Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Clonidine hydrochloride 25 microgram tablets

(clonidine hydrochloride)

UK/H/1448/01/DC
UK licence number: PL 17507/0094

Auden Mckenzie Limited

LAY SUMMARY

On 18th November 2008, the MHRA granted Auden Mckenzie Limited a Marketing Authorisation (licence) for the medicinal product Clonidine hydrochloride 25 microgram tablets (PL 17507/0094). This is a prescription-only medicine (POM) that is used to prevent attacks of migraine and similar types of headache. The tablets are also used to prevent hot flushes that may occur in women during the menopause ('change of life').

The active ingredient, clonidine hydrochloride, belongs to a class of drugs known as 'vasodilators', which cause widening of the blood vessels and therefore an increase in blood flow.

This application is based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Clonidine hydrochloride 25 microgram tablets outweigh the risks; hence a Marketing Authorisation (MA) has been granted.

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Module 1

Information About Initial Procedure

Product Name	Clonidine hydrochloride 25 microgram tablets
Type of Application	Generic, Article 10.1
Active Substance	clonidine hydrochloride
Form	tablets
Strength	25 mcg
MA Holder	Auden McKenzie (Pharma Division) Ltd. Unit 30 Stadium Business Centre North End Road Wembley Middlesex HA9 0AT UK
RMS	UK
CMS	Ireland
Procedure Number	UK/H/1448/01/DC
Timetable	Day 210 – 30th October 2008

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clonidine Hydrochloride 25 microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains clonidine hydrochloride 25 micrograms.

Excipients:

Clonidine Hydrochloride 25 microgram Tablets contain 48 mg lactose monohydrate per tablet.

For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white circular tablet, engraved with ‘CD 25’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

a) The prophylactic management of migraine or recurrent vascular headache.

b) The management of vasomotor conditions commonly associated with the menopause and characterised by flushing.

4.2 Posology and method of administration

Adults:

Initially 2 tablets twice daily. If after two weeks there has been no remission, increase to 3 tablets twice daily.

The duration of treatment depends upon the severity of the condition.

If symptoms continue to occur the patient should be informed that it may take 2 - 4 weeks until Clonidine Hydrochloride 25 microgram Tablets are fully effective.

Children:

Not generally recommended for administration to children under 12 years.

Elderly:

No specific information on the use of this product in the elderly is available.

4.3 Contraindications

Clonidine Hydrochloride 25 microgram Tablets should not be used in patients with severe bradyarrhythmia resulting from either sick-sinus syndrome or AV block of 2nd or 3rd degree, or in patients with known hypersensitivity to the active ingredient, clonidine, or other components of the product.

4.4 Special warnings and precautions for use

Clonidine Hydrochloride 25 microgram Tablets should be used with caution in patients with cerebrovascular disease, coronary insufficiency, heart failure, occlusive peripheral vascular disorders, such as Raynaud's disease, constipation or those with a history of depression.

At doses higher than those recommended above, clonidine is an effective antihypertensive agent. Caution should therefore be observed where antihypertensive agents are being used, as potentiation of

the hypotensive effect may occur. Provided the recommended dosage regimen is followed, no difficulty with hypotension should arise during the routine management of patients with either migraine or menopausal flushing.

Depending on the dose given, clonidine hydrochloride can cause bradycardia. In patients with pre-existing cardiac conduction abnormalities, arrhythmias have been observed after high doses of clonidine hydrochloride.

Patients with renal failure require extreme care.

Where clonidine is already being used for the management of hypertension, Clonidine Hydrochloride 25 microgram Tablets therapy is not indicated.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of antihypertensive agents, vasodilators or diuretics may lead to an increased hypotensive effect.

Substances with alpha$_2$-receptor blocking properties, such as mirtazapine, may abolish the alpha$_2$-receptor mediated effects of clonidine in a dose-dependent manner.

Concomitant use of beta-blockers and/or cardiac glycosides can cause bradycardia or dysrhythmia (AV-block) in isolated cases.

