Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Doxepin 10 mg Capsules
Doxepin 25 mg Capsules
Doxepin 50 mg Capsules

Doxepin hydrochloride

PL 20117/0343 - 0345

Morningside Healthcare Limited

LAY SUMMARY

Doxepin 10 mg Capsules
Doxepin 25 mg Capsules
Doxepin 50 mg Capsules
Doxepin hydrochloride

This is a summary of the Public Assessment Report (PAR) for Doxepin 10 mg, 25 mg and 50 mg Capsules. 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 Doxepin Capsules in this lay summary for ease of reading.

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

What are Doxepin Capsules and what are they used for?
The application for Doxepin 10 mg Capsules is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the United Kingdom (UK) called Sinepin 50 mg Capsules, albeit with certain differences. In this case, Doxepin 10 mg Capsules are a different strength to the reference product.

The applications for Doxepin 25 mg and 50 mg Capsules are for generic medicines. This means these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the UK called Sinepin 25 mg and 50 mg Capsules.

Doxepin Capsules are used in the treatment of depression.

How do Doxepin Capsules work?
These medicines contain the active ingredient doxepin hydrochloride, which belongs to a group of medicines called tricyclic antidepressants.

Depression is a clinical illness. If the patient has been feeling sad, tearful or unable to enjoy life as they used to, this medicine may help them to feel better. It may also help if the patient has difficulty sleeping because of their depression.

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

Recommended dose:
- The usual starting dose is 75 mg daily. This dose may be increased if necessary.
- The maximum recommended dose is 100 mg three times daily.
- The capsules may be prescribed once, twice or three times daily.
- Up to 100 mg can be given as a single dose.

Use in elderly patients and/or patients with liver problems
- If the patient is elderly these doses may be reduced.

- If the patient is elderly and requires an increased dose of the medicine their doctor may wish to see them regularly.
- If the patient suffers from liver problems, they may also be started on a low dose.

Method of administration:
- Take this medicine only by mouth.
- Swallow the capsules whole with a drink of water.
- Take the capsules while standing or when sitting upright.
- Do not crush or chew the capsules.
- Keep taking the capsules every day.

For further information on how Doxepin Capsules 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 Doxepin Capsules have been shown in studies?
Because Doxepin 10 mg Capsules are a hybrid medicine, studies in healthy volunteers consist of tests to determine that they are bioequivalent to an equal dose of the reference medicine.

Because Doxepin 25 mg and 50 mg Capsules are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Doxepin Capsules?
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 these medicines.

Because Doxepin 10 mg Capsules are a hybrid medicine and are bioequivalent to an equal dose of the reference medicine, their benefits and possible side effects are taken as being the same as the reference medicine.

Because Doxepin 25 mg and 50 mg Capsules are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

Why were Doxepin Capsules approved?
It was concluded that Doxepin Capsules have been shown to be comparable to and to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the

reference medicines, 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 Doxepin Capsules?
A Risk Management Plan (RMP) has been developed to ensure that Doxepin 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 Doxepin Capsules
Marketing Authorisations for Doxepin Capsules were granted in the United Kingdom (UK) on 19 October 2021.

The full PAR for Doxepin Capsules follows this summary.

This summary was last updated in December 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 Doxepin 10 mg, 25 mg and 50 mg Capsules (PL 20117/0343 - 0345) could be approved.

The products are approved for the following indication:
Symptoms of depressive illness in adults, especially where sedation is required.

The mechanism of action of doxepin is not definitely known. It is not a central nervous system stimulant nor a monoamine oxidase inhibitor. The current hypothesis is that the clinical effects are due, at least in part, to influences on the adrenergic activity at the synapses so that deactivation of noradrenaline by reuptake into the nerve terminals is prevented. In animal studies anticholinergic, anti-serotonergic and anti-histaminergic effects on smooth muscle have been demonstrated. At higher than usual clinical doses, adrenaline response was potentiated in animals. This effect was not demonstrated in humans.

The application for Doxepin 10 mg Capsules was approved under Regulation 52B of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Sinepin 50 mg Capsules that has been licensed within the UK for a suitable time, in line with the legal requirements.

The applications for Doxepin 25 mg and 50 mg Capsules 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, Sinepin 25 mg and 50 mg Capsules, that have been licensed within the UK for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for hybrid and generic medicinal products of suitable reference products.

