Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Cinnarizine / Dimenhydrinate

Proprietary Product Names: Cizigo / Cizinate / Cizere

Sponsor: Southern Cross Pharma Pty Ltd

November 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARTG	Australian Register of Therapeutic Goods
AUC_{0-t}	Area under the drug concentration time curve from dosing to infinity
ASA	Australian specific annex
BPPV	Benign paroxysmal positional vertigo
CCG	Craniocorpography
CI	Confidence interval
C_{max}	Maximum plasma concentration
CMI	Consumer Medicine Information
CSSm	Mean concomitant symptom score
CNS	Central nervous system
CYP	Cytochrome P450 system
DIP	Drug induced parkinsonism
EEG	Electroencephalogram
EMA	European Medicine Agency (EU)
ENG	Electronystagraphy
EPAR	European Public Assessment Report (EMA)
ERP	Auditory event-related potential
EU	European Union
FDC	Fixed dose combination
GCP	Good Clinical Practice
H1	Histamine H1 receptor
hERG	Human ether-à-go-go

Abbreviation	Meaning
IC_{50}	Half maximal inhibitory concentration
ITT	Intent-to-treat
K_d	Dissociation constant
Ki	Inhibitor constant
LBS	Literature based submission
LOCF	Last observation carried forward
MD	Movement disorders
MHRA	Medicine and Healthcare products Regulatory Agency (UK)
MVS	Mean vertigo score
NHMRC	National Health and Medical Research Council (of Australia)
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PI	Product Information
PP	Per protocol
QTc	Corrected QT interval
RCT	Randomised controlled trial
RMP	Risk management plan
SAS	Special Access Scheme
SPC	Summary of Product Characteristics (EU)
SPECT	Single-photon emission computed tomography
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisoning
VAS	Visual Analog Scale
VSm	Mean vertigo score
UK	United Kingdom

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity in a fixed dose combination with a currently approved medicine
Decision:	Approved
Date of decision:	21 December 2018
Date of entry onto ARTG:	8 January 2019
ARTG numbers:	288565 (Cizigo); 288566 (Cizinate); and 288567 (Cizere)
, *Black Triangle Scheme*	No
Active ingredients:	Cinnarizine / dimenhydrinate
Product names:	Cizigo; Cizinate; and Cizere
Sponsor's name and address:	Southern Cross Pharma Pty Ltd Suite 5/118 Church St Hawthorn VIC 3122
Dose form:	Uncoated tablet
Strength:	Cinnarizine 20 mg / dimenhydrinate 40 mg
Container:	Blister pack
Pack sizes	20, 30, 50 and 100 tablets
Approved therapeutic use:	*Cizigo, Cizinate, Cizere (fixed-dose combination tablets) are indicated for the short-term, symptomatic treatment of vertigo of various causes, in adults who have not responded to alternative treatments.*
Route of administration:	Oral
Dosage:	The recommended dose for adults is one tablet three times daily. The lowest dose for the shortest duration to achieve symptom control should be used. The recommended dose should not be exceeded. In general, the duration of treatment should not exceed four weeks. For further details please see the Product Information.

Product background

This AusPAR describes the application by Southern Cross Pharma Pty Ltd (the sponsor) to register Cizigo/Cizinate/Cizere fixed dose combination (FDC) tablets containing cinnarizine 20 mg / dimenhydrinate 40 mg uncoated tablets blister pack for the following indication:

Treatment of vertigo symptoms of various origins.

Cinnarizine is a new chemical entity not previously registered in Australia.[1] Dimenhydrinate is registered in Australia as Dramamine tablets (AUST R 46979, 46980, and 46911) containing 50 mg dimenhydrinate and is also supplied in a FDC with caffeine and hyoscine hydrobromide as Travacalm Original tablets (AUST R 78192, and 14864).

Vertigo is an illusion of motion, which is most often experienced as a rotatory sensation, although it may also be linear in quality (for example, a sensation of falling or pitching). It is frequently accompanied by autonomic symptoms such as nausea, retching, vomiting, pallor and sweating.

Vertigo is often a result of pathology in one of the inner ear balance organs. This may be due to hypofunction (for example, with vestibular neuritis) or hyperfunction (as with benign paroxysmal positional vertigo). It can also result from central neurological disorders affecting vestibular pathways in in the brain stem, cerebellum and cortex (for example, with migraine).

Treatment of vertigo is dependent on the cause. Vestibular neuritis is a common cause of severe spontaneous vertigo. Therapeutic guidelines recommend treatment with a short course of prednisolone. Symptomatic treatment of acute vertigo can include: prochlorperazine, promethazine or diazepam.

Betahistine is a vasodilator that has been used on the basis that it may increase blood supply to the inner ear, though this may not be its only mechanism of action in Meniere's disease.

Cinnarizine is a selective calcium channel antagonist that acts mainly as a vestibular sedative through inhibition of calcium influx into the vestibular sensory cells, thus acting predominantly on the peripheral vestibular system.

Dimenhydrinate is a salt of diphenhydramine (an antiemetic) and 8-chlorotheophylline (a stimulant). Dimenhydrinate is an antihistamine with anticholinergic (antimuscarinic) properties. The antiemetic properties of dimenhydrinate are primarily produced by diphenhydramine's antagonism of H1 histamine receptors in the vestibular system, while the excitatory effects are thought to be produced by 8-chlorotheophylline's adenosine receptor blockade.

Long term daily symptomatic treatment of chronic dizziness or vertigo with these drugs is not recommended due to the risk of tardive dyskinesia (tardive syndromes), drug-induced parkinsonism (DIP) (extrapyramidal adverse effects) and dependence.

The sponsor's rationale for combining both compounds into the proposed FDC is to provide a product with a dual mechanism of action, with cinnarizine primarily acting peripherally on the labyrinth, and dimenhydrinate acting predominately centrally on the vestibular nuclei and related vegetative centres in the brainstem. This product may then be useful in treating vertigo of various origins.

[1] Clarification: Cinnarizine has previously been included in the ARTG; listed as an export only medicine (ARTG R83308).

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 8 January 2019.

This combination has not previously been registered in Australia. Dramamine tablets (AUST R 46979, 46980, 46911) containing 50 mg dimenhydrinate as the only active ingredient, for the prevention and relief of motion sickness and treatment of vertigo, nausea or vomiting was previously registered on the ARTG but was withdrawn by its sponsor during evaluation of this submission (June 2017). Dimenhydrinate was available as an over the counter (Schedule 2; Pharmacy medicine) product.

Dimenhydrinate has been included in other fixed dose combination products currently registered in Australia, such as Travacalm Original tablets (AUST R 78192, and 14864) containing 50 mg dimenhydrinate, 20 mg caffeine and 0.2 mg hyoscine hydrobromide as active ingredients, for the prevention of travel sickness.

Cinnarizine is not registered in Australia as but, has been registered overseas as a stand-alone tablet (trade name Stugeron, United Kingdom (UK)).

A fixed dose combination (FDC) of cinnarizine 20 mg and dimenhydrinate 40 mg (trade name Arlevert) obtained a European marketing authorisation license in 2005, via the mutual recognition process. It is licenced in Austria, Belgium, Denmark, Ireland, Italy, Luxembourg, the Netherlands, Poland, Slovenia, Sweden and the UK. The date of first authorisation was 20 May 2005. It is not clear whether this is a prescription only product in the European Union (EU). Arlevert has the same indication and dose regimen as has been proposed for Cizigo/Cizinate/Cizere.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for submission PM-2017-00806-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	31 May 2017
First round evaluation completed	25 January 2018
Sponsor provides responses on questions raised in first round evaluation	28 March 2018
Second round evaluation completed	15 May 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	25 June 2018

Description	Date
Sponsor's pre-Advisory Committee response	19 November 2018
Advisory Committee meeting	6 December 2018
Registration decision (Outcome)	21 December 2018
Completion of administrative activities and registration on ARTG	8 January 2019
Number of working days from submission dossier acceptance to registration decision*	246

*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Introduction

Cinnarizine is not currently registered in Australia as a stand alone product or in a fixed dose combination product. However cinnarizine has been registered overseas as a stand alone tablet (trade name Stugeron;[2] UK) as well as in a fixed dose combination product with dimenhydrinate (tradename name Arlevert;[3] cinnarizine 20 mg, dimenhydrinate 40 mg, Germany).

Dimenhydrinate has been included in other standalone and fixed dose combination products currently registered in Australia, such as:

- Travacalm Original tablets (AUST R 78192, and 14864); containing 50 mg dimenhydrinate, 20 mg caffeine and 0.2 mg hyoscine hydrobromide as active ingredients, for the prevention of travel sickness.
- Dramamine tablets (AUST R 46979, 46980, and 46911) containing 50 mg dimenhydrinate as the only active ingredient, for the prevention and relief of motion sickness and treatment of vertigo, nausea or vomiting.