It cannot be ruled out that concomitant administration of a beta-receptor blocker will cause or potentiate peripheral vascular disorders.

If during combined treatment with a beta-blocker there is a need to interrupt or discontinue antihypertensive therapy, the beta-blocker must always be discontinued slowly first (reducing the dose gradually to avoid sympathetic hyperactivity), and then the Clonidine Hydrochloride 25 microgram Tablets, which should also be reduced gradually over several days if previously given in high doses.

Orthostatic hypotension may be provoked or aggravated by concomitant administration of tricyclic antidepressants or neuroleptics with alpha-receptor blocking properties.

As the effects of clonidine can be antagonised by tricyclic anti-depressants, it may be necessary to adjust the dosage of Clonidine Hydrochloride 25 microgram Tablets, if these agents are administered concurrently.

Although there is no experience from clinical trials, the effect of tranquillisers, hypnotics or alcohol could theoretically be potentiated by Clonidine Hydrochloride 25 microgram Tablets.

4.6 Pregnancy and lactation

Clonidine Hydrochloride 25 microgram Tablets should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh any possible risk to the foetus.

In animal studies involving doses higher than the equivalent maximum therapeutic dose in man, effects on foetal development were only seen in one species. Foetal malformations did not occur.

Careful monitoring of mother and child is recommended.

Clonidine passes the placental barrier and may lower the heart rate of the foetus. Post partum a transient rise in blood pressure in the newborn cannot be excluded.

There is no adequate experience regarding the long-term effects of prenatal exposure.

The use of Clonidine Hydrochloride 25 microgram Tablets during lactation is not recommended due to a lack of supporting information.

4.7 Effects on ability to drive and use machines

Because of different individual reactions including drowsiness, the ability to drive or operate machinery may be impaired, particularly in the initial phase of treatment with Clonidine Hydrochloride 25 microgram Tablets.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥1/10,000, < 1/1,000), very rare (< 1/10,000) and unknown (cannot be calculated from the available data).

Cardiac disorders: Bradyarrhythmic conditions such as sinus bradycardia or AV-block.

Nervous system disorders: Initial sedation in some patients when therapy is started; dizziness; nocturnal unrest; headache; paraesthesia of the extremities. Very rarely: perceptual disorders; nightmares.

Eye disorders: Disturbances of accommodation. Very rarely: reduced lachrymal flow (caution: contact lens wearers).

Respiratory, thoracic and mediastinal disorders: Very rarely: drying of nasal mucosa.

Gastrointestinal disorders: Initial dry mouth in some patients when therapy is started; nausea; vomiting. Rarely: constipation. Very rarely: pain in the parotid gland; pseudo-obstruction of the large bowel.

Skin and subcutaneous tissue disorders: Very rarely: alopecia.

Vascular disorders: Orthostatic hypotension, but only following the first administration of high doses. Rarely: disturbances in peripheral blood flow, such as Raynaud's phenomenon.

General disorders and administration site conditions: Malaise.

Immune system disorders: Very rarely, and only after very high doses of clonidine: hypersensitivity reactions, for example skin rash, urticaria and pruritus.

Reproductive system and breast disorders: Rarely: impotence. Very rarely: gynaecomastia.

Psychiatric disorders: Decreased libido; hallucinations; confusion. Very rarely: depressive moods.

Investigations: Rarely: transient elevations of blood sugar levels.

4.9 Overdose

Symptoms:

Manifestations of intoxication are due to generalised sympathetic depression and include pupillary constriction, sedation to coma, hypotension, orthostatic hypotension, bradycardia, hypothermia, apnoea, occasionally vomiting, very occasionally hypertension, dryness of the mouth.

Treatment:

Gastric lavage and/or administration of activated charcoal should be performed where appropriate. In most cases all that is required are general supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code N02C X02

Clonidine is an antihypertensive agent which acts centrally by stimulating alpha$_2$-adrenergic receptors and producing a reduction in sympathetic tone, resulting in a fall in diastolic and systolic blood pressure and a reduction in heart rate.