Data from two bioequivalence studies were submitted with these applications. These studies were conducted in-line with current Good Clinical Practice (GCP).

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.

National marketing authorisations were granted in the UK on 19 October 2021.

II QUALITY ASPECTS

II.1 Introduction

Each capsule contains doxepin hydrochloride equivalent to 10 mg, 25 mg or 50 mg of doxepin.

In addition to doxepin hydrochloride, these products also contain the excipients:
Capsule content:
Colloidal anhydrous silica, magnesium stearate and co-processed starch.

Capsule shell (10 mg):
Gelatin, titanium dioxide (E171) and iron oxide red (E172)

Capsule shell (25 mg):
Gelatin, FD & C blue 2 (E132), titanium dioxide (E171) and iron oxide red (E172)

Capsule shell (50 mg):
Gelatin, FD & C blue 2 (E132) and titanium dioxide (E171)

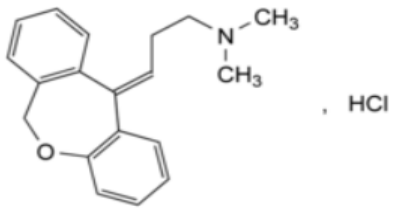
White printing ink:
Shellac (E904), titanium dioxide (E171) and propylene glycol (E1520).

The finished products are packaged in polyvinyl chloride (PVC)/polyvinylidene chloride (PVDC) - aluminium blisters, in a pack size of 28 capsules.

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: **Doxepin hydrochloride**
Chemical Name: (*E*)-3-(Dibenzo[b,e]oxepin-11(6*H*)-ylidene)-*N*,*N*-dimethylpropan-1-amine hydrochloride
Molecular Formula: $C_{19}H_{22}ClNO$
Chemical Structure:



Molecular Weight: 315.8
Appearance: White or almost white, crystalline powder
Solubility: Freely soluble in water, in ethanol (96%) and in methylene chloride .

Doxepin 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 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.

With the exception of gelatin, no excipients of animal or human origin are used in the final products. EDQM certificates of suitability have been provided for the gelatin.

Confirmation has 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 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 30 months, with the storage conditions ‘Do not store above 25°C’, 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 doxepin hydrochloride 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 these are hybrid and generic applications of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations 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
In accordance with the regulatory requirements, data from two bioequivalence studies has been submitted with these applications. These studies were conducted in-line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics
In support of the applications, the applicant submitted the following bioequivalence studies.

Study 1
This study was an open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study comparing the test product Doxepin 50 mg Capsules and the reference product Sinepin 50 mg Capsules, in healthy, adult, male subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single oral dose (1 x 50 mg capsule) of either the test or reference product. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 14 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic data

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product (T)	Reference Product (R)
$AUC_{0\text{-}72h}$ (µg.hr/mL)	450.9084 ± 501.26900	498.9823 ± 671.66219
C_{max} (ng/mL)	35.5422 ± 29.59574	37.4898 ± 34.80835
T_{max} (hr)[1]	2.000 (1.00, 4.50)[1]	2.000 (1.50, 4.50)[1]

Bioequivalence evaluation

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV %
AUC_{0-72h}	95.73	87.70 - 104.50	23.56
C_{max}	99.34	86.74 - 113.77	37.16

According to 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 25 mg strength of the product meets the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 50 mg product strength can be extrapolated to the 25 mg strength.

Study 2
This study was a an open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study comparing the test product Doxepin 10 mg Capsules (5 x 10 mg), versus the reference product Sinepin 50 mg Capsules, in healthy, adult, male subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single oral dose (5 x 10 mg capsules or 1 x 50 mg capsule) of either the test or reference product. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 11 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic data

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product (T)	Reference Product (R)
AUC_{0-72h} (µg.hr/mL)	360.1469 ± 202.22599	369.8080 ± 254.73128
C_{max} (ng/mL)	31.4171 ± 18.80605	32.1262 ± 21.04435
T_{max} (hr)[1]	2.000 (1.00, 4.50)[1]	2.165 (1.50, 5.00)[1]

Bioequivalence evaluation

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV %
AUC_{0-72h}	99.04	93.05 - 105.41	16.67
C_{max}	99.03	91.11 - 107.64	22.39

According to 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.

