



## **Public Assessment Report**

# **UKPAR**

## **Clonidine hydrochloride 50micrograms/5ml Oral Solution**

**(clonidine hydrochloride)**

**UK Licence Number: PL 39307/0082**

**Syri Limited t/a Thame Laboratories**

## LAY SUMMARY

### Clonidine hydrochloride 50micrograms/5ml Oral Solution

This is a summary of the Public Assessment Report (PAR) for Clonidine hydrochloride 50micrograms/5ml Oral Solution (PL 39307/0082). It explains how Clonidine hydrochloride 50micrograms/5ml Oral Solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Clonidine hydrochloride 50micrograms/5ml Oral Solution

The product will be referred to as Clonidine hydrochloride oral solution throughout the remainder of this public assessment report (PAR).

For practical information about using Clonidine hydrochloride oral solution, patients should read the package leaflet or contact their doctor or pharmacist.

#### **What is Clonidine hydrochloride oral solution and what is it used for?**

Clonidine hydrochloride oral solution is a 'generic medicine'. This means that Clonidine hydrochloride oral solution is similar to a 'reference medicine' already authorised in the European Union (EU) called Dixarit Tablets 25 micrograms (Boehringer Ingelheim Limited).

Clonidine hydrochloride oral solution is used to prevent migraine attacks and similar types of headache. It is also used to prevent hot flushes that may occur in women during the menopause (change of life).

#### **How does Clonidine hydrochloride oral solution work?**

The active ingredient is clonidine hydrochloride which belongs to a group of medicines called vasodilators. Vasodilators widen the blood vessels and this helps the blood to flow more easily.

#### **How is Clonidine hydrochloride oral solution used?**

The pharmaceutical form of this medicine is an oral solution and the route of administration is oral (by mouth).

#### Dose

The usual starting dose is 5ml (50micrograms), two times a day. If necessary, after two weeks, your doctor may increase the dose to 7.5ml (75micrograms), two times a day.

Clonidine hydrochloride oral solution is not recommended for children.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Clonidine hydrochloride oral solution is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

#### **What benefits of Clonidine hydrochloride oral solution have been shown in studies?**

Clonidine hydrochloride oral solution is a generic medicine, and is considered to be therapeutically equivalent, to the reference medicine Dixarit Tablets 25 micrograms (Boehringer Ingelheim Limited).

**What are the possible side effects of Clonidine hydrochloride oral solution?**

Because Clonidine hydrochloride oral solution is a generic medicine its benefits and possible side effects are taken as being the same as those of the reference medicine Dixarit Tablets 25 micrograms (Boehringer Ingelheim Limited).

For a full list of all the side effects reported with Clonidine hydrochloride oral solution see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

**Why is Clonidine hydrochloride oral solution approved?**

It was concluded that, in accordance with EU requirements, Clonidine hydrochloride oral solution has been shown to have comparable quality and to be therapeutically equivalent to Dixarit Tablets 25 micrograms (Boehringer Ingelheim Limited). The benefits are greater than the risks and it was recommended that Clonidine hydrochloride can be approved for use.

**What measures are being taken to ensure the safe and effective use of Clonidine hydrochloride oral solution?**

A risk management plan (RMP) has been developed to ensure that Clonidine hydrochloride oral solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Clonidine hydrochloride oral solution 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 Clonidine hydrochloride oral solution**

A marketing authorisation was granted in the UK on 10 August 2018.

The full PAR for Clonidine hydrochloride oral solution follows this summary.

For more information about treatment with Clonidine hydrochloride oral solution, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2018.

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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) granted Syri Limited t/a Thame Laboratories, a marketing authorisation for the medicinal product Clonidine hydrochloride 50micrograms/5ml Oral Solution (PL 39307/0082).

Clonidine hydrochloride oral solution is indicated for the prophylactic management of migraine or recurrent vascular headache, and for management of vasomotor conditions commonly associated with the menopause and characterised by flushing.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference product for this application is Dixarit Tablets 25 micrograms (Boehringer Ingelheim Limited; PL 00015/5014R) which has been authorised in the UK since 22 December 1986.