Treatment with Clonidine Hydrochloride 25 microgram Tablets 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.

5.2 Pharmacokinetic properties

Clonidine is well absorbed from the gastro-intestinal tract. Peak plasma concentrations are observed 3 to 5 hours post administration, decreasing with a half life of up to approximately 23 hours. Clonidine is metabolised in the liver. About 65% is excreted in the urine, partly as unchanged clonidine and about 20% is excreted in the faeces.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Maize starch

Pregelatinised maize starch

Lactose monohydrate

Talc

Sodium starch glycolate Type A

Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium blister.

Each box contains 112 tablets (4 blister strips of 28 tablets each).

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Auden Mckenzie (Pharma Division) Ltd
Unit 30 Stadium Business Centre
North End Road
Wembley
Middlesex
HA9 0AT
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 17507/0094

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/11/2008

10 DATE OF REVISION OF THE TEXT

18/11/2008

Module 3

Product Information Leaflet

PATIENT INFORMATION LEAFLET

Clonidine Hydrochloride 25 microgram Tablets

Keep this leaflet. You may need to read it again.
If you have any further questions, ask your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What is Clonidine Hydrochloride and what is it used for?

Clonidine Hydrochloride 25 microgram Tablets belong to a group of medicines called 'vasodilators', which cause widening of the blood vessels and therefore an increase in blood flow.

Your doctor has prescribed Clonidine Hydrochloride 25 microgram Tablets for you to prevent attacks of migraine and similar types of headache. The tablets are also used to prevent hot flushes that may occur in women during the menopause ('change of life').

2. Before you take Clonidine Hydrochloride 25 microgram Tablets

Do not take Clonidine Hydrochloride 25 microgram Tablets:
- if you think that you may have had an allergic, or any other type of, reaction to Clonidine Hydrochloride 25 microgram Tablets, or a similar medicine, in the past. An allergic reaction may be recognised as a rash, itching, swollen face or lips, or shortness of breath;
- if you have a slow heart rate resulting from a disease of the heart called 'sick-sinus syndrome' or severe heart problems.

Clonidine Hydrochloride 25 microgram Tablets must only be used to treat the condition(s) your doctor has given you this medicine for.

Other things to do or know before you take the tablets
If the answer to any of the following questions is '**Yes**', you may still be able to take Clonidine Hydrochloride 25 microgram Tablets, but you should discuss this with your doctor before taking the tablets:

- Do you have cerebrovascular disease (problems with blood flow to the brain)?
- Do you have heart or severe kidney problems?
- Do you suffer from cold and numb hands and feet, eg Raynaud's disease?
- Do you suffer from constipation?
- Have you ever suffered from depression?

Taking other medicines
Always tell your doctor if you are taking any other medicines (including those you bought yourself without a prescription) because taking some medicines together with Clonidine Hydrochloride 25 microgram Tablets can be harmful.

In particular, you should tell your doctor if you are taking any of the following medicines, as they can affect the way the tablets work:

- certain medicines used to lower blood pressure *(antihypertensives and alpha-blockers); alpha-blockers* are medicines also used to treat swelling of the prostate gland
- certain medicines that relax blood vessels *(vasodilators)*
- water tablets *(diuretics)*
- medicines which are often used to slow the heart rate or lower the blood pressure *(beta blockers)*
- medicines used to treat heart failure *(cardiac glycosides)*
- certain medicines used to treat depression *(tricyclic antidepressants)*
- other antidepressants, eg mirtazapine
- certain medicines used to relieve anxiety such as tranquillisers, hypnotics (and also alcohol) *(neuroleptics)*

Pregnancy and breast feeding
Tell the doctor if you are pregnant, think you might be pregnant or are trying to become pregnant. Clonidine Hydrochloride 25 microgram Tablets can reach your baby and may lower your baby's heart rate.

Clonidine Hydrochloride 25 microgram Tablets are not recommended for use while breast feeding; tell your doctor if you are breast feeding.