IV.4 Clinical efficacy
No new efficacy data have been submitted for these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data from the clinical studies submitted with these applications, no new safety data were submitted. The safety data submitted showed that the products were well-tolerated. No new or unexpected safety issues were raised from these 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

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.

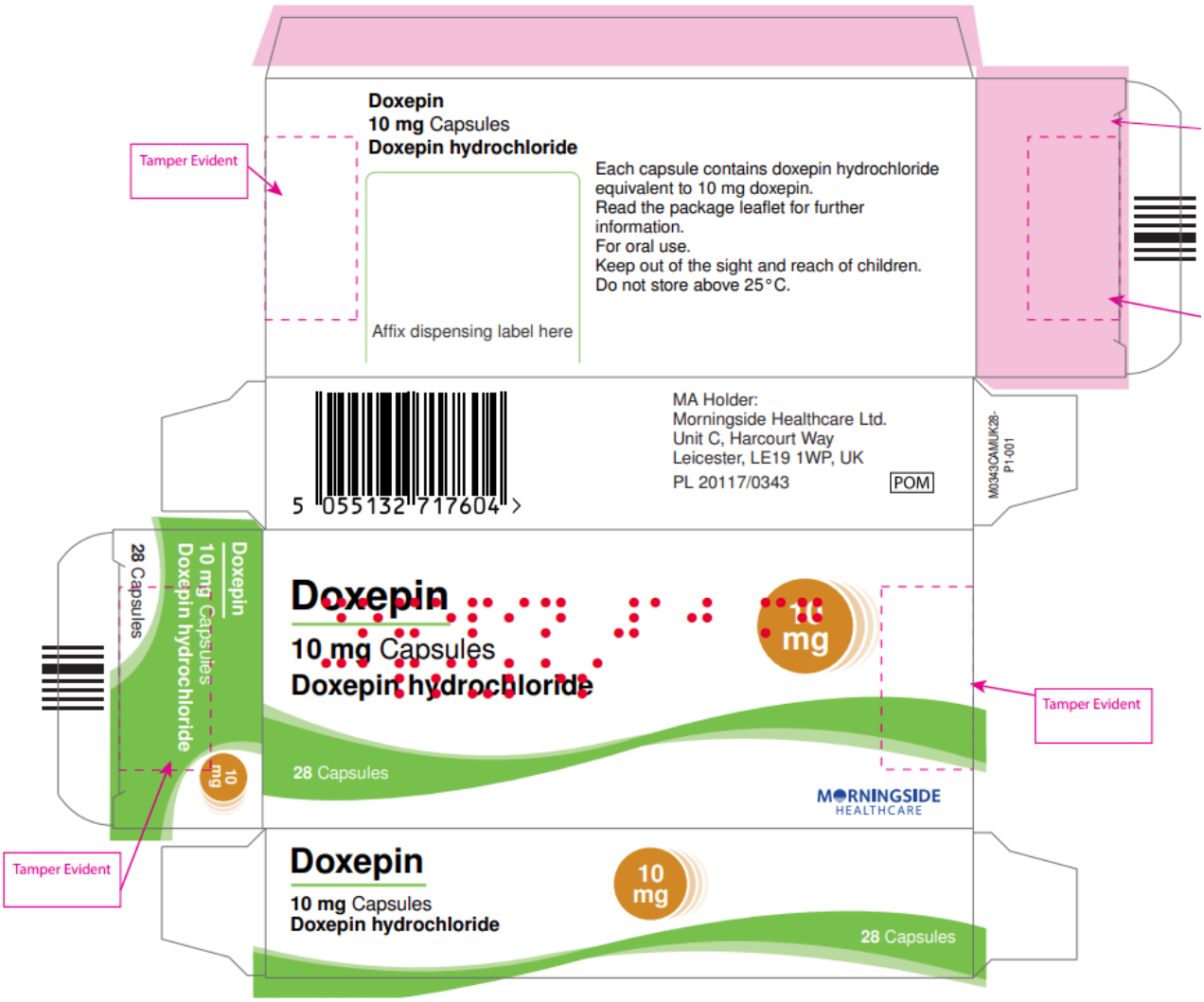
Extensive clinical experience with doxepin hydrochloride is considered to have demonstrated the therapeutic value of the products.