The proposed cinnarizine 20 mg and dimenhydrinate 40 mg tablet product is to be packaged in polyamide (OPA)-Al-PVC/Al blister packs in pack sizes of 20, 30, 50 and 100 tablets. This product is indicated for the treatment of vertigo symptoms of various origins.

This application was submitted with the data package that address the criteria for a literature based submission.

[2] https://www.medicines.org.uk/emc/product/1529/smpc.
Stugeron is for the control of vestibular disorders such as vertigo, tinnitus, nausea and vomiting such as is seen in Meniere's Disease. Stugeron is also effective in the control of motion sickness.
[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4875047/
Arlevert is indicated for the treatment of vertigo symptoms of various origin.

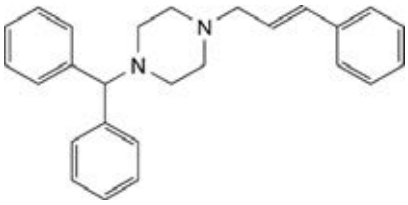
- As part of the literature based submission, the sponsor stated that Arlevert cinnarizine/dimenhydrinate 20/40 mg tablets, which contains the same quantitative and qualitative amount of active ingredients as the proposed product (the sponsor's FDC), has been licensed in 11 EU countries since May 2005. Therefore, the proposed product meets the necessary criteria as part of the provision of the literature based submission guideline.
- However, it is noted that the product proposed under the literature based submission application is not Arlevert tablet but is a product with the same active ingredients as Arlevert. Therefore, a bioequivalence study was requested during the quality evaluation to bridge the safety and efficacy of Arlevert (Germany) to the proposed product under this application. This study was provided after 2 rounds of evaluation and has been subsequently evaluated.[4]

Drug substance (active ingredient)

Cinnarizine

The drug substance cinnarizine (shown in Figure 1) is a selective calcium channel antagonist that acts mainly as a vestibular sedative through inhibition of calcium influx into the vestibular sensory cells, thus acting predominantly on the peripheral vestibular system.

Figure 1: Cinnarizine drug structure



Cinnarizine is manufactured by chemical synthesis and is obtained as a crystalline powder. No polymorphism was reported. It is practically insoluble in water and is slightly soluble in ethanol and methanol. The aqueous solubility is pH dependent (high solubility under pH 1.2 but insoluble at pH 4.5 to 7.4).

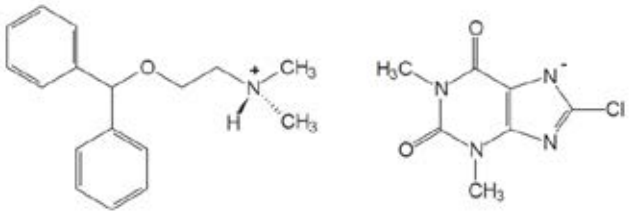
Cinnarizine is of Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) grade and has been adequately controlled by the finished product manufacture in compliance with British Pharmacopoeia (BP) monograph requirements plus additional parameters for heavy metals, residual solvents and particle size distribution.

Dimenhydrinate

The drug substance dimenhydrinate (shown in Figure 2) is a salt of diphenhydramine (an antiemetic) and 8-chlorotheophylline (a stimulant).

[4] Clarification: the sponsor questioned the rationale of the TGA in requiring a bioequivalence study of the sponsor's product against European Arlevert, as this product, in particular the cinnarizine, is essentially a new chemical entity for Australia

Figure 2: Dimenhydrinate drug structure



Dimenhydrinate is an antihistamine with anticholinergic (antimuscarinic) properties. The antiemetic properties of dimenhydrinate are primarily produced by diphenhydramine's antagonism of H1 histamine receptors in the vestibular system, while the excitatory effects are thought to be produced by 8-chlorotheophylline's adenosine receptor blockade.

Dimenhydrinate is a white to almost white crystalline powder or colourless crystal. It has high solubility in water and in pH 1.2 to 6.8 aqueous media. It is hygroscopic.
No polymorphism is reported in the literature.

Drug product

Formulation and manufacture

The proposed fixed dose combination uncoated tablets contain cinnarizine 20 mg and dimenhydrinate 40 mg as the active ingredients. They contain conventional excipients for an immediate release dosage form. The excipients in the proposed formulation are qualitatively the same as the excipients used in the German reference product Arlevert.

The proposed product was manufactured using dry granulation by roller compaction followed by two stages of blending and tableting. The process was appropriately validated.

Bioequivalence formulation

One of the process validation batches (pilot scale) was used in a two sequence, two period, cross over bioequivalence study which compared bioequivalence of the proposed tablet and the German reference Arlevert tablet.

The test biobatch and the German reference product, Arlevert, have comparative dissolution profiles in acidic media (pH 1.2 and 4.5).

There are no differences in the formulation and the manufacturing process of the biobatch compared to those proposed for registration.

Quality control

There is no British Pharmacopoeia (BP) or United States Pharmacopeia (USP) monograph for the fixed dose combination product; however, there is a USP monograph for dimenhydrinate tablet.

The finished product is controlled in accordance with an acceptable in-house specification. All manufacture and quality control issues raised at the first round evaluation have been adequately resolved at the second round.

Shelf-life

Acceptable stability data has been generated under accelerated and long-term conditions to support a shelf-life of '36 months when stored below 25°C'.

Biopharmaceutics

The point estimate and 90% confidence interval (CI) for maximum plasma concentration C_{max} and the area under the drug concentration time curve from dosing (time zero) to infinity (AUC_{0-t}) for both cinnarizine and diphenhydramine are within the criteria (80.0 to 125.0%) required to demonstrate bioequivalence between the test product and the product referenced in the sponsor's literature-based submission (that is, Arlevert cinnarizine/dimenhydrinate 20/40 mg tablet, Germany).

Quality summary and conclusions

From a pharmaceutical chemistry perspective:

- approval is recommended with regard to chemistry and quality controls aspect of the finished product. All outstanding issues for this aspect have been adequately resolved;
- the sponsor has demonstrated that the proposed product under this application is bioequivalent to the product referenced in the literature based submission (Arlevert cinnarizine/dimenhydrinate 20/40mg tablets, Germany; with efficacy and safety data);
- the bioequivalence study outcome has been referred to the Delegate, to determine its suitability in extending the efficacy and safety of the overseas reference product Arlevert (referenced in the literature-based submission) to the proposed product under this application.

IV. Nonclinical findings

Introduction

The sponsor has applied to register Cizinate, Cizere, and Citigo, a fixed-dose combination of cinnarizine and dimenhydrinate, proposed to be used for the treatment of vertigo symptoms of various origins in persons of 18 years of age and over. The standard dose for this product is one tablet (that is, 20 mg cinnarizine/40 mg dimenhydrinate) three times a day (that is, a daily dose of 60 mg of cinnarizine and 120 mg of dimenhydrinate). The length of treatment does not appear to be specified by the sponsor, although studies in the literature have utilised a patient dosing period of 4 weeks.

It should be noted that both the individual active ingredients in the sponsor's product and the combination have lengthy histories of clinical use. Diphenhydramine (Benadryl), a first generation antihistamine, became commercially available in 1946; whilst cinnarizine was first synthesised in 1955 and (although not on the ARTG) has been licensed in the UK as Stugeron since 1973. The fixed combination of cinnarizine and dimenhydrinate, marketed as Arlevert, has been available on prescription in Germany since 1982.

The non-clinical data section of the sponsor's dossier was comprised of published literature, much of which was very old. This literature was used to support out dated concepts of the clinical actions of cinnarizine and dimenhydrinate (a combination of diphenhydramine and 8-chlorotheophylline). Accordingly, the nonclinical evaluator was obliged to consider more modern literature on the pharmacology of these drugs.

Pharmacology

Documents from the sponsor (such as the nonclinical overview, the Product Information (PI), and the Consumer Medicine Information (CMI)) contain two central assumptions regarding the pharmacology of the cinnarizine / dimenhydrinate combination:

- inhibition of calcium currents through voltage-gated channels is central to an understanding of the clinical effects of cinnarizine dosing; and
- the peripheral (includes the inner ear and vestibular nerve) and central components (brainstem, cerebellum, and cortex) of the vestibular system are selectively targeted by cinnarizine and diphenhydramine, respectively.