Driving and using machines
Medicines like Clonidine Hydrochloride 25 microgram Tablets may occasionally cause drowsiness. If you are affected in this way, do not drive or operate machinery.

Important information about some of the ingredients in Clonidine Hydrochloride 25 microgram Tablets
This medicine contains **lactose monohydrate**. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Clonidine Hydrochloride 25 microgram Tablets

Take the tablets by mouth, exactly as your doctor, pharmacist or medicine label tells you to.

The usual recommended dose is as follows:

Adults:	**Two to three tablets twice a day**
Children:	**Clonidine Hydrochloride 25 microgram Tablets should not be given to children under 12 years of age**

The tablets should be swallowed whole with water, with or without food.

It may take 2 to 4 weeks for the medicine to work properly.

If you take too many tablets
Contact your doctor or pharmacist as soon as possible. Always take the labelled medicine container with you whether or not there are any Clonidine Hydrochloride 25 microgram Tablets left.

If you forget to take a dose
Take a dose as soon as you remember, then carry on as before.

4. Possible side effects

Like all medicines, these tablets may cause side effects, although not everyone gets them.

Clonidine Hydrochloride 25 microgram Tablets may occasionally cause drowsiness, a dry mouth, dizziness, nausea (feeling sick) and restlessness at night. A fall in blood pressure on standing, which can cause light headed feelings or dizziness (orthostatic hypotension), has been reported, but only following the first time a high dose was taken.
Other possible side effects include vomiting, headache, generally feeling unwell (malaise), reduction in sexual desire (libido), tingling or numbness of the hands or feet, hallucinations (visions), confusion and blurred vision. Irregular heart beat has also been reported.

Rarely, constipation, an inability to get or maintain an erection (impotence) and problems with the blood flow in the limbs (eg Raynaud's type symptoms) have occurred. A brief rise in blood sugar levels has also been reported.

Very rarely, and only after very high doses of clonidine, there have been reports of hypersensitivity (allergic) reactions (including skin rash, localised swelling of the face, tongue and lips, and difficulty with breathing),

hair loss (alopecia), problems with awareness, nightmares, enlargement of male breast tissue, pain in the parotid gland (a gland below the ear), feeling depressed, dry nose and eyes (this may be a problem for people who wear contact lenses).

Very rarely, a condition known as pseudo-obstruction of the large bowel has been seen; symptoms include colicky pain, constipation and vomiting.

If you experience any of these side effects and they continue, or become troublesome, please tell your doctor or pharmacist. Also tell your doctor or pharmacist if you experience any other effect not mentioned above.

5. How to store Clonidine Hydrochloride 25 microgram Tablets

Keep out of the reach and sight of children.

Do not use Clonidine Hydrochloride 25 microgram Tablets after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Clonidine Hydrochloride 25 microgram Tablets contain

Active substance:
Each tablet contains clonidine hydrochloride 25 micrograms.

Other ingredients: Microcrystalline cellulose, maize starch, pregelatinised maize starch, lactose monohydrate, talc, sodium starch glycolate Type A and magnesium stearate.

Each box of Clonidine Hydrochloride 25 microgram Tablets contains 112 white to off-white, circular tablets with 'CD 25' engraved on one side, in 4 blister strips of 28 tablets each.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation holder
Auden Mckenzie (Pharma Division) Ltd
30 Stadium Business Centre
North End Road
Middlesex
HA9 0AT
UK

Manufacturer
TioFarma BV
Benjamin Franklinstraat 9
Oud-Beijerland
The Netherlands

This leaflet was last approved in October 2008

For information in large print, tape, CD or Braille, telephone +44 (0)20 8900 2122