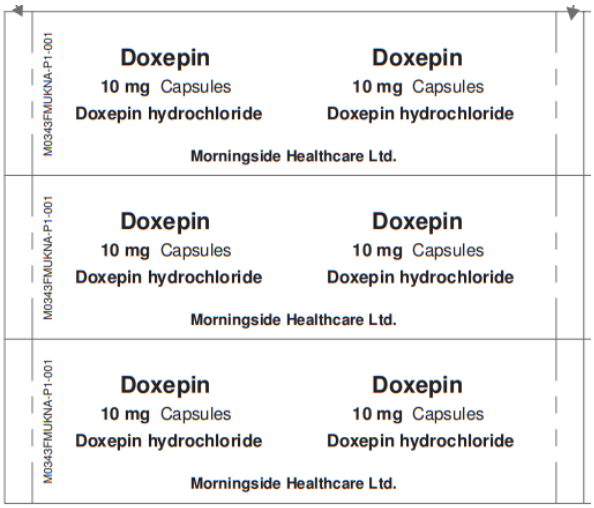
The benefit/risk is, therefore, considered to be positive.

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 versions of the SmPCs and PIL for these products are available on the MHRA website.

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


Doxepin
10 mg Capsules
Doxepin hydrochloride
Tamper Evident
Each capsule contains doxepin hydrochloride equivalent to 10 mg doxepin.
Read the package leaflet for further information.
For oral use.
Keep out of the sight and reach of children.
Do not store above 25°C.
Affix dispensing label here
5 055132 717604
MA Holder:
Morningside Healthcare Ltd.
Unit C, Harcourt Way
Leicester, LE19 1WP, UK
PL 20117/0343
POM
M0343OAMUK28-P1-001
28 Capsules
10 mg
MORNINGSIDE HEALTHCARE
Tamper Evident
Tamper Evident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Doxepin
10 mg Capsules
Doxepin hydrochloride
