Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Cinnarizine 15mg Tablets

cinnarizine

PL 48836/0014

Osgen Pharmaceuticals Limited

LAY SUMMARY

Cinnarizine 15mg Tablets
cinnarizine

This is a summary of the Public Assessment Report (PAR) for Cinnarizine 15mg tablets. It explains how this product 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 this product.

This product will be referred to as Cinnarizine tablets in this lay summary for ease of reading.

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

What is Cinnarizine tablets and what is it they used for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Stugeron 15 mg Tablets.

Cinnarizine tablets are used:
- to control motion sickness
- for problems with balance (such as Ménières disease) to treat symptoms of:
- feeling dizzy or lightheaded
- ringing in the ears
- feeling sick (nausea) and being sick (vomiting)

This medicine is for use in adults and children aged over 5 years.

How do Cinnarizine tablets work?
The tablets contain a medicine called cinnarizine that helps symptoms caused by balance or movement problems.

How is Cinnarizine tablets used?
The pharmaceutical form of this medicine is tablets and the route of administration is by mouth (oral).

Patients must not exceed the recommended dose.

This medicine should be taken after a meal. The tablets may be sucked, chewed, or swallowed whole with water.

This medicine is not recommended for children aged under 5 years old.

Dose for control of motion sickness

Adults and children over 12 years old:
2 tablets 2 hours before travelling then 1 tablet every 8 hours during the journey.

Children aged 5 – 12 years old
1 tablet 2 hours before travelling then half a tablet every 8 hours during the journey.

For problems with balance

Adults and children over 12 years old:
2 tablets 3 times a day.

Children aged 5 – 12 years old
1 tablet 3 times a day.

For further information on how Cinnarizine tablets is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can be obtained without 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 Cinnarizine tablets have been shown in studies?
Because Cinnarizine tablets is 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 Cinnarizine tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC 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 Cinnarizine tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was Cinnarizine tablets approved?
It was concluded that, Cinnarizine tablets 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 Cinnarizine tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Cinnarizine tablets The RMP details the important risks of Cinnarizine tablets, how these risks can be minimised, any uncertainties about Cinnarizine tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Cinnarizine tablets:

Important identified risks:
- Hypersensitivity, including allergic reactions to cinnarizine or any excipients.
- Use in patients with Parkinson's Disease
- Use in patients with porphyria
- Increased sedation when taken concomitantly with alcohol and CNS depressants

Important potential risks:
- Effect on ability to drive and use machines
- Overdose

Missing information:
- Use in pregnancy and lactation
- Use in patients with hepatic or renal insufficiency

The information included in the SmPC 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 Cinnarizine tablets 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 this application and are satisfactory.

Other information about Cinnarizine tablets
A marketing authorisation for Cinnarizine tablets was granted in the United Kingdom (UK) on 30 May 2022.

The full PAR for Cinnarizine tablets follows this summary.

This summary was last updated in July 2022.

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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 application for Cinnarizine 15 mg tablets (PL 48836/0014) could be approved.

The product is approved for the following indications:
Disorders of balance - maintenance therapy for symptoms of labyrinthine disorders, including vertigo, tinnitus, nystagmus, nausea and vomiting such as is seen in Meniere's Disease.

Prophylaxis of motion sickness

Cinnarizine has been shown to be a non-competitive antagonist of the smooth muscle contractions caused by various vasoactive agents including histamine.

Cinnarizine also acts on vascular smooth muscle by selectively inhibiting the calcium influx into depolarised cells, thereby reducing the availability of free Ca^{2+} ions for the induction and maintenance of contraction.

Vestibular eye reflexes induced by caloric stimulation of the labyrinth in guinea pigs are markedly depressed by cinnarizine.

Cinnarizine has been shown to inhibit nystagmus.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Stugeron 15 mg Tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a 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 this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Cinnarizine tablets was granted in the United Kingdom (UK) on 30 May 2022.

II QUALITY ASPECTS

II.1 Introduction

The active substance is cinnarizine. Each tablet contains 15 mg of cinnarizine. The other ingredients are lactose anhydrous, maize starch, mannitol, povidone K90, talc, and magnesium stearate.

The finished product is packaged in PVC/PVdC /Aluminium foil blister packs in pack sizes of 10, 20, 30, 50 and of 100 tablets. Not all pack sizes may be marketed.

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.

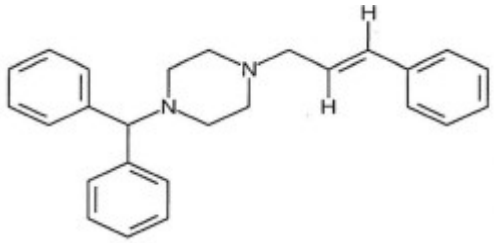
II.2 ACTIVE SUBSTANCE

rINN: Cinnarizine

Chemical Name: (E)-1-(Diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine

Molecular Formula: $C_{26}H_{28}N_2$

Chemical Structure:



Molecular Weight: 368.5 g/mol

Appearance: A white or almost white powder.