Clonidine Hydrochloride 25 microgram tablets
PL 17507/0094
PA 1352/4/1

Auden Mckenzie

AUDEN MCKENZIE (PHARMA DIVISION) LIMITED

C822/1

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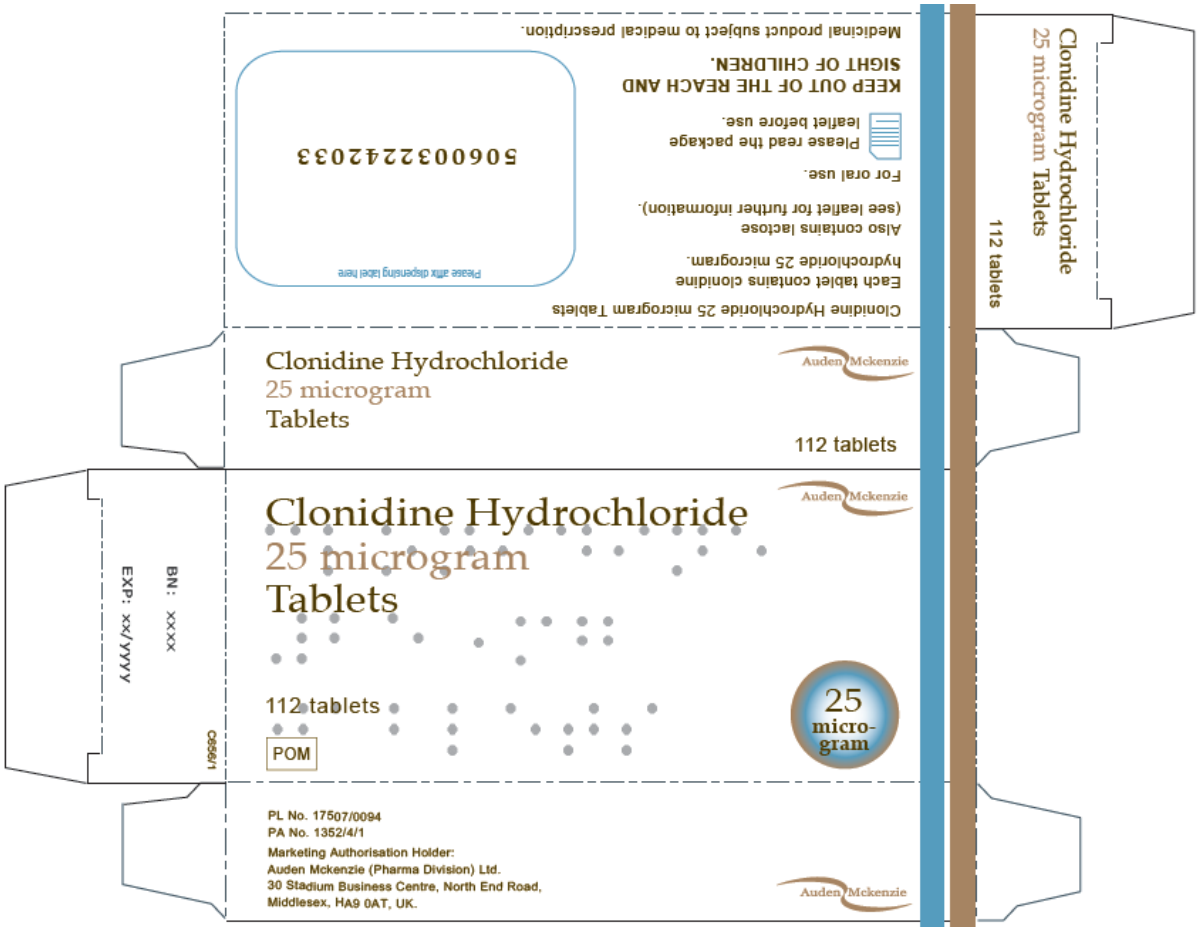
Module 4

Labelling

Carton with Braille



Blister foil

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Auden Mckenzie Limited a Marketing Authorisation for the medicinal product Clonidine hydrochloride 25 microgram tablets (PL 17507/0094, UK/H/1448/01/DC). The product is a prescription-only medicine, indicated for the prophylactic management of migraine or recurrent vascular headache, and for the management of vasomotor conditions commonly associated with the menopause and characterised by flushing.