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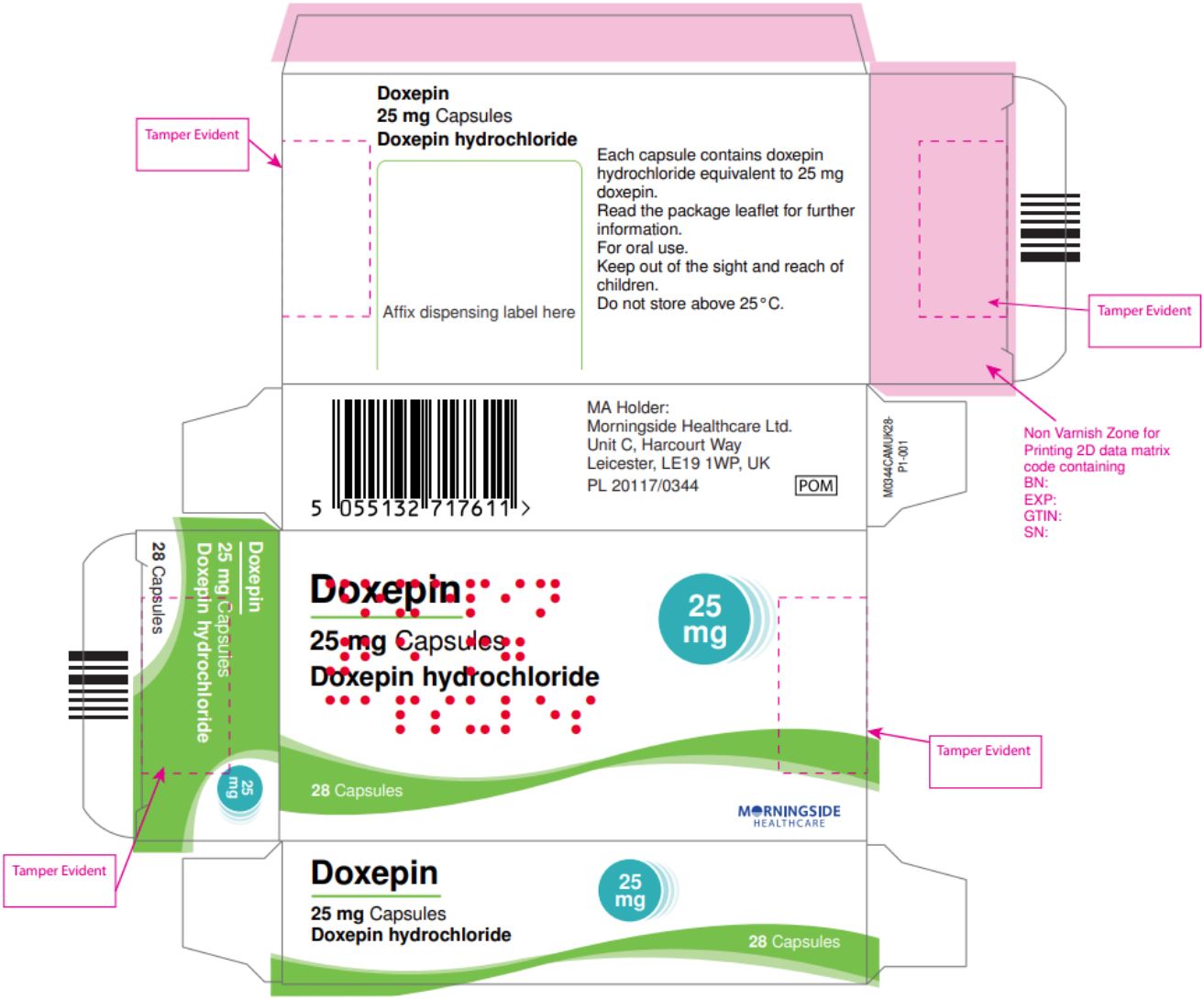
Tamper Evident
Doxepin
25 mg Capsules
Doxepin hydrochloride
Each capsule contains doxepin hydrochloride equivalent to 25 mg doxepin.
Read the package leaflet for further information.
For oral use.
Keep out of the sight and reach of children.
Do not store above 25°C.
Affix dispensing label here
Tamper Evident
MA Holder:
Morningside Healthcare Ltd.
Unit C, Harcourt Way
Leicester, LE19 1WP, UK
PL 20117/0344
POM
5 055132 717611
M0344CAMUK28-P1-001
Non Varnish Zone for Printing 2D data matrix code containing
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EXP:
GTIN:
SN:
28 Capsules
Doxepin
25 mg Capsules
Doxepin hydrochloride
25 mg
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Doxepin hydrochloride
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Tamper Evident
Tamper Evident
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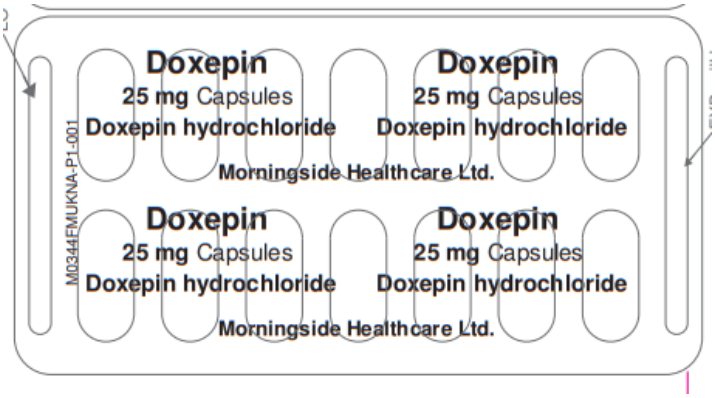