Solubility: Practically insoluble in water, freely soluble in methylene chloride, soluble in acetone and slightly soluble in ethanol (96%) and in methanol.

Cinnarizine 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 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, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

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

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does 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 formulation data 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 Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, without special storage conditions, 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 a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of cinnarizine 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 this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of a marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of cinnarizine is well-known. With the exception of data from ARL/20/265 a bioequivalence study undertaken, 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 study,ARL/20/265.

A randomised, open-label, balanced, two treatment, two period, two sequence, single dose, two-way crossover, bioequivalence study of Cinnarizine 15 mg Tablets (Test) and Stugeron 15 mg Tablets (Reference) in healthy subjects under fed conditions.

A single dose of cinnarizine 15 mg tablet (test or reference product) was swallowed whole with water after an overnight fast of 10.00 hours before consumption of high-fat and high-calories breakfast which was started by each subject 30 min prior to dosing. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 12 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Parameters	*Geometric LSM		% Ratio (T/R)	Power (%)	ISCV (%)	90 % Confidence Interval for T/R Ratio	
	Test (T)	Reference (R)				Lower Limit	Upper Limit
AUC_{0-t} (ng*hr/mL)	553.7013	544.8159	101.6309	99.9957	8.7762	96.2358	107.3285
C_{max} (ng/mL)	60.7530	62.2933	97.5273	96.0398	17.4004	87.5828	108.6011

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 have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application 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 application.

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 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.

This is acceptable.

IV.7 Discussion on the clinical aspects

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

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 with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to Cinnarizine 15 mg Tablets, (MAH – Teva UK Limited;PL 00289/1440). The bridging report submitted by the applicant is acceptable.

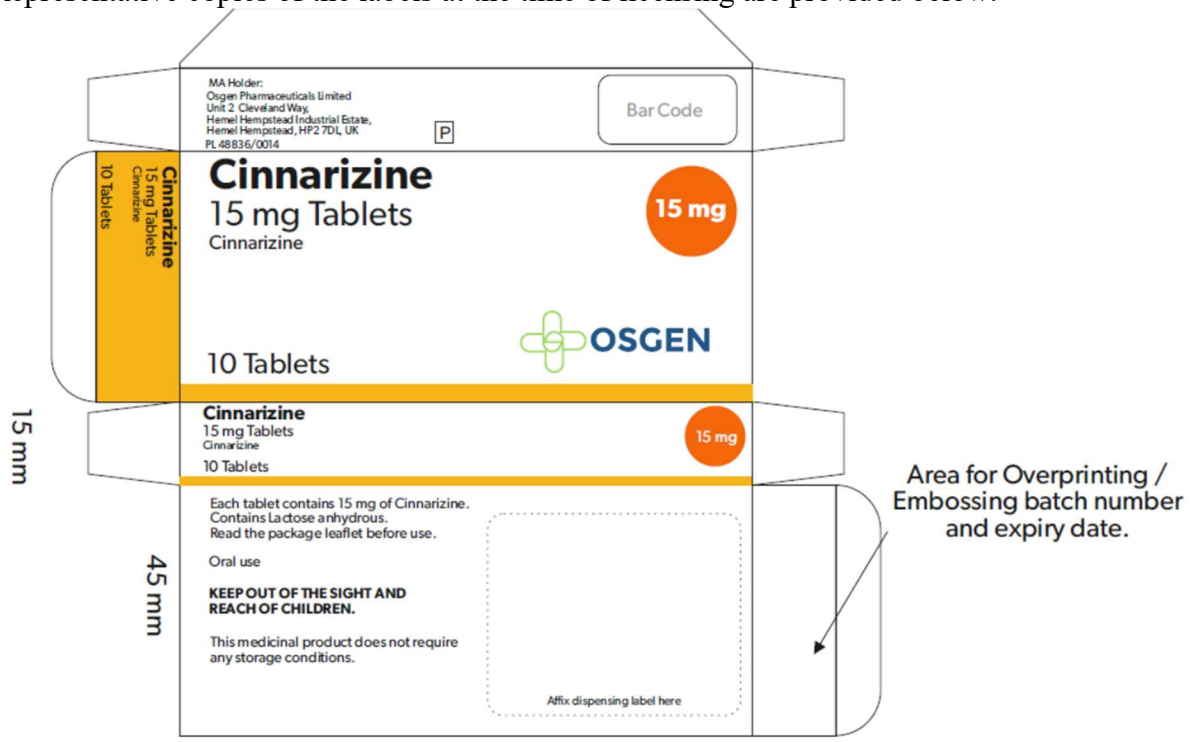
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

In accordance with legal requirements, 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 licensing are provided below.



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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**