The first assumption is likely incorrect. Circulating unbound concentrations of cinnarizine, following dosing with the cinnarizine: dimenhydrinate combination, are probably less than 90 nM, whereas data on the inhibition of calcium channels indicate a requirement for micromolar range concentrations of cinnarizine (for example, the interaction of actin and myosin in bovine artery was inhibited with a half-maximal inhibitory concentration (IC_{50}) of 60 μM). In vitro studies show that cinnarizine is a potent inhibitor of the histamine H1 receptor (inhibitor constant (Ki) for the mouse H1 receptor = 47 nM) and histamine H4 receptor (Ki for the human H4 receptor = 7 nM). Cinnarizine also shows inhibitory activity towards dopamine receptors D1, D2 (Ki for the rat D2 receptor = 13 nM), and D3 (IC_{50} for the human D3 receptor = 252 nM), serotonin 2 receptors (IC_{50} for the rat serotonin 2 receptor = around 1 μM), and pressure-sensitive potassium currents (guinea pig potassium currents inhibited at around 0.3 μM). The major molecular targets for the inhibitory action of diphenhydramine include the histamine H1 receptor (Ki for the human H1 receptor = 13 nM), the five muscarinic acetylcholine receptors M1, M2, M3, M4, and M5 (dissociation constant (K_d) values for the human receptors range from 100 to 260 nM), and the noradrenaline reuptake transporter (K_d for the human transporter = 1.0 μM). Hence, both cinnarizine and diphenhydramine are primarily antihistamines, although it is likely that their various other inhibitory activities contribute to their anti-vertigo activity.

The second central assumption of the sponsor's submission is that cinnarizine and diphenhydramine selectively target the peripheral and central components of the vestibular system, respectively. Histamine is known to be a modulator of neural activity in the central vestibular system, and expression of H1 receptors has been detected in the medial vestibular nucleus. Both cinnarizine and diphenhydramine are able to cross the blood-brain barrier, although the presence of an active uptake mechanism (H+/OC antiporter) into the brain parenchyma for diphenhydramine (but apparently not for cinnarizine) suggests that anti-histaminergic activity in the brain may be primarily attributable to diphenhydramine. Histamine H4 receptors are known to be important mediators of neural activity in vestibular neurons, whilst dopamine D1 and D2 receptors are known to be expressed by type I and type II vestibular hair cells and on associated neurons, and dopamine D2 receptors are expressed by vestibular nucleus neurons, suggesting that there may be important targets for the anti-vertiginous activity of cinnarizine in both the central and peripheral vestibular system. Acetylcholine and various muscarinic acetylcholine receptors are present in components of both the central and peripheral vestibular systems. Hence, the anti-muscarinic activity of diphenhydramine could modulate the central and/or peripheral vestibular systems. Pressure-sensitive potassium channels are expressed by type II vestibular hair cells and are another likely target in the peripheral vestibular system for inhibition by cinnarizine. In summary, there are potential targets in both the central and peripheral vestibular systems for inhibition by cinnarizine or diphenhydramine. In the absence of various pieces of information (for example, the abilities of cinnarizine and diphenhydramine to cross the blood-labyrinth barrier), ascribing specific sites of action to these drugs is of questionable validity.

Vertigo/dizziness is a common and serious complaint for the elderly, the population that will be the principle users of the sponsor's product. Another common issue for the elderly is polypharmacy which, in combination with the multiple molecular targets and pathways that can be modulated by dosing with cinnarizine and diphenhydramine, suggests that the sponsor's product could have serious potential for drug interactions in the affected population. For example, diphenhydramine interacts with various drugs, including enhancing the central nervous system (CNS) depressant effects of alcohol and barbiturates and enhancing the effects of monoamine oxidase inhibitors. Cinnarizine has also been shown to interact with many drugs.

Secondary pharmacodynamics and safety pharmacology

Both cinnarizine and diphenhydramine have been associated with extensive lists of adverse effects in humans. For elderly humans dosed with diphenhydramine, the list includes cognitive decline and behavioural disturbance, and for the elderly dosed with cinnarizine, the list includes drug-induced parkinsonism. It has been reported that around 3% of patients, treated with cinnarizine for more than one month, developed drug induced parkinsonism (DIP) within a 3 year observation period (by comparison, 0.5% of a control group developed DIP). Such figures for DIP may under-estimate the problem for, as noted by Laporte and Capella (1986)[5]: *'Cinnarizine is mainly prescribed to old people with intellectual impairment and/or focal neurological signs, in whom extrapyramidal signs may easily be attributed to spontaneous deterioration rather than drug-induced parkinsonism'*. The possible effect of combination of diphenhydramine with cinnarizine, on the induction of DIP, does not appear to have been examined.

The UK Medicine and Healthcare Products Regulatory Agency (MHRA) report on Stugeron states that: '*Cinnarizine blocked the cardiac hERG channel in vitro, however in isolated cardiac tissue and following intravenous application in guinea-pigs, no QTc prolongation or proarrhythmic effects were observed at substantially higher exposures than those expected clinically*.' The potency of human ether-à-go-go (hERG) channel inhibition by cinnarizine is not provided in the report and there is apparently no information on this issue in the literature. In contrast, diphenhydramine was reported to be a weak inhibitor of hERG channels (IC_{50} = 27 μM) and yet typical therapeutic doses of diphenhydramine have been shown to produce increases in corrected QT interval (QTc) that were modest in most individuals but could be greater when diphenhydramine was combined with other drugs. In addition, cohort analysis of human populations suggested that dosing with diphenhydramine was associated with a significant increase in life-threatening ventricular arrhythmias. Such results are a concern given the effect of cinnarizine on hERG and the problem of polypharmacy in the elderly.

Pharmacokinetics

The serum elimination half-life of diphenhydramine has been reported to depend significantly on age, having values of 5.4, 9.2, and 13.5 h in children (mean age = 8.9 years), young adults (31.5 years), and old adults (69.4 years), respectively, and clearance rates of 49.2, 23.3, and 11.7 mL/min/kg, respectively. There is also indirect evidence suggesting that the metabolism of cinnarizine is slower in older subjects. There appear to have been no studies performed examining the pharmacokinetics of the cinnarizine: dimenhydrinate combination. The effect of age on pharmacokinetics suggests that the elderly would be at particular risk for the development of side-effects from cinnarizine: diphenhydramine dosing.

[5] Laporte J.R. and Capella D. (1986) Useless drugs are not placebos: lessons from flunarizine and cinnarizine. *Lancet*, 1986; 2: 853–854.

As noted above, diphenhydramine is actively transported into the brain parenchyma by the H+/OC antiporter, and it is possible that this transporter is also active in the intestine. However, it appears unlikely that clinical doses of diphenhydramine would alter the pharmacokinetics of other substrates of the H+/OC antiporter. No other transporters (including p-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic cation transporter (OCT)) have been identified for diphenhydramine. Cinnarizine is not a substrate of P-gp and no transporters for it have been identified.

Cinnarizine and diphenhydramine are predominantly metabolised in the liver, with cytochrome P450 system (CYP) enzyme CYP2D6 prominently involved in both cases. Diphenhydramine has been shown to act as a competitive inhibitor of CYP2D6. Possible inhibitory activity of cinnarizine towards CYP enzymes does not appear to have been examined, and there appear to be no studies examining possible effects of the cinnarizine: dimenhydrinate combination on CYP activity. Consistent with its ability to inhibit CYP2D6, clinically significant interactions can occur between diphenhydramine and other CYP2D6 substrates.

As well as being involved in the metabolism of around 25% of all medications (including many prominent cardiovascular and CNS drugs), CYP2D6 is of toxicological interest because of the large inter-individual differences in its enzymic activity (around 7 to 10% of Europeans are CYP2D6-poor metabolisers). It has been suggested that CYP2D6-poor metabolisers are at increased risk of developing DIP following cinnarizine dosing.

Toxicology

Toxicity

The MHRA report gives the results of acute dose toxicity studies using mice and rats, which indicate that the cinnarizine: dimenhydrinate combination is of moderate to slight toxicity in rodents. The MHRA report also discusses a study by Heisler (1986) in which rats were fed the cinnarizine: dimenhydrinate combination at doses of around 250, 333, and 416 mg/kg/day (representing exposure ratios on a mg/m2 basis as cf. a 70 kg human receiving 180 mg/day of 16, 21, and 26, respectively) for up to 9 months. The rats showed slight increases in body weight gain at mid- (females only) and high-doses (males only). Increases in weight for liver (high-dose males) and adrenal gland (high-dose females) were apparently not accompanied with histopathological changes and were not considered dose related.

Note, the assessor could not find the study by Heisler (1986) in the literature and it may represent an unpublished pharmaceutical company internal report.

Reproductive toxicity

There is very little information in the scientific literature on possible effects of dimenhydrinate or cinnarizine on fertility or development. Relevant studies, apparently performed by pharmaceutical companies and not available to this assessor, are reported by the MHRA to show that cinnarizine dosing had no effect on fertility and was not teratogenic in rats, rabbits, and dogs. Exposure of pregnant rats to high doses of cinnarizine (approximately 60 times the recommended human exposure to the sponsor's product) produced maternal and fetal toxicity. Similarly, repeat dosing of pregnant rats or rabbits with dimenhydrinate at exposure ratios of around 7 and 12 times clinical levels, respectively, was stated in an MHRA report to not be teratogenic. Human trial results also suggest that dimenhydrinate/diphenhydramine does not have teratogenic potential. Diphenhydramine is, however, oxytocic in humans.