This is an abridged application for Clonidine hydrochloride 25 microgram tablets, submitted under Article 10.1 of 2001/83 EC, as amended, making reference to Dixarit Tablets 25mcg (PL 00015/5014R, Boehringer Ingelheim Limited), which was granted a Marketing Authorisation in the UK on 22nd December 1986. The reference product has been authorised in the European Community for more than 10 years, so the period of data exclusivity has expired. The test product was considered to be a generic version of the originator product, Dixarit Tablets 25mcg, based on the data submitted by Auden Mckenzie Limited.

Clonidine hydrochloride is an antihypertensive agent which acts centrally by stimulating alpha$_2$-adrenergic receptors and producing a reduction in sympathetic tone, resulting in a fall in diastolic and systolic blood pressure and a reduction in heart rate.

Treatment with Clonidine Hydrochloride 25 microgram Tablets 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.

No new preclinical or clinical efficacy studies were conducted, which is acceptable given that the application was for a generic version of a product that has been licensed for over 10 years.

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product to that of the reference product, Dixarit Tablets 25mcg (Boehringer Ingelheim Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Clonidine hydrochloride 25 microgram tablets
Name(s) of the active substance(s) (INN)	clonidine hydrochloride
Pharmacotherapeutic classification (ATC code)	Anti-migraine preparations (N02C X02)
Pharmaceutical form and strength(s)	tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/1448/01/DC
Reference Member State	United Kingdom
Member States concerned	Ireland
Marketing Authorisation Number(s)	PL 17507/0094
Name and address of the authorisation holder	Auden McKenzie (Pharma Division) Ltd. Unit 30 Stadium Business Centre North End Road Wembley Middlesex HA9 0AT UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

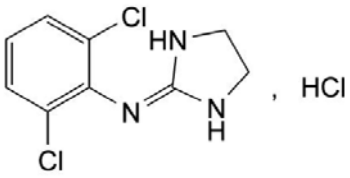
Clonidine hydrochloride

Nomenclature:

INN: Clonidine hydrochloride

Chemical name: 2-(2,6-dichloroanilino)-2-imidazoline hydrochloride

Structure:



Molecular formula: $C_9H_{10}Cl_3N_3$

Molecular weight: 266.6

CAS No: 4205-91-8

Physical form: White or almost white, crystalline powder

Solubility: Soluble in water and dehydrated alcohol

The active substance, clonidine hydrochloride, is the subject of a European Pharmacopeia (EP) monograph.

All aspects of the manufacture and control of clonidine hydrochloride are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of clonidine hydrochloride for inclusion in this medicinal product.

Active clonidine hydrochloride is stored in appropriate packaging. The active substance is packed in double polyethylene bags, tightly sealed, and is then placed in a carton closed with a plastic lid. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance satisfies Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed packaging. These data demonstrate the stability of the active substance and an appropriate retest period of 36 months has been set.

DRUG PRODUCT

Other ingredients

The drug product is presented as a white to off-white circular tablet, engraved with 'CD 25' on one side, and contains 25 micrograms of the active substance, clonidine hydrochloride.

Other ingredients consist of pharmaceutical excipients, namely pregelatinised maize starch, microcrystalline cellulose, maize starch, lactose monohydrate, talc, sodium starch glycolate Type A and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

There were no novel excipients used and no overages.

Dissolution profiles

Satisfactory comparative dissolution profiles for the test and innovator products were provided.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specification is provided for both release and shelf life and is satisfactory; it provides an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished products are licensed for marketing in polyvinylchloride (PVC) / aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in a pack size of 112 tablets (4 blister strips of 28 tablets).

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. There are no special storage instructions.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Clonidine hydrochloride 25 microgram tablets, to the reference product, Dixarit Tablets 25mcg (Boehringer Ingelheim Limited).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Quality Overall Summary

A satisfactory QOS is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling fulfils the statutory requirements for Braille.

