SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cinnarizine/Dimenhydrinate 20 mg/40 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg cinnarizine and 40 mg dimenhydrinate.

Excipient with known effect

Sodium (in croscarmellose sodium) 0.42 mg per tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white, round, biconvex, uncoated tablets debossed with ‘C’ on one face and plain on other face with a diameter of approximately 8.00 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of vertigo symptoms of various origins.
Cinnarizine/dimenhydrinate is indicated in adults.

4.2 Posology and method of administration

Posology

Adults:

1 tablet three times daily.

Elderly:

Dosage as for adults.

Renal impairment:

Cinnarizine/dimenhydrinate should be used with caution in patients with mild to moderate renal impairment. Cinnarizine/dimenhydrinate should not be used by patients with a creatinine clearance of ≤ 25 ml/min (severe renal impairment).

Hepatic impairment:

No studies in patients with hepatic impairment are available. Cinnarizine/dimenhydrinate should not be used by patients with severe hepatic impairment.

Paediatric population:

The safety and efficacy of cinnarizine/dimenhydrinate in children and adolescents under the age of 18 years has not been established. No data are available.

In general, the duration of treatment should not exceed four weeks. The physician shall decide whether longer treatment is required.

Method of administration

Cinnarizine/dimenhydrinate tablets are to be taken unchewed, with some liquid after meals.

4.3 Contraindications

Hypersensitivity to the active substances, diphenhydramine or other antihistamines of similar structure or to any of the excipients listed in section 6.1.

Diphenhydramine is completely excreted renally, and patients with severe renal impairment were excluded from the clinical development programme. Cinnarizine/dimenhydrinate should not be used by patients with a creatinine clearance of ≤ 25 ml/min (severe renal impairment).

Since both active components of cinnarizine/dimenhydrinate are extensively metabolised by hepatic cytochrome P450 enzymes, the plasma concentrations of the unchanged drugs and their half-lives will increase in patients with severe hepatic impairment. This has been shown for diphenhydramine in patients with cirrhosis. Cinnarizine/dimenhydrinate should therefore not be used by patients with severe hepatic impairment.

Cinnarizine/dimenhydrinate should not be used in patients with angle-closure glaucoma, convulsions, suspicion of raised intracranial pressure, alcohol abuse or urine retention due to urethroprostatic disorders.

4.4 Special warnings and precautions for use

Cinnarizine/dimenhydrinate does not reduce blood pressure significantly, however, it should be used with caution in hypotensive patients.

Cinnarizine/dimenhydrinate should be taken after meals to minimise any gastric irritation.

Cinnarizine/dimenhydrinate should be used with caution in patients with conditions that might be aggravated by anticholinergic therapy, e.g. raised intra-ocular pressure, pyloro-duodenal obstruction, prostatic hypertrophy, hypertension, hyperthyroidism or severe coronary heart disease.

Caution should be exercised when administering cinnarizine/dimenhydrinate to patients with Parkinson's disease.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
The anticholinergic and sedative effects of cinnarizine/dimenhydrinate may be potentiated by monoamine oxidase inhibitors. Procarbazine may enhance the effect of cinnarizine/dimenhydrinate.
In common with other antihistamines, cinnarizine/dimenhydrinate may potentiate the sedative effects of CNS depressants including alcohol, barbiturates, narcotic analgesics and tranquillisers. Patients should be advised to avoid alcoholic drinks. Cinnarizine/dimenhydrinate may also enhance the effects of antihypertensives, ephedrine and anticholinergics such as atropine and tricyclic antidepressants.
Cinnarizine/dimenhydrinate may mask ototoxic symptoms associated with amino glycosidic antibiotics and mask the response of the skin to allergic skin tests.
The concomitant administration of medicines that prolong the QT interval of the ECG (such as Class Ia and Class III anti-arrhythmics) should be avoided.
The information about potential pharmacokinetic interactions with cinnarizine and diphenhydramine and other medicinal products is limited.
Diphenhydramine inhibits CYP2D6 mediated metabolism and caution is advised if Cinnarizine/dimenhydrinate is combined with substrates of this enzyme, especially those with narrow therapeutic range.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of cinnarizine/dimenhydrinate in human pregnancy has not been established. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development and postnatal development (see section 5.3). The teratogenic risk of the single actives

dimenhydrinate/diphenhydramine and cinnarizine is low. No teratogenic effects were observed in animal studies.

There are no data from the use of cinnarizine/dimenhydrinate in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
Based on human experience dimenhydrinate is suspected to have an oxytocic effect and may shorten labour.
Cinnarizine/dimenhydrinate is not recommended during pregnancy.
Breast-feeding
Dimenhydrinate and cinnarizine are excreted in human breast milk.
Cinnarizine/dimenhydrinate should not be used during breast-feeding.
Fertility
Not known.

4.7 Effects on ability to drive and use machines

Cinnarizine/dimenhydrinate may have minor influence on the ability to drive and use machines.

Cinnarizine/dimenhydrinate may cause drowsiness, especially at the start of treatment. Patients affected in this way should not drive or operate machinery.

4.8 Undesirable effects

The most frequently occurring ADRs are somnolence (including drowsiness, tiredness, fatigue, daze) occurring in about 8% of patients and dry mouth occurring in about 5% of patients in clinical trials. These reactions are usually mild and disappear within a few days even if treatment is continued. The frequency of ADRs associated with cinnarizine/dimenhydrinate in clinical trials and following spontaneous reports are included in the next table.