Significantly, no reproductive toxicology studies appear to have been performed using the cinnarizine / dimenhydrinate combination.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3.[6] The minimal adverse effects seen in a set of quite inadequate animal studies suggest that Pregnancy Category B2;[7] is more appropriate for this product.

Paediatric use

An MHRA review reported that diphenhydramine was commonly associated with adverse effects in children younger than six years, and it was recommended that cough and cold remedies containing diphenhydramine should no longer be used for that age group.[8] Similarly, Church et al., (2010);[9] detailed the occurrence of infant deaths associated with the use of diphenhydramine and other first-generation antihistamines and strongly recommended against their use in this age group. Fortunately, vertigo is an uncommon complaint in children and adolescents (Gruber et al., 2012);[10] and the sponsor's product is not proposed for use in a paediatric population.

Genotoxicity and carcinogenicity

MHRA reports state that the dimenhydrinate: cinnarizine combination was negative (up to 0.5 mg/plate) in Ames-type assays and that cinnarizine was negative for clastogenicity in hamster V79 cells. Comprehensive carcinogenicity studies have apparently not been conducted with diphenhydramine or cinnarizine.

Given the lengthy period of commercial availability and clinical experience for both the individual drug substances and the combination, and the lack of chemical structure concerns related to genotoxicity/carcinogenicity for the drug substances, the MHRA considered it reasonable that a complete package of genotoxicity/carcinogenicity studies was not available. This is acceptable.

Comments on the nonclinical safety specification of the risk management plan

There is mention in the sponsor's draft risk management plan (RMP) that vertigo/dizziness is a common and serious issue for the elderly and that this is the population that will be predominantly using the sponsor's product. It is not mentioned, however, that the elderly are a group that are particularly vulnerable to the adverse

[6] Pregnancy Category B3 is defined as Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
[7] Pregnancy Category B2 is defined as 'Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.'
[8] Anonymous (2009) http://webarchive.nationalarchives.gov.uk/20141206123425/http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con041374.pdf In: Press release: Better medicines for children's coughs and colds. http://webarchive.nationalarchives.gov.uk/20141206030140/http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON038902
[9] Church M.K. et al. (2010) Risk of first-generation H1-antihistamines: a GA2LEN position paper. *Allergy*, 2010; 65: 459–466.
[10] Gruber M., et al. (2012) Vertigo in children and adolescents: characteristics and outcome. *Scientific World Journal*, http://dx.doi.org/10.1100/2012/109624.

effects of both diphenhydramine and cinnarizine. Indeed, many authors have suggested that first generation anti-histamines, such as diphenhydramine, should be used with great caution or not at all in the elderly.[9,11,12,13] Likewise, it has been suggested that cinnarizine should not be prescribed for the elderly.[14]

Nonclinical summary and conclusions

- Modern pharmacological studies and consideration of the likely free therapeutic plasma levels of cinnarizine suggest that calcium channel blockade is not its main mechanism of action and that anti-histamine, anti-dopamine and blockade of pressure-sensitive potassium channel mechanisms may be involved.
- Individually, cinnarizine and diphenhydramine have been noted in the literature as undergoing pharmacodynamic interactions with various other drugs.
- Individually, cinnarizine and diphenhydramine have been noted in the literature as undergoing pharmacokinetic interactions with various other drugs.
- There are various concerns related to the use of a cinnarizine: dimenhydrinate combination, particularly the association of cinnarizine with drug-induced parkinsonism (DIP) with long-term use.
- The sponsor has proposed Pregnancy Category B3;[6] for Cizinate, Cizere, and Citigo. The minimal adverse effects seen in a very limited set of animal studies suggest that Pregnancy Category B2 is more appropriate.[7]
- While the nonclinical submission was limited in terms of primary, evaluable data, given the long-term clinical history of use there are no nonclinical objections to the registration of Cizinate, Cizere, and Citigo provided that the clinical data provides a favourable risk benefit given the concerns with extrapyramidal adverse events with cinnarizine with long term use.

The nonclinical evaluator also made recommendations with regard to the PI but these are beyond the scope of the AusPAR.

V. Clinical findings

Introduction

As noted in the Australian Therapeutic Guidelines;[15] vertigo is an illusion of motion, which is most often experienced as a rotatory sensation, although it may also be linear in quality (for example, a sensation of falling or pitching). It is frequently accompanied by autonomic symptoms such as nausea, retching, vomiting, pallor and sweating.

Vertigo is often a result of pathology in one of the inner ear balance organs. This may be due to hypofunction (for example, vestibular neuritis) or hyperfunction (for example,

[11] Kaliner M.A. (2002) H1-antihistamines in the elderly. *Clinical Allergy and Immunology*, 2002; 17: 465–481.
[12] Chen Y.C., *et al*. (2009) Potentially inappropriate medication for emergency department visits by elderly patients in Taiwan. *Pharmacoepidemiology and Drug Safety*, 2009; 18: 53–61.
[13] Slavin R.G. (2009) Treating rhinitis in the older population: special considerations. *Allergy, Asthma, and Clinical Immunology*, 2009; 5: 9. doi: 10.1186/1710-1492-5-9
[14] Laporte J.R. and Capella D. (1986) Useless drugs are not placebos: lessons from flunarizine and cinnarizine. *Lancet*, 1986; 2: 853–854.
[15] Therapeutic Guidelines: Symptomatic treatment of acute vertigo. Therapeutic Guidelines Ltd. https://tgldcdp.tg.org.au/viewTopic?topicfile=vestibular-disorders&guidelineName=Neurology&topicNavigation=navigateTopic

benign paroxysmal positional vertigo). It can also result from central neurological disorders affecting vestibular pathways in in the brain stem, cerebellum and cortex (for example, migraine). Acoustic neuromas and acute middle ear infections seldom cause vertigo.

The following has been summarised from information submitted by the sponsor:

Vertigo is a primary symptom of vestibular disease. It has a reported prevalence in the primary care setting of 5 to 7%. The prevalence increases with age, and may be as high as 50% in the population over 70 years. Vertigo is commonly associated with significant morbidity including falls, which may lead to immobilisation and significant health costs.

Vertigo may arise from disease, injury or degenerative processes affecting either component of the vestibular system, or a combination of both.

The sponsor has noted that both cinnarizine and dimenhydrinate are known to be effective in the treatment of vertigo. At the time of submission dimenhydrinate was listed on the ARTG as a single ingredient product containing 50 mg of the medicine (Dramamine; Aust R 10270). The approved indications were:

> *Prevention and relief of motion sickness and treatment of vertigo, nausea and vomiting associated with: electroshock therapy, anaesthesia and surgery, labyrinthine disturbances and radiation sickness. (Helps prevent travel sickness).*

Dimenhydrinate is in Schedule 2 (Pharmacy Medicine) of the Standard for the Uniform Scheduling of Medicines and Poisoning (SUSMP);[16] when in primary packs of 10 doses or less for the prevention or treatment of motion sickness, except in preparations for the treatment of children under 2 years of age. It is in Schedule 3 (Pharmacy Only Medicine) when in oral preparations except when included in Schedule 2. Registration of dimenhydrinate 50 mg tablets (Dramamine) was cancelled by the sponsor on 30 June 2017, after acceptance of this submission for evaluation. The registrations of other products containing dimenhydrinate were cancelled in 2009. The recommended dose regimen of the 50 mg dimenhydrinate product available in the UK for motion sickness is 50 mg three times daily. For other treatment 4 hourly administration may be required. The maximum recommended total daily dose is 300 mg.

Currently cinnarizine is not listed on the ARTG. Cinnarizine 15mg tablets (Stugeron) have been available in the UK since 1989 (date of first authorisation 14 September 1989). The European Summary of Product Characteristics (SPC) indications are:

> *Control of vestibular disorders such as vertigo, tinnitus and vomiting such as is seen in Meniere's disease. Effective in the control of motion sickness.*

Cinnarizine is also accessed via the TGA's Special Access Scheme (SAS) to treat vertigo associated with various medical conditions, particularly Meniere's disease and motion sickness. Cinnarizine is not available in the USA or Canada. Stugeron appears to be available without prescription in the UK.

The proposed indication is the same as the approved indication for the FDC product that has a marketing authorisation in the EU, that is, *Treatment of vertigo symptoms of various origins*. It is not clear whether a prescription is required for the FDC product, Arlevert in other countries.

Current treatment options

Treatment of vertigo is dependent on the cause. Vestibular neuritis is a common cause of severe spontaneous vertigo. Therapeutic guidelines recommend treatment with a short

[16] The SUSMP is also known under the legal title of the Poisons Standard.

course of prednisolone. Symptomatic treatment of acute vertigo can include: prochlorperazine, promethazine or diazepam.