Doxepin hydrochloride
25 mg
28 Capsules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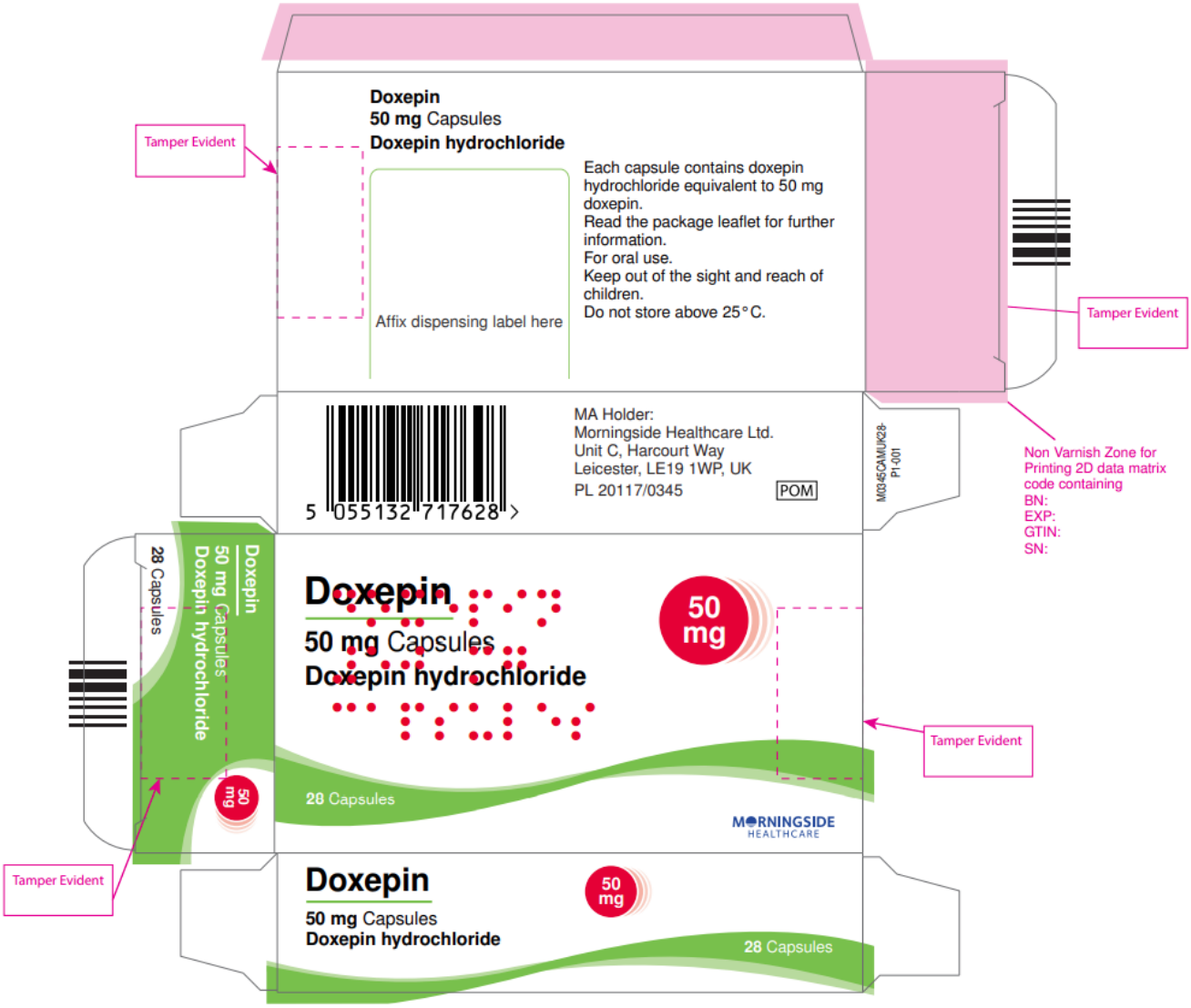
Doxepin
50 mg Capsules
Doxepin hydrochloride
Each capsule contains doxepin hydrochloride equivalent to 50 mg doxepin.
Read the package leaflet for further information.
For oral use.
Keep out of the sight and reach of children.
Do not store above 25°C.
Affix dispensing label here
Tamper Evident
Tamper Evident
Non Varnish Zone for Printing 2D data matrix code containing
BN:
EXP:
GTIN:
SN:
MA Holder:
Morningside Healthcare Ltd.
Unit C, Harcourt Way
Leicester, LE19 1WP, UK
PL 20117/0345
POM
5 055132 717628
M0345CAMUK28-P1-001
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28 Capsules

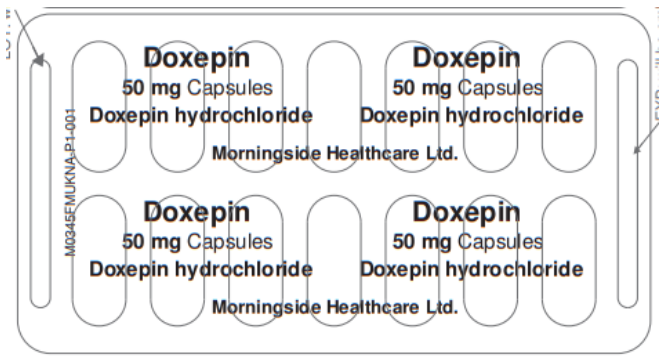
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TABLE OF CONTENT OF THE PAR UPDATE

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**