Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Doxepin 25 mg capsules
Doxepin 50 mg capsules

doxepin hydrochloride

PL 33155/0102-0103

Rivopharm UK Ltd

LAY SUMMARY

Doxepin 25 mg capsules
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This is a summary of the Public Assessment Report (PAR) for Doxepin 25 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?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Sinepin 25 & 50 mg hard capsules.

Doxepin capsules is used in the treatment of depression. Depression is a clinical illness. If the patient has been feeling sad, tearful or unable to enjoy life, Doxepin capsules may help the patient to feel better. It may also help the patient with difficulty sleeping which can be associated with depression. If the patient is not sure why they are taking these capsules, they should ask their doctor.

How do Doxepin capsules work?
Doxepin capsules contain the active substance doxepin hydrochloride which belongs to a group of medicines called tricyclic antidepressants.

How are Doxepin capsules used?
The pharmaceutical form of these medicines is capsules and the route of administration is by mouth (oral).

- The capsules should be swallowed whole with a glass of water.
- The capsules must not be crushed or chewed.
- The patient should keep taking the capsules every day.
- 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.
- For elderly patient their doctor will usually prescribe a lower dose.
- For elderly patients that require an increased dose of the medicine the doctor may wish to see their patient more regularly.
- Patients that have liver problems may also be started on a low dose.
- The capsules may be prescribed once, twice or three times daily.
- Up to 100 mg can be given as a single dose.

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 capsules are generic medicines, studies in healthy volunteers have been limited to tests to determine that it is 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 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 Doxepin 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 has been shown 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 it can be approved for use.

What measures are being taken to ensure the safe and effective use of Doxepin capsules?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Doxepin capsules. The RMP details the important risks of Doxepin capsules, how these risks can be minimised, any uncertainties about Doxepin capsules (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Doxepin capsules:

Summary of safety concerns	
Important identified risks	• Suicide/ suicidal thoughts or clinical worsening; • Apnoea and drowsiness when used during lactation; • Use in pregnancy. •
Potential identified risks	None
Missing information	None

The information included in the SmPCs 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 Doxepin capsules 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 Doxepin capsules
Marketing Authorisations for Doxepin capsules were granted in the United Kingdom (UK) on 25 October 2022.

The full PAR for Doxepin capsules follows this summary.

This summary was last updated in March 2023.

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 25 and 50 mg capsules (PL 33155/0102-0103) could be approved.

The products are approved for the following indication: treatment of 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.

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, Sinepin 25 & 50 mg hard capsules that has been licensed for suitable time, in line with the legal requirements.

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

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the application is for generic medicinal product of suitable reference product. The bioequivalence study was 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.

Marketing Authorisations for Doxepin 25 and 50 mg capsules were granted in the United Kingdom (UK) on 25 October 2022.

II QUALITY ASPECTS

II.1 Introduction

These products consist of:

Doxepin 25 mg capsules – Each capsule contains 25 mg doxepin as doxepin hydrochloride. Other ingredients in the capsule fill are lactose monohydrate, maize starch and magnesium stearate. The capsule shells contain gelatin, titanium dioxide (E171), erythrosine (E127), sunset yellow (E110), patent blue V (E131) and amaranth (E123).

Doxepin 50 mg capsules – Each capsule contains 50 mg doxepin as doxepin hydrochloride. Other ingredients in the capsule fill are lactose monohydrate, maize starch and magnesium stearate. The capsule shells contain gelatin, titanium dioxide (E171), erythrosine (E127) and patent blue (E131).

The finished products are packaged in in blister packs containing 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.

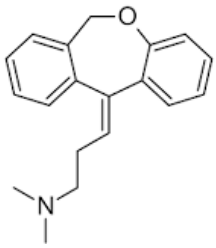
II.2 ACTIVE SUBSTANCE

rINN: **Doxepin hydrochloride**

Chemical Name: (*E*)-3-(Dibenzo[*b*,*e*]oxepin-11(6*H*)-ylidene)-*N*,*N*-dimethylpropan-1-amine hydrochloride

Molecular Formula: $C_{19}H_{21}NO.HCl$

Chemical Structure:



.HCl

Molecular Weight: 315.8

Appearance: White or almost white, crystalline powder

Solubility: Freely soluble in water, in ethanol (96 per cent) 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 suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatine and lactose monohydrate no excipients of animal or human origin are used in the final products. EDQM certificates have been provided for gelatin.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation was given that the magnesium stearate was 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 products stored in the packaging proposed for marketing. Based on the results, for the 25 mg product a shelf-life of 24 months, with the storage condition “Do not store above 25°C” is acceptable, and for the 50 mg product a shelf-life of 36 months, with the storage condition “Do not store above 30ºC” 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 the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated 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

The clinical pharmacology, efficacy and safety of doxepin hydrochloride are well-known. With the exception of data from two bioequivalence studies, 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 these studies is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the applications, the applicant submitted the following:

Study 1

This study was a single-dose, single-centre, randomised, laboratory-blinded, 2-period, 2-sequence, crossover study comparing the test product Doxepin 50 mg Capsules (test) and the reference product Sinepin 50 mg hard capsules in healthy subjects under fasted conditions.

Under fasted conditions, subjects were administered with a single dose of either the test or reference product in each period. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 21 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Pharmacokinetic Parameters

Doxepin

PARAMETER	TEST (n=16)		REFERENCE (n=16)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	11.913	(54.7)	11.632	(47.9)
ln (C_{max})	2.3358	(23.7)	2.3357	(22.3)
T_{max} (hours)[a]	2.50	(1.50-6.00)	2.51	(1.75-4.00)
AUC_{0-T} (ng·h/mL)	181.478	(60.8)	168.301	(53.6)
ln (AUC_{0-T})	5.0277	(12.2)	4.9764	(11.7)
$AUC_{0-\infty}$ (ng·h/mL)	197.038	(63.5)	181.293	(55.9)
ln ($AUC_{0-\infty}$)	5.0949	(12.5)	5.0376	(12.1)
Residual Area (%)	6.41	(63.0)	5.89	(52.3)
λ_Z ($hours^{-1}$)	0.0414	(33.9)	0.0403	(29.8)
T_{half} (hours)	18.32	(29.4)	18.32	(23.2)

[a] Median and range are presented

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=16)	REFERENCE (n=16)		LOWER	UPPER
C_{max}	33.9	10.338	10.337	100.01	81.43	122.82
AUC_{0-T}	21.9	152.581	144.956	105.26	92.01	120.42

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T}

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.

Study 2
This study was single-dose, randomised, open-label, two-way crossover study, comparing the test product Doxepin 25 mg Capsules (test) and the reference product Sinepin 25mg hard capsules in healthy subjects under fasted conditions.

Under fasted conditions subjects were administered with a single dose of either the test or reference product in each period. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 21 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Bioequivalence Analysis Results of Plasma Doxepin

TREATMENT A vs TREATMENT B

Parameter (N_A /N_B)	Geometric Means Arithmetic Means (CV %) TRT A	TRT B	Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (pg.h/mL) (52 /52)	93018.52 132206.46 (110.85)	97972.09 133938.54 (96.78)	94.94	90.59 - 99.51	14.36
AUCinf (pg.h/mL) (52 /52)	102925.46 159036.94 (137.29)	107441.23 159265.91 (127.98)	95.80	91.38 - 100.43	14.42
Cmax (pg/mL) (52 /52)	7692.17 10432.78 (91.39)	7900.59 10403.40 (77.60)	97.36	91.41 - 103.70	19.37
Tmax* (h) (52 /52)	2.50 (1.00 - 6.02)	2.00 (1.00 - 8.00)			
Lambda** (1/h) (52 /52)	0.0315 (27.86)	0.0336 (27.67)			
T1/2** (h) (52 /52)	24.26 (38.25)	22.82 (40.58)			
AUCt/AUCinf** (52 /52)	0.9069 (8.03)	0.9180 (7.95)			
AUC(res%)** (52 /52)	0.0931 (78.22)	0.0850 (85.59)			

Note: N_A /N_B are the number of observations for Treatment A and B , respectively
*: Presented as median and range
**: Presented as arithmetic mean (CV%) only

TRT A: Doxepin 25 mg capsules; Batch/Lot No: TF0038/19; (Develophama SA, Switzerland)

TRT B: Doxepin Hydrochloride BP 25 mg; Batch/Lot No: 1902001; (MAH: Marlborough Pharmaceuticals- Sovereign House, Miles Gray Road, Basildon, Essex SS14 3FR, United Kingdom.
Manufacturer : Allphamed PHARBIL GmbH- Hildebrandstrasse 12, D- 37081 Gottingen, Germany

Commented [ADE1]: Do you need to disclose the batch number details, site of manufacture etc for the test and reference products?