Clonidine is an  $\alpha$ -adrenergic agent that appears to act on both peripheral and central structures. Clonidine acts centrally to produce its antihypertensive effects by stimulating  $\alpha_2$ -adrenergic receptors. Activation of these central alpha-adrenergic receptors reduces the sympathetic tone of the heart, kidneys, and peripheral vasculature causing vasodilatation and lowering blood pressure. Peripherally clonidine is a typical alpha-sympathomimetic agent. Treatment with clonidine diminishes the responsiveness of peripheral vessels to constrictor and dilator stimuli, thereby preventing the vascular changes associated with migraine. The same direct action on peripheral vessels moderates the vascular changes associated with menopausal flushing

One bioequivalence study (conducted under fasting conditions) was submitted to support the application. The applicant has stated that the bioequivalence study was conducted in accordance with the study protocol and the guidelines for good laboratory practice (GLP).

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

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of the product.

For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

## II QUALITY ASPECTS

### II.1 Introduction

The finished product is an oral solution containing 50 micrograms per 5 ml of solution. Other ingredients consist of the pharmaceutical excipients methyl parahydroxybenzoate (E218), sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, sucralose (E955), purified water.

The finished product is packaged in a Type III amber glass bottle with a tamper evident, child resistant white plastic cap which consists of a polypropylene inner, polyethylene outer, and expanded polyethylene (EPE) liner. The bottle is placed in a carton with a 10ml polypropylene oral syringe with 0.5ml graduation mark and an adaptor for the syringe.

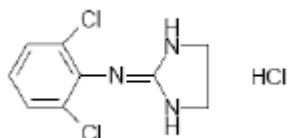
Clonidine hydrochloride oral solution is supplied in a bottle containing 100ml oral solution.

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 Drug Substance

INN: Clonidine hydrochloride  
 Chemical name: 2-[(2,6-Dichlorophenyl)imino]imidazolidine hydrochloride  
 or  
 2-(2,6-dichloroanilino)-2-imidazolidine hydrochloride

Structure:



Molecular formula: C<sub>9</sub>H<sub>9</sub>Cl<sub>2</sub>N<sub>3</sub>. HCl  
 Molecular weight: 266.6  
 Appearance: White or almost white crystalline powder  
 Solubility: Soluble in water, soluble in ethanol and slightly soluble in chloroform.

All aspects of the manufacture and control of the active substance, clonidine hydrochloride, are covered by the 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 has been shown to comply with current guidelines concerning contact with food. Appropriate stability will be generated supporting a suitable retest period when stored in the proposed packaging.

### II.3. Medicinal Product

#### Pharmaceutical Development

The objective of the development programme was to develop a safe, efficacious, oral solution containing 50micrograms of clonidine hydrochloride per 5 ml of solution that is a generic version of the reference product Dixarit Tablets 25 micrograms (Boehringer Ingelheim Limited). The development of the product has been described, the choice of excipients is justified, and their functions explained.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with their respective European Pharmacopoeia or British Pharmacopoeia monographs.

Satisfactory specifications and Certificates of Analysis have been provided for the packaging components.

No materials of animal origin covered by the TSE guideline are contained or used in the manufacturing process of the medicinal product.

This product does not contain or consist of genetically modified organisms (GMO).

### **Manufacture of the product**

Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on commercial batch sizes have been provided. The results are satisfactory.

### **Finished Product Specification**

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

### **Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 24 months, the product should be discarded 30 days after first opening. This medicinal product does not require any special storage conditions, but the product must not be refrigerated or frozen.

Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

## **II.4 Discussion on chemical, pharmaceutical and biological aspects**

There are no objections to the approval of this application from a pharmaceutical viewpoint.

## **III NON-CLINICAL ASPECTS**

### **III.1 Introduction**

As the pharmacodynamic, pharmacokinetic and toxicological properties of clonidine 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.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

### **III.2 Pharmacology**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### **III.3 Pharmacokinetics**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### **III.4 Toxicology**

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

### **III.5 Ecotoxicity/environmental risk assessment (ERA)**

Since Clonidine hydrochloride 50micrograms/5ml Oral Solution is intended for generic substitution, this will not lead to an increase in the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

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

There are no objections to the approval of this application from a non-clinical viewpoint.

## **IV CLINICAL ASPECTS**

### **IV.1 Introduction**

The clinical pharmacology of clonidine hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for the application.