Long-term daily symptomatic treatment of chronic dizziness or vertigo with these drugs is not recommended due to the risk of tardive dyskinesia (see *Tardive syndromes* in the Therapeutic Guideline), drug-induced parkinsonism (see *Extrapyramidal adverse effects* in the Therapeutic Guideline) and dependence.[17] Betahistine is a vasodilator that has been used on the basis that it may increase blood supply to the inner ear, though this may not be its only mechanism of action in Meniere disease. It may be a useful preventive treatment in some patients.

Clinical rationale

The sponsor's rationale for combining both compounds into the proposed FDC is to provide a product with a dual mechanism of action, with cinnarizine primarily acting peripherally on the labyrinth, and dimenhydrinate acting predominately centrally on the vestibular nuclei and related vegetative centres in the brainstem. This product may then be useful in treating vertigo of various origins.

Guidance

- CPMP/EWP/240/95 Rev. 1 Guideline on Clinical Development of Fixed Combination Medicinal Products
- TGA Guidance on literature based submissions https://www.tga.gov.au/publication/literature-based-submissions

Contents of the clinical dossier

- The clinical data comprised a tabular listing of all clinical studies and literature references. A total of 9 published randomised control trials (RCT) evaluating the safety and/or efficacy of the FDC in vertigo of peripheral, central or combined peripheral and central origin, were included in the submission. All published studies meet the National Health and Medical Research Council (of Australia) (NHMRC) 1999 criteria of level II evidence, ensuring that sufficient details of design methodology and statistical analysis is provided to allow an independent assessment of the results in relation to the safety and efficacy of the FDC. In addition, a randomised control trial (RCT) compared the effect of a single dose of FDC, 50 mg dimenhydrinate or betahistine 12 mg on patient vigilance (impairment of alertness and development of sedation).
- Five studies examining efficacy and safety of cinnarizine as monotherapy were also included in the submission.
- The submission also included the requirements of a literature based submission, including documentation of the methodology of the literature search and a record of the approval for the search strategy provided by the TGA.
- Also included were a Clinical Overview, Clinical Summary of Efficacy and a Clinical Summary of Safety, literature references pertaining to the Clinical Overview and a tabulation of the individual published studies referred to in the submission. The European SPC for Arlevert and cinnarizine were also provided.

[17] https://tgldcdp.tg.org.au/viewTopic?topicfile=vestibular-disorders&guidelineName=Neurology#toc_d1e47

Paediatric data

No paediatric data was submitted. This product is not proposed for use in children or adolescents.

Good clinical practice

Full study reports were not available. An assurance on Good Clinical Practice (GCP) and adherence to ethical guidelines was not present in all published study reports.

Pharmacokinetics

Studies providing pharmacokinetic data

The structured and systematic review of scientific data bases did not identify any published study evaluating the pharmacokinetic profile of cinnarizine and dimenhydrinate when administered concomitantly or as single mono-components.

One study, on the pharmacokinetics (PK) of cinnarizine was included in the submission. It was published in 1993.

Summary of pharmacokinetics

Physicochemical characteristics of the active substance

Cinnarizine is a selective calcium channel antagonist that 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.

Dimenhydrinate is a H1 receptor antagonist antihistamine that acts with anticholinergic (antimuscarinic) properties, exerting parasympathetic and centrally-depressant effects. The substance exhibits anti-emetic and anti-vertiginous effects through the chemoreceptor trigger zone in the region of the fourth ventricle. Dimenhydrinate thus acts predominantly on the central vestibular system.

Pharmacokinetics in healthy subjects

Absorption

Cinnarizine: C_{max} is reached in 2.5 to 4 hours after oral ingestion.

Dimenhydrinate: Dimenhydrinate rapidly releases its diphenhydramine moiety after oral administration. Antiemetic effects occur within 15 to 30 minutes after oral administration, are maximal within 1 to 2 hours and last for 3 to 6 hours.

Bioavailability

Cinnarizine: No specific statement on oral bioavailability of cinnarizine was included in the submission.

Dimenhydrinate is well absorbed from the gastro-intestinal tract after oral dosing with extensive first-pass effect.

Distribution (volume of distribution)

Cinnarizine: The plasma protein binding of cinnarizine is 91%.

Dimenhydrinate: Like other antihistamines, the drug probably is widely distributed into body tissues, crosses the placenta. Small amounts of dimenhydrinate are distributed into milk.

Elimination

Cinnarizine is mainly eliminated via the faeces (40 to 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 to 60%).

Interactions

Dimenhydrinate will interact with anticholinergic drugs, anti-depressants (tricyclics and monoamine oxidase inhibitors) and anti-parkinsonian drugs increasing the anticholinergic side effects, dry mouth, urine retention, confusion, and so on.

The effects of betahistine may be antagonised.

Sedating antihistamines may enhance the sedative effects of CNS depressants including alcohol, other sedating antihistamines, barbiturates, hypnotics, opioids, anxiolytic sedatives and antipsychotics.

The dose of narcotic analgesics and of barbiturates should be reduced by quarter or half when used concomitantly.

Evaluator's conclusions on pharmacokinetics

While there are very limited clinical trial data on the PK of cinnarizine, the PK study of single and repeat dosing published in 1993 was consistent with the published information from other regulatory sources. Dimenhydrinate, while on the ARTG, has been registered for many years and a detailed description of its PK is not available. The information above it however consistent with the information available internationally.

There was no clinical study assessing whether the pharmacokinetics of either active component is affected by the presence of the other. That is the major deficiency with regard to pharmacokinetics in the submission.

In the Clinical Overview, is was stated that an evaluation of any potentially clinically significant pharmacokinetic interaction between the two component medicines is therefore based on other relevant information submitted in this application, specifically information provided in the European SPC, non-clinical studies evaluating the potential metabolic interaction of these medicines, and the safety and efficacy data comparing the FDC to individual components administered in equivalent doses, or in doses 2.5 times larger than those provided in the FDC.

It was also stated that the clinical studies submitted in this application comparing FDC to equivalent doses of the component medicines, and to mono-component doses 2.5 times greater than those included in the FDC consistently demonstrate increased efficacy for FDC, without significantly impacting on the established safety profile of the mono-component medicines.

These data suggest that there is unlikely to be a clinically significant detrimental PK or pharmacodynamic (PD) interaction associated with combining cinnarizine and dimenhydrinate in a single FDC tablet.

Pharmacodynamics

Studies providing pharmacodynamic data

Two published studies were submitted, detailed below.

Philipova (2004)[18]

This paper described a double blind, randomised, three arm, cross over study to compare the tolerability and impact on alertness and performance of a fixed dose combination (FDC) medicine containing 20mg of cinnarizine and 40mg of dimenhydrinate to 50mg dimenhydrinate or placebo in healthy volunteers.

21 healthy volunteers received 4 doses within 24 hours of the FDC (Arlevert), or dimenhydrinate or placebo in randomised order at 1 week intervals. Auditory event-related potentials (ERP), reaction time and psychometric tests were assessed before as well as 60 minutes and 150 minutes after the intake on the first and 4th days of study medication.

None of the medications affected the latency and amplitude of the sensory ERP component N100 (on electroencephalogram (EEG)). It was reported that these results gave no evidence for an impairment of central information processing and psychomotor performance after multiple dosing with fixed combination cinnarizine/ dimenhydrinate in healthy volunteers.

Evaluator's conclusions on study

This was a very small crossover study with limited assessment of psychomotor parameters. That it failed to show significant sedation or impaired performance may be due to methodological issues rather than an absence of effect. The clinical evaluator noted that sedation and impaired alertness have been reported with both cinnarizine and dimenhydrinate.

Brücke (1995)[19]

This paper reported a single photon emission computed tomography (SPECT) study to identify D2 receptor blockade by cinnarizine and its di-fluorinated derivative, flunarizine in order to examine the cause of the extrapyramidal side effects associated with these medicines. 26 patients (19 women and 7 men) aged between 22 to 77 years treated with flunarizine (n=22) or cinnarizine (n=4) and 21 volunteers (healthy subjects or patients with peripheral neurologic problems aged 25 to 77 years) took part in the study.

For visualisation of dopamine D2 receptors subjects underwent SPECT using 123I labelled S (-) iodobenzamide, a substance with high affinity and high specificity for D2 receptors. A highly significant decline of dopamine D2 receptor binding with increasing age was found in the control group (0.6% per year in the putamen). D2 receptor binding, expressed as a percentage of the age-matched control value, was reduced in all patients under flunarizine or cinnarizine treatment. The extent of reduction ranged from 14 to 63%. Patients treated for >6 months had significantly larger reductions than patients treated for shorter periods. Age > 50 years was also associated with a larger reduction in D2 receptor binding (13.2% versus 31.8%). The presence of parkinsonian symptoms was also associated with a significantly larger reduction of D2 receptor binding (46% versus 33.9%). No correlation was found between the severity of extrapyramidal symptoms and the degree of this reduction.