Tabulated list of adverse reactions:

Frequency of ADR	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1 000 to < 1/100**	**Rare ≥ 1/10 000 to < 1/1 000**	**Very rare < 1/10 000**
System organ class:				
Blood and Lymphatic System disorders				Leukopenia Thrombopenia Aplastic anaemia
Immune System disorders			Hypersensitivity reactions (e.g. cutaneous reactions)	

Nervous System disorders	Somnolence Headache	Paraesthesia Amnesia Tinnitus Tremor Nervousness Convulsions		
Eye disorders			Visual disorders	
Gastrointestinal disorders	Dry mouth Abdominal pain	Dyspepsia Nausea Diarrhoea		
Skin and subcutaneous tissue disorders		Perspiration Rash	Photosensitivity	
Renal and urinary disorders			Urinary hesitancy	

In addition the following adverse reactions are associated with dimenhydrinate and cinnarizine (frequency cannot be estimated from the available data):

Dimenhydrinate: paradoxical excitability (especially in children), worsening of an existing angle-closure glaucoma, reversible agranulocytosis.

Cinnarizine: constipation, weight gain, tightness of the chest, cholestatic jaundice, extrapyramidal symptoms, lupus-like skin reactions, lichen planus.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store.

4.9 Overdose

Symptoms of overdosage with cinnarizine/dimenhydrinate include drowsiness, dizziness and ataxia with anticholinergic effects such as dry mouth, flushing of the face, dilated pupils, tachycardia, pyrexia, headache and urinary retention. Convulsions, hallucinations, excitement, respiratory depression, hypertension, tremor and coma may occur, particularly in cases of massive overdosage.

Management of overdose: General supportive measures should be used to treat respiratory insufficiency or circulatory failure. Gastric lavage with isotonic sodium chloride solution is recommended. Body temperature should be closely monitored, since pyrexia may occur as a consequence of antihistamine intoxication, especially in children.

Cramp-like symptoms may be controlled by careful application of a short-acting barbiturate. In cases of marked central-anticholinergic effects, physostigmine (after physostigmine test) should be administered slowly intravenously (or, if necessary, intramuscularly): 0.03 mg/kg body weight (adults max. 2 mg, children max. 0.5 mg).

Dimenhydrinate is dialyzable, however treatment of overdosage by this measure is considered as unsatisfactory. Sufficient elimination can be achieved by means of haemoperfusion using activated charcoal. No data are available concerning the dialysability of cinnarizine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivertigo preparations. ATC code: N07CA52.
Dimenhydrinate, the chlorotheophylline salt of diphenhydramine, acts as antihistamine with anticholinergic (antimuscarinic) properties, exerting parasympatholytic and centrally depressant effects. The substance exhibits anti-emetic and antivertiginous effects through influencing the chemoreceptor trigger zone in the region of the 4th ventricle. Dimenhydrinate thus acts predominantly on the central vestibular system.
Due to its calcium antagonistic properties, cinnarizine acts mainly as a vestibular sedative through inhibition of the calcium influx into the vestibular sensory cells. Cinnarizine thus acts predominantly on the peripheral vestibular system.
Both cinnarizine and dimenhydrinate are known to be effective in the treatment of vertigo. The combination product is more effective than the individual compounds in the population studied.
The product has not been evaluated in motion sickness.

5.2 Pharmacokinetic properties

Absorption and distribution:

Dimenhydrinate rapidly releases its diphenhydramine moiety after oral administration.

Diphenhydramine and cinnarizine are rapidly absorbed from the gastro-intestinal tract. Maximum plasma concentrations (Cmax) of cinnarizine and diphenhydramine are reached in humans within 2-4 hours. The plasma elimination half-lives of both substances range from

4-5 hours, when given either alone or as the combination product.

Biotransformation:

Cinnarizine and diphenhydramine are extensively metabolised in the liver. The metabolism of cinnarizine involves ring hydroxylation reactions that are in part catalysed by CYP2D6 and N- desalkylation reactions of low CYP-enzyme specificity. The main pathway in the diphenhydramine metabolism is the sequential N-demethylation of the tertiary amine. Studies in human liver microsomes in vitro indicate the involvement of various CYP-enzymes, including CYP2D6.

Elimination:

Cinnarizine is mainly eliminated via the faeces (40-60 %) and to a lower extent also in urine, mainly in the form of metabolites conjugated with glucuronic acid. The major route of elimination of diphenhydramine is in the urine, mainly in the form of metabolites, with the deaminated compound, diphenylmethoxy acetic acid, being the predominant metabolite

(40-60 %).

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of repeated dose toxicity with the combination of cinnarizine and dimenhydrinate, fertility with cinnarizine or dimenhydrinate, embryo/foetal development with dimenhydrinate and teratogenicity with cinnarizine. In one study in rats, cinnarizine decreased litter size, increased the number of resorbed foetuses and decreased the birth weight of pups.

The genotoxic and carcinogenic potential of the cinnarizine/dimenhydrinate combination has not been fully evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Croscarmellose sodium
Cellulose, microcrystalline (Grade 101 and 102)
Hypromellose (5 mPa S)
Silica, colloidal anhydrous (Grade 200)
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Cinnarizine/Dimenhydrinate 20 mg/40 mg tablets are available in PVC/PVDC-Alu blister pack.
Pack sizes:
Blister packs: 10, 20, 25, 28, 30, 40, 50, 60, 70, 80, 90 and 100 tablets.
Not all pack size may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Brown & Burk UK Ltd
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TW4 5DQ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25298/0366

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/12/2023

10 DATE OF REVISION OF THE TEXT

04/03/2024