A comprehensive review of the published literature has been provided by the applicant. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of clonidine hydrochloride.

### **IV.2 Pharmacokinetics**

A randomised, open label, balanced, two treatment, two period, two sequence, single dose, crossover bioequivalence study comparing the pharmacokinetics of the Clonidine hydrochloride 50micrograms/5ml Oral Solution versus the reference product Dixarit Tablets 25 micrograms (Boehringer Ingelheim Limited), under fasting conditions.

After a fast of at least 10.00 hours the product was administered orally, 5 ml of oral solution for test product (T) and (2 × 25 micrograms tablet) for reference product (R) in each study period. The wash out period was adequate. Blood samples were drawn from pre-dose and up to 120.00 hours post-dose in each study period.



## Summary of Pharmacokinetic results

Table 1. Pharmacokinetic parameters: non-transformed values; arithmetic mean  $\pm$  SD (N=35)

Formulations		$C_{max}$ (pg/mL)	$AUC_{0-t}$ (pg*hr/mL)	$AUC_{0-inf}$ (pg*hr/mL)	$T_{max}$ (hrs)	$K_{el}$ (hrs <sup>-1</sup> )	$t_{1/2}$ (hrs)	$AUC_{0-t}/$ $AUC_{0-inf}$ Ratio (%)
Test Product T	Arithmetic Mean	278.160	5036.684	5253.352	1.985	0.051	13.985	95.618
	$\pm$ SD	$\pm$ 52.168	$\pm$ 1312.239	$\pm$ 1296.265	$\pm$ 0.999	$\pm$ 0.011	$\pm$ 2.581	$\pm$ 3.573
Reference Product R	Arithmetic Mean	265.237	5192.305	5376.901	2.319	0.052	13.989	96.306
	$\pm$ SD	$\pm$ 41.474	$\pm$ 1375.094	$\pm$ 1347.075	$\pm$ 1.053	$\pm$ 0.012	$\pm$ 3.092	$\pm$ 4.304

Table 2. ln-transformed pharmacokinetic parameters: geometric mean and 90% confidence interval (N=35)

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
$AUC_{0-t}$	4869.4671	5030.9502	96.7902	92.3887	101.4014
$C_{max}$	273.4482	262.0298	104.3577	101.0561	107.7671

\*Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data.

The 90% confidence intervals of the test/reference ratio for AUC, and  $C_{max}$  values for clonidine lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr\*\*). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Dixarit Tablets 25 micrograms (Boehringer Ingelheim Limited).

### IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted, and none were required for an application of this type.

### IV.4 Clinical efficacy

No new efficacy data were submitted, and none were required for an application of this type.

### IV.5 Clinical safety

No new data on safety have been submitted and none are required for an application of this type.

### IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL), which is acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the competent authority;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a Periodic Safety Update Report and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

#### **IV.7 Discussion on the clinical aspects**

The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

#### **V User consultation**

The package leaflet has been evaluated, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to understand and act upon the information that it contains.