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.

IV.3 Pharmacodynamics
No new pharmacodynamic data were 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 studies, no new safety data were submitted with these applications.

The safety data from the bioequivalence studies 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 doxepin 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, 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 PIL for these products are available on the MHRA website.

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

Commented [ADE2]: What about labelling for the 50 mg strength?

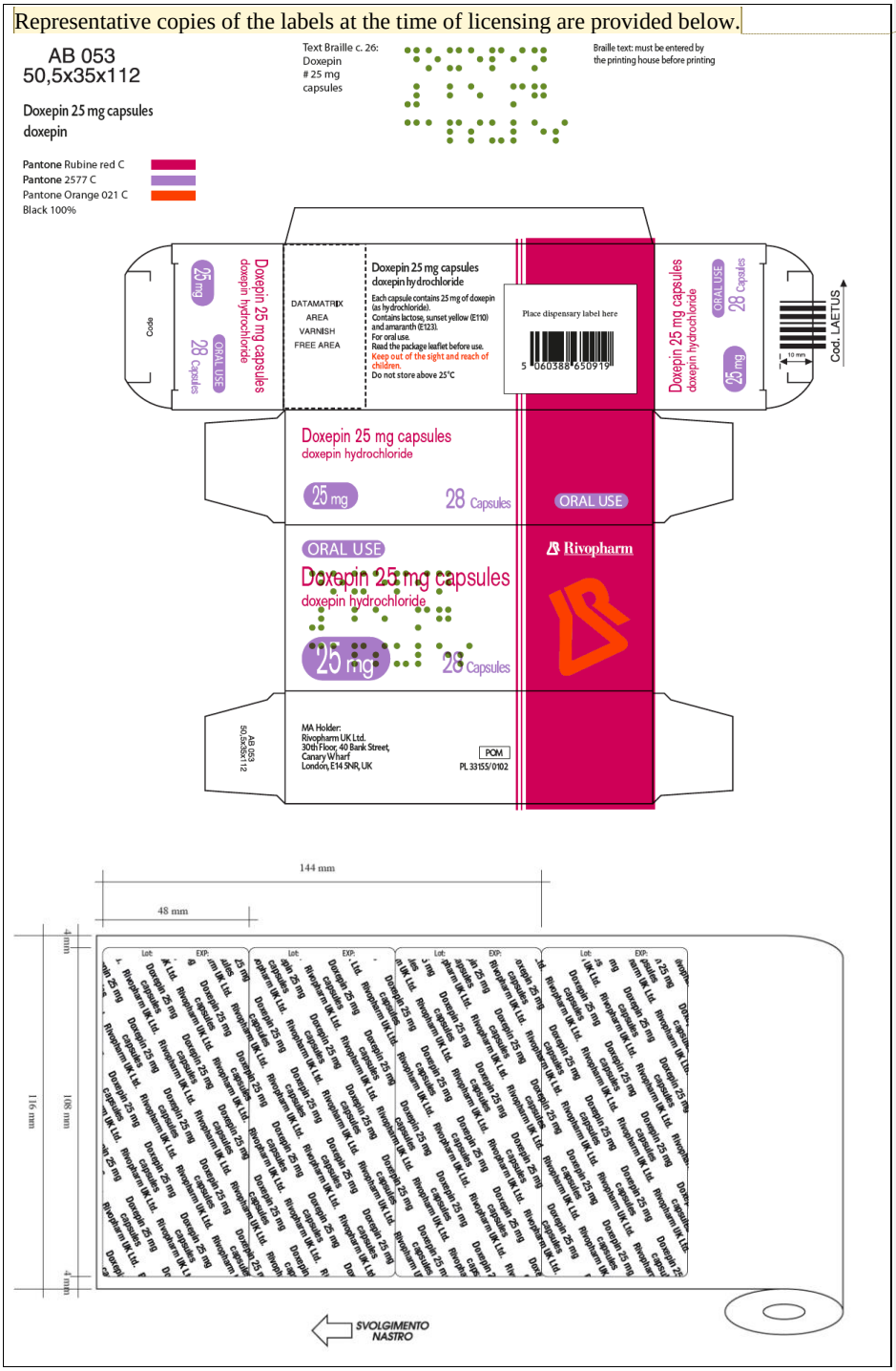


TABLE OF CONTENT OF THE PAR UPDATE

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