The authors noted that a clear-cut dosage-response relationship could not be established.

[18] Philipova D, et al. Influence of an antivertiginous combination preparation of cinnarizine and dimenhydrinate on event-related potentials, reaction time and psychomotor performance – a randomized, double-blind, 3-way cross over study in healthy volunteers*. International Journal of Clinical Pharmacology and Therapeutic*s 2004; 42: 218-231

[19] Brucke T, et al. D2 receptor blockade by flunarizine and cinnarizine explains extrapyramidal side effects. A SPECT study. *Journal of Cerebral Blood Flow and metabolism* 1995; 15: 513-518

Evaluator's conclusions on pharmacodynamics

Limited details concerning the pharmacodynamics of both compounds are available. This is likely because these actives have been in use for many years prior to the routine detailed exploration of the pharmacology of an active compound. Still it is clear that both cinnarizine and dimenhydrinate have relatively rapid onset of action when given orally and relatively short (generally < 6 hours) duration of action. That compatibility and the differing mechanisms of action suggest that they would be suitable to be co-administered in the management of vertigo, whether it is predominantly of central or peripheral origin.

Dosage selection for the pivotal studies

Efficacy

Studies providing efficacy data

Studies providing evaluable efficacy data for cinnarizine

Five published reports of randomised, controlled clinical trials (RCT) evaluating the tolerability and/or efficacy of cinnarizine were identified. One of these studies was included as a reference to the Clinical Summary rather than in clinical module (Bodla et al., 2011). Remaining studies were in the clinical module. The studies are listed below:

- Bodla R, et al. Comparison of Efficacy and Tolerability of Cinnarizine with Betahistine in the Treatment of Otogenic Vertigo. *International Journal of Pharmaceutical Research* 2011; 3: 36-40.
- Deering RB, et al. A double-blind crossover study comparing betahistine and cinnarizine in the treatment of recurrent vertigo in patients in general practice. *Current Medical Research and Opinion* 1986; 10: 209-214.
- Mangabeira-Albernaz PL, et al. Flunarizine and cinnarizine as vestibular depressants: A statistical study. *Journal for Oto-Rhino-Laryngology, Head and Neck Surgery* 1978; 40: 92-100.
- Pianese CP, et al. New Approaches to the Management of Peripheral Vertigo: Efficacy and Safety of Two Calcium Antagonists in a 12-week, Multinational, Double-Blind Study. *Otology & Neurology* 2002; 23: 357-363.
- Gananca MM, et al. Controlled clinical trial of pentoxifylline versus cinnarizine in the treatment of labyrinthine disorders. P*armatherapeutica* 1988; 5: 170-176.

Studies providing evaluable efficacy data for cinnarizine/dimenhydrinate

Five published reports describing 9 individual RCTs evaluating the efficacy and tolerability of the FDC were identified. The FDC used in all these trials contained the same quantities of cinnarizine and dimenhydrinate as has been proposed for the Australian formulation.

Four of the 9 RCTs compared the efficacy of the FDC to equivalent doses of the individual component medicines and 3 studies compared the FDC to doses of the component monotherapies which were 2.5 times greater (cinnarizine 50 mg and dimenhydrinate 100 mg) than the amount included in the FDC. Two of the RCTs included a placebo arm. The remaining study compared the FDC to betahistine 12 mg three times daily. The papers describing these studies are listed below:

- Hahn A, et al. Comparison of cinnarizine/dimenhydrinate fixed combination with the respective monotherapies for vertigo of various origins. A randomized, double-blind, active-controlled, multicentre study. *Clinical Drug Investigation* 2011; 31: 371-383.

- Pytel J, et al. Efficacy and tolerability of a fixed low-dose combination of cinnarizine and dimenhydrinate in the treatment of vertigo: A 4-week, randomized, double-blind, active- and placebo-controlled, parallel-group, outpatient trial. *Clinical Therapeutics* 2007; 29: 84-98.
- Schremmer D, et al. Efficacy and tolerability of a fixed combination of cinnarizine and dimenhydrinate in treatment of vertigo. Analysis of data from five randomized, double-blind clinical studies. *Clinical drug Investigati*on 1999; 18: 355-368.
- Scholtz AW, et al. Treatment of vertigo due to acute vestibular loss with a fixed combination of cinnarizine and dimenhydrinate: A double-blind, randomized, parallel-group clinical study. *Clinical Therapeutics* 2004; 26: 866-877.
- Novotny M, et al. The efficacy of Arlevert for vertigo and tinnitus. *International Tinnitus Journal* 1999; 5; 60-62.

Other efficacy studies

These included Scholtz et al., (2004) and Novotny et al., (1999) listed above.

Analyses performed across studies: pooled and meta-analyses

Schremmer (1999) presented an analysis of a series of controlled clinical studies (5 RCTs) to evaluate the efficacy and tolerability of the FDC product Arlevert (cinnarizine 20 mg/ dimenhydrinate 40 mg) in the treatment of central, peripheral or combined central/peripheral vestibular vertigo.

Evaluator's conclusions on efficacy

The submission contained one study in which the proposed FDC product, given using the proposed dose regimen to patients with various causes for vertigo was superior to placebo and to monotherapy with the constituent actives, given at higher doses than is contained in the proposed FDC product. Additionally, 2 studies comparing the FDC with monotherapy constituents given at the same doses as is contained in the FDC product also showed superiority with respect to reduction in vertigo symptoms.

Mean vertigo score (MVS) was the primary efficacy measure in most studies. This is a composite endpoint, derived from a set of symptoms associated with vertigo. While it is subjective, so is the sensation of vertigo. Various objective measures were also assessed as secondary efficacy measures and while the statistical management of these secondary efficacy measures may not have met current requirements this evaluator considers that, given the primary efficacy measure consistently demonstrated superiority of the active constituents given as monotherapy that efficacy of the FDC has been demonstrated for its proposed indication.

The evaluator notes that patients with Meniere's disease were generally excluded from the pivotal efficacy studies. This is acceptable given the long term nature of symptoms in Meniere's disease. The evaluator does not consider that exclusion from these studies is sufficient for the FDC to be specifically not recommended for management of vertigo associated with Meniere's disease. This is a symptomatic treatment for vertigo, not a treatment of the underlying disease. Efficacy of continuous use for longer than 4 weeks has not been adequately assessed and given the known safety concerns of long term use of either component it will be important to note that the FDC should not be taken continuously in the long term.

Assessment of the efficacy of monotherapy cinnarizine in the treatment of vertigo was quite limited. This was due to the age and design of the clinical trial evidence available. Study results suggest that cinnarizine is inferior to betahistine in the treatment for vertigo associated with Meniere's disease. The use of a monotherapy cinnarizine arm in the study by Pytel et al., showed that a 50 mg dose of cinnarizine had efficacy in the management of

vertigo compared with placebo, though a statistical comparison of that effect was not performed in that study. Efficacy of the proposed dose of cinnarizine used with dimenhydrinate relies primarily on the increase in efficacy seen when the FDC was compared with dimenhydrinate alone (Hahn et al.).

Safety

Studies providing safety data

Four RCTs and one pseudo-randomised study included safety data for subjects exposed to cinnarizine as monotherapy. A total of 228 subjects were exposed to at least one dose of cinnarizine. All studies used an active control. Two studies compared cinnarizine to betahistine, one to nimodipine, one to pentoxifylline and one to placebo and hyoscine.

For the FDC there were 11 published clinical reports which contained some safety data with 9 of these describing RCTs.

Patient exposure

All but one study administered cinnarizine for between 28 days and 3 months, with the majority, 128 (60%) treated for 3 months. The dose of cinnarizine ranged from 30 to 75 mg as a single dose and 15 mg three times daily to 75 mg three times daily, as an oral tablet to patients with peripheral vertigo or equilibrium disturbances of vascular origin, or volunteers. A total of 228 individuals were exposed to at least one dose of monotherapy cinnarizine.

In the FDC studies a further 344 patients were exposed to cinnarizine as a single component medicine for 4 weeks in the control arms of the RCT. These studies were conducted in patients with central, peripheral or mixed vertigo.

Safety data published in the clinical studies summarised in this application represent approximately 29.5 patient/years exposure to the FDC, in the proposed dosage regimen of cinnarizine 20 mg and dimenhydrinate 40 mg three times daily for a duration of therapy ranging from one day to 4 weeks. All the safety and efficacy studies were performed in adult patients with an average age in the early 50's. More females than males were included in the studies, with most recruiting around 60% females. Patients aged > 65 years were also included in the studies, though safety was not reported separately for that subgroup.

Safety issues with the potential for major regulatory impact

Renal function

The SPC for Arlevert recommends that it should be used with caution in patients with mild to moderate renal impairment. Arlevert should not be used by patients with a creatinine clearance of < 25 mL/min (severe renal impairment). While dimenhydrinate is metabolised, its metabolites are excreted renally.