Conclusion

The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. On this basis, and considering the bioequivalence data provided, the applicant's claim that Clonidine hydrochloride 25 microgram tablets is a generic medicinal product of Dixarit Tablets 25mcg (Boehringer Ingelheim Limited) is justified.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation has therefore been granted.

III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for this application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacological, pharmacokinetic and toxicological properties of clonidine hydrochloride, which is a widely used and well-known active substance.

III.3 CLINICAL ASPECTS

INDICATIONS

Clonidine hydrochloride 25 microgram tablets are indicated for the prophylactic management of migraine or recurrent vascular headache, and for the management of vasomotor conditions commonly associated with the menopause and characterised by flushing.

The indications are consistent with those for the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY

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

CLINICAL PHARMACOLOGY

The clinical pharmacology of clonidine hydrochloride is well known. No novel pharmacodynamic data are supplied or required for this application.

Pharmacokinetics – bioequivalence study

The applicant has conducted a single bioequivalence study comparing the pharmacokinetic profiles of Clonidine hydrochloride 25 microgram tablets (test) and Dixarit Tablets 25mcg, Boehringer Ingelheim Limited (reference). The study was of an appropriate design and was conducted to principles of good clinical and laboratory practice (GCP and GLP).

This was an open-label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioavailability and bioequivalence study conducted in healthy adult human male subjects under fasting conditions.

A single dose of the investigational products was administered orally to each subject (while in a sitting position) in each period with 240 ml of water, after an overnight fast of at least 10 hours. Subjects were instructed not to chew or crush the tablets but to consume them as a whole. The subjects were not allowed to lie down for two hours after dosing. A satisfactory washout period of 8 days was maintained between the two dosing days in each group.

Serial blood sampling before dosing and up to 96 hours after drug administration was carried out in each group. Plasma samples for all subjects that completed the trial successfully were analysed to quantify the concentration of clonidine using a validated LC/MS/MS bio-analytical method.

The primary pharmacokinetic parameters for this study were $\mathbf{C}_{max}$, AUC_{0-t}, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

The results are summarised in the table below:

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} pg/ml/h	$AUC_{0-\infty}$ pg/ml/h	C_{max} pg/ml
Test (N=33)	2969.61	4265.22	255.13
Reference (N=33)	2843.93	4618.98	245.88
*Ratio (90% CI)	100.52 (90.33-111.86)	95.27 (81.89-110.84)	104.52 (96.81-112.84)
$AUC_{0-\infty}$ - area under the plasma concentration-time curve from time zero to infinity AUC_{0-t} - area under the plasma concentration-time curve from time zero to t hours. C_{max} - maximum plasma concentration.			

ln-transformed values

No serious or significant adverse events were reported during the study.

Conclusion on Bioequivalence

The results of the study show that the test product and reference product are bioequivalent as the confidence intervals for C_{max} and AUC fall within the acceptance criteria range of 80-125% in line with current guidelines.

Clinical efficacy

No novel efficacy data are supplied or required for this application.

Clinical safety

No novel safety data are supplied or required for this application.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The final SmPC is consistent with that for the innovator product, and is acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

Expert report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSIONS & DISCUSSION

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test and reference formulations within normal acceptance limits. The use of clonidine hydrochloride is well established. It has recognised efficacy and acceptable safety in the approved indications. Sufficient clinical information has been submitted to support this application, including an adequate review of published clinical data. A Marketing Authorisation was therefore granted.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Clonidine hydrochloride 25 microgram tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Clonidine hydrochloride 25 microgram tablets and the reference product, Dixarit Tablets 25mcg (Boehringer Ingelheim Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The testing shows that the patients/users are able to act upon the information that the leaflet contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and other data provided support the claim that the applicant's Clonidine hydrochloride 25 microgram tablets is a generic version of the reference product, Dixarit Tablets 25mcg. Extensive clinical experience with clonidine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

Date submitted	Application type	Scope	Outcome