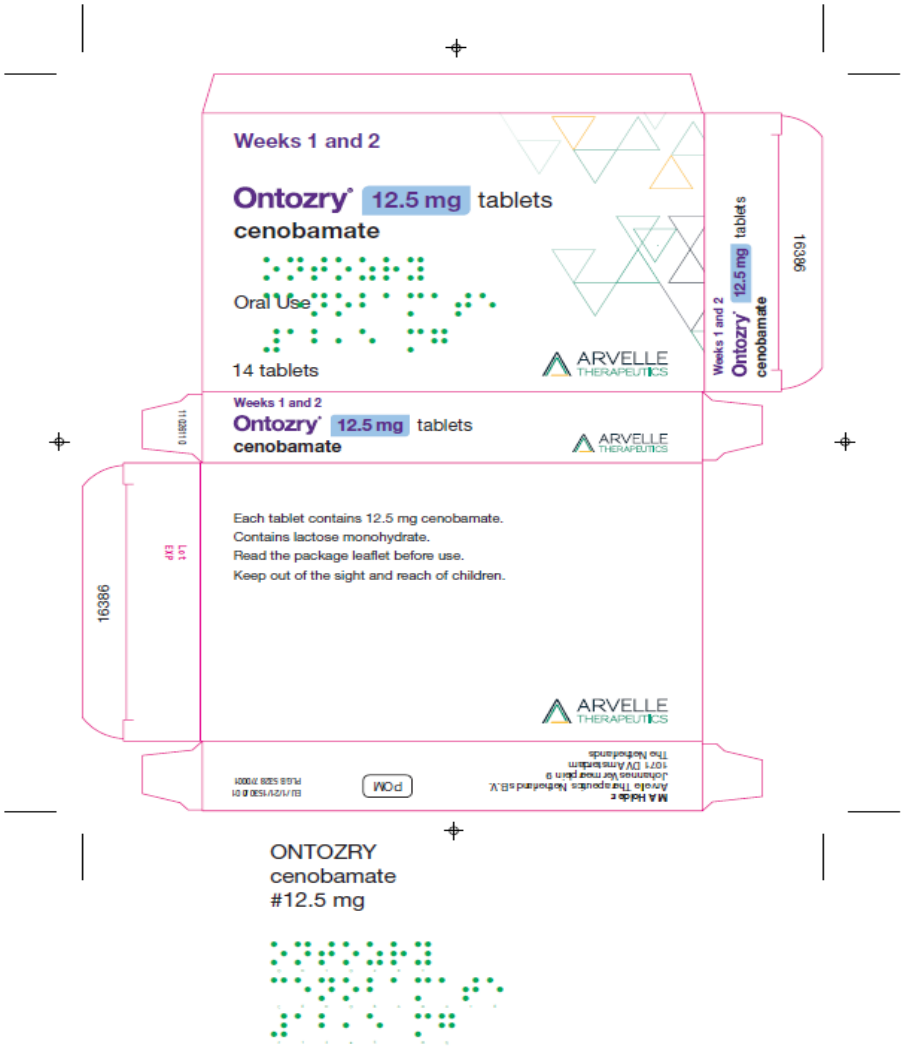
ONTOZRY
cenobamate
#200 mg



ONTOZRY
cenobamate
#200 mg



ONTOZRY
cenobamate
#12.5 mg #25 mg



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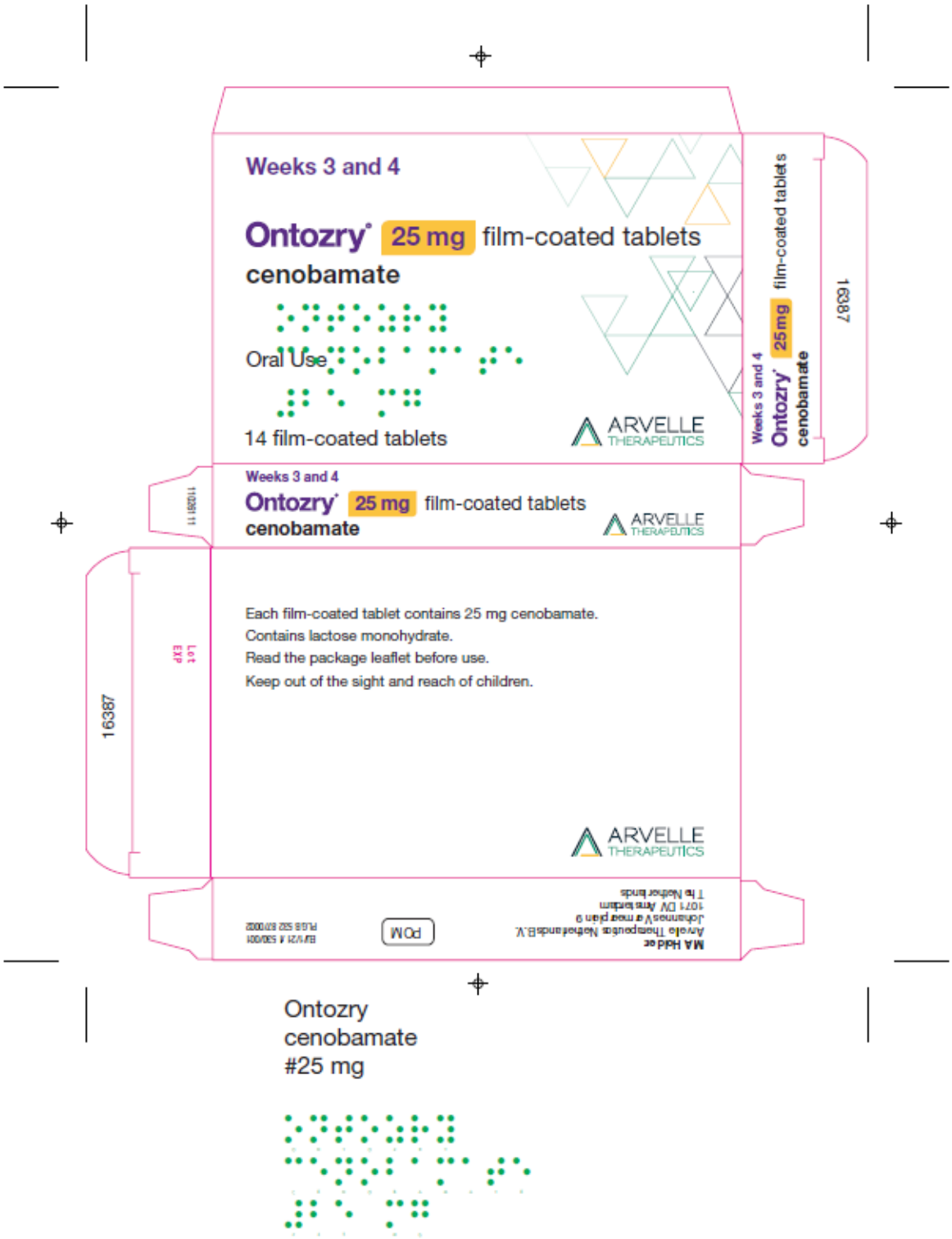
Weeks 3 and 4
Ontozry® 25 mg film-coated tablets
cenobamate
Oral Use
14 film-coated tablets
ARVELLE THERAPEUTICS
Weeks 3 and 4
Ontozry® 25 mg film-coated tablets
cenobamate
ARVELLE THERAPEUTICS
Each film-coated tablet contains 25 mg cenobamate.
Contains lactose monohydrate.
Read the package leaflet before use.
Keep out of the sight and reach of children.
ARVELLE THERAPEUTICS
16387
Lot
EXP
POM
Ontozry
cenobamate
#25 mg

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 SmPCs and/or PIL available on the MHRA website.

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