Hepatic function

The SPC for Arlevert states that no studies in patients with hepatic impairment are available. Arlevert should not be used by patients with severe hepatic impairment.

Given dimenhydrinate is metabolised by the liver, this is a reasonable statement.

Drug interactions

The following information on drug interactions has been extracted from SPCs for monotherapy dimenhydrinate, cinnarizine and combination cinnarizine/ dimenhydrinate:

- CNS depressants: Dimenhydrinate may enhance the effects of other CNS depressants such as alcohol and barbiturates. If dimenhydrinate is used concomitantly with other CNS depressants, caution should be used to avoid overdosage.
- Drugs with anticholinergic effects: Because dimenhydrinate also has anticholinergic activity, it may potentiate the effects of other drugs with anticholinergic activity including tricyclic antidepressants.
- Ototoxic drugs: When given concurrently with aminoglycoside antibiotics or other ototoxic drugs, dimenhydrinate may mask the early symptoms of ototoxicity. (See Cautions: Precautions and Contraindications.)
- Other Drugs: Although dimenhydrinate has been reported to induce hepatic microsomal enzymes in animals, there is no clinical evidence that dimenhydrinate influences the metabolism of other drugs in humans.
- Diphenhydramine inhibits CYP2D6 mediated metabolism and caution is advised if Arlevert is combined with substrates of this enzyme, especially those with narrow therapeutic range.

The SPC for cinnarizine (Stugeron) states that concurrent use of alcohol, CNS depressants or tricyclic antidepressants may potentiate the sedative effects of either these drugs or of Stugeron. Precautionary statements are listed below:

- As with other antihistamines, Stugeron may cause epigastric discomfort; taking it after meals may diminish the gastric irritation.
- In patients with Parkinson's disease, Stugeron should only be given if the advantages outweigh the possible risk of aggravating this disease.
- Because of its antihistamine effect, Stugeron may prevent an otherwise positive reaction to dermal reactivity indicators if used within 4 days prior to testing.
- Use of cinnarizine should be avoided in porphyria.
- There have been no specific studies in hepatic or renal dysfunction. Stugeron should be used with care in patients with hepatic or renal insufficiency.

The SPC for Arlevert lists the following adverse events associated with either of the actives:

- 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.
- Dimenhydrinate and cinnarizine are excreted in human breast milk. Arlevert should not be used during breast-feeding.

Post marketing data

There is a long post-marketing history for both the FDC combination of cinnarizine/ dimenhydrinate and for each of the active constituents given separately. The FDC product has been marketed in parts of the EU for over 20 years under the tradename Arlevert.

For Arlevert the contraindications to use in the EU are: hypersensitivity, severe renal impairment (due to renal excretion of dimenhydramine).

Contraindications to dimenhydrinate in Canada are: hypersensitivity to dimenhydrinate, its components (diphenhydramine or 8-chlorotheophylline) or any component of the formulation; concurrent use of or use within 14 days following therapy with a monoamine oxidase inhibitor; narrow angle glaucoma; chronic pulmonary disease; prostatic hypertrophy.

The SPC for Arlevert states that there are reports of dimenhydrinate being abused as a recreational drug for induction of delirium.

The American Health Formulary Service (AHFS) refers to the following adverse events for dimenhydrinate:

- Drowsiness commonly occurs after administration of dimenhydrinate. Paradoxical CNS stimulation may occur in children and occasionally in adults.
- Other adverse effects include headache, blurred vision, tinnitus, dryness of the mouth and respiratory passages, incoordination, palpitation, dizziness, and hypotension. Anorexia, constipation or diarrhoea, urinary frequency, and dysuria are less common. Pain may occur at the site of IM injection. Because dimenhydrinate contains diphenhydramine, the possibility of other diphenhydramine-related adverse effects should also be considered.
- Dimenhydrinate should be used with caution in patients with seizure disorders. The anticholinergic effects of the drug should be considered when administering dimenhydrinate to patients with conditions that might be aggravated by anticholinergic therapy (for example, , angle-closure glaucoma, enlargement of the prostate gland). The drug may mask symptoms of ototoxicity and therefore should be administered with caution to patients receiving known ototoxic drugs. These patients should be closely monitored during therapy with dimenhydrinate.
- Accidental antihistamine overdose occurs frequently in infants and children. Symptoms of dimenhydrinate toxicity in children may resemble atropine overdosage and include dilated pupils, flushed face, excitation, hallucinations, confusion, ataxia, intermittent clonic convulsions, coma, cardiorespiratory collapse, and death. Symptoms may be delayed for up to 2 hours after ingestion; death may occur within 18 hours.
- In adults, 500 mg or more of dimenhydrinate may cause extreme difficulty in speech and swallowing, and produces a psychosis indistinguishable from that of atropine poisoning. CNS excitation may be preceded by sedation, leading to a cycle of CNS excitation, seizures, and postictal depression.

Evaluator's conclusions on safety

The adverse events most frequently associated with cinnarizine/ dimenhydrinate are sedation and dry mouth. Although it wasn't clear from the clinical trial reporting data that the sedation reduces over time in many patients as is the case with other centrally acting antihistamines.

Dimenhydrinate has been abused for its delirium-inducing effects in the past and this product would also have potential for abuse.

The potential side effect that the evaluator considers was not adequately highlighted in the submission or in the SPC for Arlevert is the propensity for cinnarizine to cause extrapyramidal symptoms, particularly parkinsonian symptoms, which may be permanent and are more likely to occur in older adults, with higher doses and with long term exposure. These effects are most likely due to the demonstrated dopamine D2 receptor blockade by cinnarizine. Extrapyramidal symptoms can occur within weeks of commencement of treatment or after many years of treatment. While many cases resolve

on ceasing treatment some cases have resulted in permanent parkinsonian movement disorders or other extrapyramidal symptoms such as other dystonias and akathisia.

If this product is approved for registration the risk of development extrapyramidal signs and symptoms should be adequately highlighted in the PI. Prescribers and the public should be advised that cinnarizine/ dimenhydrinate should be taken at the lowest dose and for the shortest time period consistent with adequate symptom control. Treatment should be ceased if any extrapyramidal signs or symptoms occur. Ideally this treatment would be prescribed only after the failure of currently available treatments for vertigo such as betahistine.

First round benefit-risk assessment

First round assessment of benefits

Table 2 summarises the assessment of benefits at the first round of evaluation.

Table 2: First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
This FDC has demonstrated clinically significant efficacy in the management of symptoms of vertigo due to central and peripheral causes. Currently there are few oral medicines available for the management of vertigo.	The combination has demonstrated greater efficacy in the reduction of the symptoms of vertigo than either of its component actives given as monotherapy either at the same dose as in the FDC or at somewhat higher doses. Patients with conditions requiring long term treatment were excluded from the pivotal efficacy studies. Efficacy in Meniere's disease, a relatively common cause of vertigo, has not been examined.

First round assessment of risks

Table 3 summarises the assessment of risks at the first round of evaluation

Table 3: First round assessment of risks

Risks	Strengths and Uncertainties
Risk of extrapyramidal adverse events which may be irreversible. Because extrapyramidal symptoms (EPS) are more likely with long term use this product should not be recommended for patients requiring long term control of vertigo symptoms. This may be difficult to enforce given the limited options for many of these patients. Sedation and decreased alertness creating a risk of harm when using machinery or when	The evidence for all listed risks has been obtained from a limited number of mostly older studies with less reporting of adverse events than would generally be the case if full study reports, rather than published reports were available. Identified risks have been supported with extensive post-marketing studies and adverse drug reaction (ADR) reporting. Long term use should be discouraged given the association between cinnarizine and

Risks	Strengths and Uncertainties
driving. Dry mouth and associated dental hygiene issues. Constipation. Potential risk of abuse due to the dimenhydrinate component causing delirium effects. Weight gain.	extrapyramidal effects, particularly in elderly patients. Dopamine D2 receptor binding has been demonstrated with cinnarizine. The European SPC for Arlevert recommends that the duration of treatment not exceed 4 weeks. This should, be adopted as a recommended maximum duration for Cizinate/ Cizere/ Citigo. Patients should undergo a benefit/risk re-analysis if treatment beyond 4 weeks is contemplated.

First round assessment of benefit-risk balance

The risks from use of Cizinate/ Cizere/ Citigo (cinnarizine 20 mg/ dimenhydrinate 40 mg) when used for the proposed indications and with the proposed dose regimen present a positive benefit/ risk balance, provided risks are adequately identified and long term use is discouraged.

First round recommendation regarding authorisation

The clinical evaluator recommends Cizinate/ Cizere/ Citigo (cinnarizine 20 mg/ dimenhydrinate 20 mg) be approved however the clinical evaluator recommends modification of the proposed indication as follows:

> *Short-term treatment of vertigo symptoms of various origins in adults who have not responded to alternative treatments.*

Approval should also be subject to satisfactory negotiation of the PI and CMI. Additionally the cinnarizine component requires entry onto the SUSMP prior to marketing.

