Public Assessment Report

National Procedure

Doxepin 25 mg Capsules
Doxepin 50 mg Capsules

(doxepin hydrochloride)

PL 20416/0652-0653

Crescent Pharma Limited
LAY SUMMARY

Doxepin 25 mg Capsules
Doxepin 50 mg Capsules
(doxepin hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Doxepin 25 mg Capsules and Doxepin 50 mg Capsules. It explains how Doxepin 25 mg Capsules and Doxepin 50 mg Capsules 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 Doxepin 25 mg Capsules and Doxepin 50 mg Capsules.

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 package leaflet or contact their doctor or pharmacist.

What is Doxepin Capsules and what is it used for?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, a reference medicines already authorised in the European Union (EU) called Sinepin 25mg Capsules and Sinepin 50mg Capsules. The reference product will be referred to as Sinepin Capsules in this lay summary for ease of reading.

Doxepin Capsules are prescribed to treat depression. This medicine is an antidepressant and belonging to a group of antidepressants called tricyclic antidepressants. This medication improves symptoms of depression and it can also help with sleeping difficulties.

How does Doxepin Capsules work?
The active ingredient in this medicine is called doxepin hydrochloride. It is not entirely clear how Doxepin works to treat depression but it is believed that its ability to prevent the brain cells from reabsorbing a chemical messenger known as norepinephrine plays a role. This action increases the levels of this chemical messenger in the brain which will is believed to improve the patient’s mood.

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

This medicine should only be taken by mouth.

- The capsules should be swallowed whole with a drink of water.
- The capsules should be taken while standing or when sitting upright.
- The capsules should not be crushed or chewed.
- This medicine should be taken regularly every day.
- The usual starting dose is 75mg daily. This dose may be increased if necessary.
- The maximum recommended dose is 100mg three times daily.
- These doses may be reduced for elderly patients.
- For an elderly patient that requires an increased dose of the medicine, the doctor may wish to see the patient regularly.
- If the patient suffers from liver problems, they may also be started on a low dose.
• The capsules may be prescribed to be taken once, twice or three times daily.
• Up to 100mg can be given as a single dose.

For further information on how Doxepin Capsules are used, refer to the package leaflet and Summaries of Product Characteristics 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 this medicine exactly as their doctor 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 a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Doxepin Capsules?**
Because Doxepin Capsules is a generic medicine and is bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicines.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summaries of Product Characteristics (SmPC) available on the MHRA website.

**Why was Doxepin Capsules approved?**
It was concluded that, in accordance with EU requirements, Doxepin Capsules has been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Doxepin Capsules?**
A Risk Management Plan (RMP) has been developed to ensure that Doxepin Capsules is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, 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 UK to the company Amega Limited on 28 March 2019. The Marketing Authorisations subsequently underwent a change of ownership procedure to the company Crescent Pharma Limited on 24 April 2019.

The full Public Assessment Report for Doxepin Capsules follows this summary.

This summary was last updated in 05-2019.
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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 Doxepin 25 mg Capsules and Doxepin 50 mg Capsules (PL 48441/0001-0002) could be approved.

The products are indicated for the treatment of symptoms of depressive illness, especially where sedation is required.

The capsules contain the active substance doxepin hydrochloride. The mechanism of action of doxepin is not fully understood. It is not a central nervous system stimulant nor a monoamine oxidase inhibitor. The current hypothesis is that the clinical effects are, at least in part, due to influences on the adrenergic activity by noradrenaline reuptake inhibition at the synapses. In animal studies anti-cholinergic, 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.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines. The reference medicinal products are Sinepin 25mg Capsules and Sinepin 50mg Capsules, which were licensed for marketing in the UK to Marlborough Pharmaceuticals Limited on 06 September 2006. The product names Doxepin 25 mg and 50 mg Capsules have also been approved for these product licences. These products were originally authorised for marketing in the UK to Pfizer Limited under the product names Sinequam 25 mg Capsules and Sinequam 50 mg on 12 September 1985.

No new non-clinical studies were conducted, which is acceptable given that these products are generic medicines similar to the reference products that have been licensed in EU for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is a generic medicinal product of a reference product that has been in clinical use for over 10 years. 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.

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 for these products on 28 March 2019. The Marketing Authorisations subsequently underwent a change of ownership procedure to the current Marketing Authorisation Holder (MAH), Crescent Pharma Limited (PL 20416/0652-0653) on 24 April 2019.
II QUALITY ASPECTS

II.1 Introduction
These products contain doxepin hydrochloride equivalent to either 25 mg or 50 mg doxepin.

Each Doxepin 25 mg Capsule is a blue cap and red body, opaque, size 3 hard gelatin
capsules, imprinted with ‘PC’ on the cap and ‘D25’ on the body with white ink.
Each 50 mg Doxepin Capsule is a Blue cap and blue body, opaque, size 2 hard gelatin
capsules, imprinted with ‘PC’ on the cap and ‘D50’ on the body with white ink.

In addition to doxepin hydrochloride, these products also contain the excipients: lactose
monohydrate, sodium lauryl sulfate, maize starch and magnesium stearate. The capsule shells
contain, gelatin, water, sodium lauryl sulfate, titanium dioxide (E171), erythrosine (E127)
and patent blue V (E131). In addition, the capsules shell for 50 mg Doxepin Capsules also
contains quinoline yellow (E104).

The finished products are packaged in PVC/PVDC foiled aluminium blister packs of 28
capsules.

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

II.2 ACTIVE SUBSTANCE(S)

rINN: Doxepin hydrochloride

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

Molecular Formula: $\text{C}_{19}\text{H}_{21}\text{NO}\cdot\text{HCl}$

Chemical Structure:

![Chemical Structure Image]

Molecular Weight: 315.841
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.
Suitable specifications have been provided for all packaging used. The primary packaging complies with the current European regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT
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. 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. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that they are manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

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

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

Satisfactory batch formulae 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 specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. 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 24 months, with the storage conditions Store below 30 °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 is 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 an 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 a marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of doxepin hydrochloride is well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV.2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence study:

STUDY
This study was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study comparing the test product Doxepin 50 mg Capsules versus the reference product Sinepin/Doxepin 50mg Capsules, (Marlborough Pharmaceuticals Limited) in subjects under fasted conditions.

Subjects were administered a single oral dose (1x 50mg capsule) of the test or reference product following an overnight fast of at least 10 hours.
Blood samples were taken pre-dose and up to 96 hours post dose, with a washout period of 19 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:
In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr*#), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strength of the product meet 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.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this/these applications and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this/these applications.

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

IV.6 Risk Management Plan (RMP)
The Applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, 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
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet 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. These products are bioequivalent to the authorised reference products and their benefit/risk is, therefore, considered to be similar and positive.

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

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.
PAR Doxepin 25 mg and 50 mg Capsules

Generic, Article 10(1)
### 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 product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

<table>
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<tr>
<th>Application type</th>
<th>Scope</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Outcome</th>
<th>Assessment report attached Y/N</th>
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