#### **VI Overall conclusion, benefit/risk assessment and recommendation**

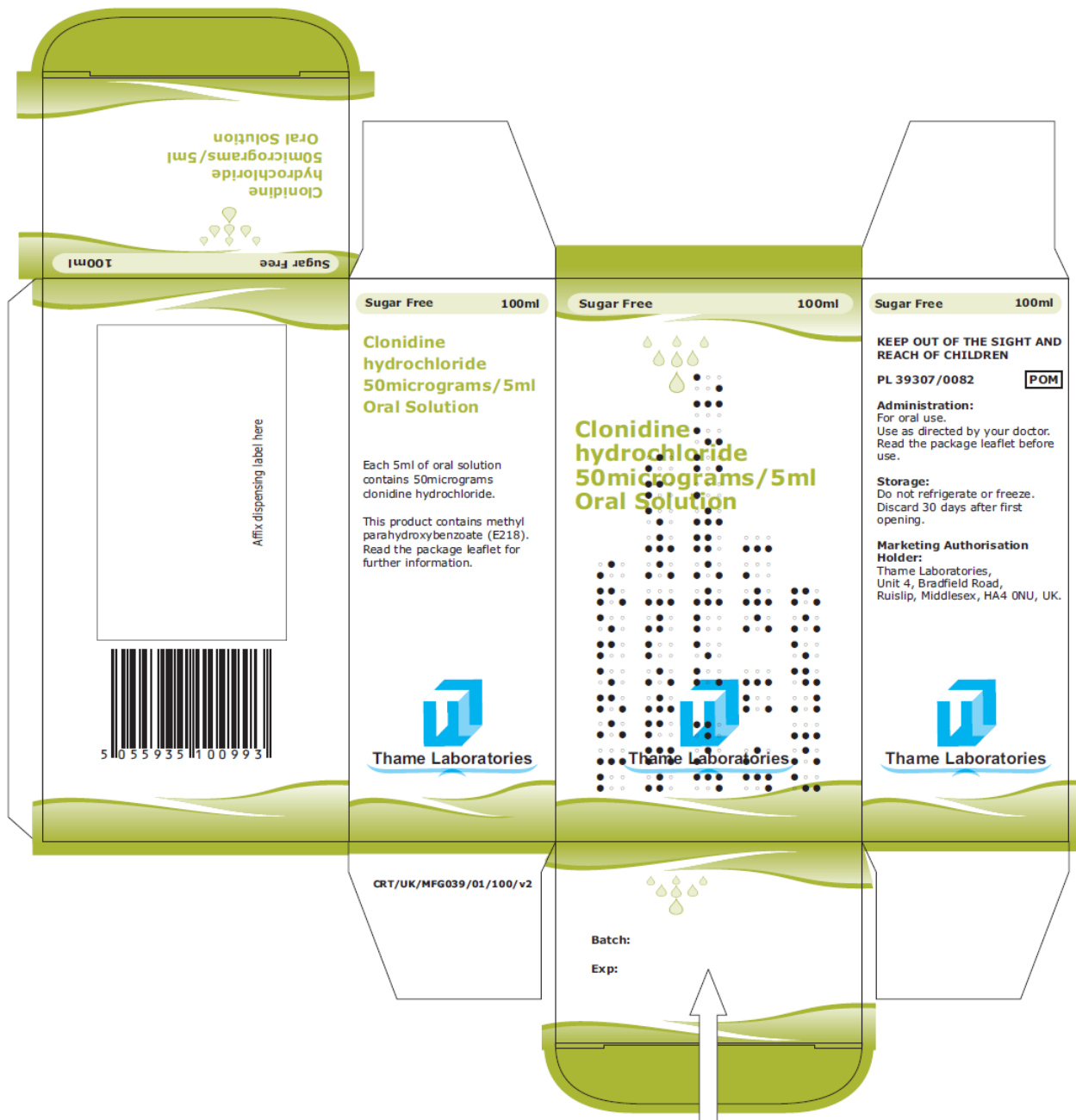
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with clonidine is considered to have demonstrated the therapeutic value of the compound, therefore, the benefit: risk balance is considered to be positive.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The MAH has submitted the following approved labelling for this medicine which is presented below:

<p>Each 5ml of oral solution contains 50micrograms clonidine hydrochloride.</p> <p>This product contains methyl parahydroxybenzoate (E218). Read the package leaflet for further information.</p> <p><b>KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.</b></p> <p><b>PL 39307/0082</b></p> <p><b>Administration:</b> For oral use. Use as directed by your doctor. Read the package leaflet before use.</p> <p><b>Storage:</b> Do not refrigerate or freeze. Discard 30 days after first opening.</p>	<p><b>Sugar Free</b>      <b>100ml</b></p>  <p><b>Clonidine hydrochloride 50micrograms/5ml Oral Solution</b></p>	<p><b>Batch:</b></p> <p><b>Exp:</b></p> <p><b>Marketing Authorisation Holder:</b> Thame Laboratories, Unit 4, Bradfield Road, Ruislip, Middlesex, HA4 0NU, UK.</p>   <p>5 0 5 9 3 5 1 0 9 9 3</p> <p style="writing-mode: vertical-rl; transform: rotate(180deg);">LBL/UK/MFG039/01/100/v2</p>
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## Annex 1

**Table of content of the PAR update**

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<b>Scope</b>	<b>Procedure number</b>	<b>Product information affected</b>	<b>Date of start of the procedure</b>	<b>Date of end of procedure</b>	<b>Approval/ non approval</b>	<b>Assessment report attached Y/N (version)</b>