Clinical questions and second round evaluation

The clinical questions together with the sponsor's response and the evaluation of the response are presented below.

Question 1

Is the sponsor able to provide an assurance that no clinical PK study is needed to verify that the PK of cinnarizine and dimenhydrinate in the product proposed for registration is the same as the PK of cinnarizine and dimenhydrinate in alternative oral formulations?

Sponsor response

The sponsor responded in 5 parts. The most reassuring part of the response was to identify summary results of a study comparing the PK of cinnarizine and dimenhydrinate alone and in combination. This study summary was included in the EPAR published in 2007 after a mutual recognition procedure, Arlevert 20 mg/ 40 mg tablets having been authorised in the UK in 2005.

The assessment report noted that using AUC 90% CI estimates, the study could not exclude that a difference in bioavailability exists between cinnarizine administered alone and as Arlevert, however this result may be due to the large intersubject variability observed in AUC calculations. Those results are shown in the table below.

Table 4: Cinnarizine and diphenhydramine mono-component versus reference FDC product (Arlevert) pharmacokinetics

Cinnarizine Pharmacokinetic Parameters (Mean ± s.e.m., n = 11)

Parameter	Units	Cinnarizine	Arlevert 20mg/40mg Tablets
C_{max}	ng/ml	38.58 ± 6.16	37.36 ± 4.46
T_{max}	h	2.05 ± 0.42	2.27 ± 0.22
AUC_{exp}	ng/ml.h	225.22 ± 49.70	238.26 ± 38.61
MRT_{exp}	h	7.89 ± 1.39	7.03 ± 0.54
$T_{½}$	h	4.94 ± 1.00	4.10 ± 0.35

Diphenhydramine Pharmacokinetic Parameters (Mean ± s.e.m., n = 12)

Parameter	Units	Dimenhydrinate	Arlevert 20mg/40mg Tablets
C_{max}	ng/ml	40.91 ± 3.45	37.36 ± 4.46
T_{max}	h	1.71 ± 0.19	1.88 ± 0.27
AUC_{exp}	ng/ml.h	265.14 ± 25.19	240.94± 23.63
MRT_{exp}	h	7.81± 0.40	7.65 ± 0.37
$T_{½}$	h	4.76 ± 0.22	4.52 ± 0.20

The paired t-test revealed no significant difference for the pharmacokinetic parameters between actives administered alone or as Arlevert 20mg/40mg Tablets.

Additional responses included:

- That the non-clinical component of the literature search had not identified evidence of a potential PK or PD interaction between cinnarizine and dimenhydrinate. In vitro liver microsomal studies demonstrated that cinnarizine metabolism is primarily mediated through CYP2D6, with CYP2C9 a secondary pathway. Inhibitors of CYP2D6 may potentially reduce the metabolism of cinnarizine. While dimenhydrinate may inhibit CYP2D6 mediated metabolism, any interaction would apply equally to the FDC formulation, or to the monocomponents administered individually.
- No clinical studies comparing the PK of cinnarizine and dimenhydrinate when administered in a single dose form, to each component administered individually, where identified in the literature search.
- The pivotal study (Pytel et al.) in the submission showed increased efficacy of the FDC and fewer adverse effects than the monocomponents given separately at higher doses. This statement was to support the sponsor's conclusion that a clinically relevant detrimental interaction between cinnarizine and dimenhydrinate is unlikely to occur in practice.
- Cinnarizine is not currently listed on the ARTG and dimenhydrinate is available only in combination with caffeine and hyoscine (Travacalm). Combination therapy with both cinnarizine and dimenhydrinate in Australia will therefore only become available upon registration of the proposed FDC. Eligible patients will be commenced and titrated on the FDC only. Any potential differences in bioavailability, between the FDC and the individual monocomponents, even if they were clinically significant, are therefore of theoretical relevance only.

Evaluator's comments

These responses are satisfactory. The results in the European Public Assessment Report (EPAR) are particularly reassuring, though it appears this study was somewhat underpowered to determine bioequivalence of the active components given alone and in the proposed FDC.

Question 2

Please indicate the location of any published information to support the claim in the proposed PI, Clinical Overview and Clinical Summary of Pharmacology that with regard to dimenhydrinate: The substance exhibits anti-emetic and antivertiginous effects through influencing the chemoreceptor trigger zone in the region of the fourth ventricle. Dimenhydrinate thus acts predominantly on the central vestibular system.

Sponsor response

In summary, the sponsor noted that the statement was extracted from the Arlevert SPC and that the non-clinical evaluator had reviewed the published evidence and provided an alternative statement which the sponsor proposes to include in the Section: Pharmacology of the PI. That statement is shown below:

> *In vitro studies have demonstrated that both diphenhydramine and cinnarizine have inhibitory activity at multiple molecular targets. Diphenhydramine is a potent inhibitor of histamine H1 receptors and muscarinic acetylcholine receptors, whilst cinnarizine is a potent inhibitor of histamine H1 and H4 receptors and dopamine D2 receptors and a less potent inhibitor of pressure-sensitive potassium channels and serotonin 2 receptors. All the aforementioned proteins are known to have functions in the central and/or peripheral vestibular system.*

Evaluator's comments

This response is satisfactory

Question 3

Please clarify the status of cinnarizine, dimenhydrinate and Arlevert in the EU. Please indicate whether these products require a prescription from a medical practitioner. Also indicate the pack sizes of Arlevert in the EU.

Sponsor response

The sponsor noted that evaluation of a generic version of Arlevert had been submission in the EU and that these products will require a prescription from a medical practitioner. Arlevert has been authorised in many EU countries and in most of them 20, 50, and/or 100 tablet pack sizes are approved. In some countries there are additional approved pack sizes such as 24, 48, and/or 96 tablets.

Additionally, the sponsor notes that the EPAR notes that Arlevert was available only on prescription in 2005.

Evaluator's comments

This response is satisfactory.

Question 4

Please supply any available information on the effect of cinnarizine/dimenhydrinate on QT interval prolongation. Particularly of interest is the source of the statement in the draft PI that concomitant administration of medicines that prolong the QT interval of the ECG should be avoided.

Sponsor response

The sponsor noted that the statement: *'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'*, was taken from the European SPC for Arlevert.

Additionally, the literature search identified nonclinical studies and that the nonclinical evaluator has stated that *'Based on the 6 studies evaluating the potential effect of cinnarizine on the cardiovascular system, it may be concluded that cinnarizine does not increase the risk of ventricular fibrillation or cardiac mortality, produces only small changes in heart electrolytes, and may protect the heart from isoprenaline induced electrolyte changes.'*

No clinical publications identified in the literature search provided specific cardiac safety data however one case each of palpitations, tachycardia and shock were reported in association with cinnarizine at doses up to 50 mg three times daily and one case of pseudoangina in a patient taking the FDC three times daily were identified.

Evaluator's comments

While there is no identified thorough QT study it appears from long term use of both components that QT prolongation is not a clinically significant issue with either cinnarizine or dimenhydrinate. This response is satisfactory.

Question 5

Is the sponsor aware of the reason Arlevert is recommended for a maximum duration of use of 4 weeks in the EU? Please supply information on the history of this restriction.

Sponsor response

The sponsor responded that [the sponsor] *'assume(s) the basis for the maximum duration of use of Arlevert being restricted to 4 weeks is based on the fact that the 8 clinical studies submitted in support of EU market authorisation included a 'treatment period usually of 4 weeks'.'*

Evaluator's comments

This response is satisfactory and supports limiting the duration of treatment of the FDC to 4 weeks. The evaluator notes the proposed indication has now been amended to specify short term treatment.

Second round benefit-risk assessment

Second round assessment of benefits

The benefits identified in the initial assessment are unchanged.

Second round assessment of risks

The major risk of extrapyramidal effects has been mitigated by restricting the recommended duration of continuous use to 4 weeks.

Second round assessment of benefit-risk balance

The benefit-risk assessment is favourable.

Second round recommendation regarding authorisation

The proposed indication has now been amended as requested and cinnarizine is now on the SUSMP. The evaluator recommends that Cizinate / Cizere / Citigo Containing cinnarizine 20 mg/ dimenhydrinate 40 mg be approved for registration.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[20]

The sponsor has submitted EU Risk Management Plan (EU-RMP) version 1.1 (dated 10 April 2017; data lock point (DLP) 30 November 2015) and Australia specific annex (ASA) version 01 (April 2017) in support of this application. In response to the recommendations made in the first round of clinical, non-clinical and RMP evaluation reports, the sponsor has provided an updated ASA (version 02; March 2018) with five Australian specific safety concerns added (see table below).

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below, with Australia-specific safety concerns highlighted in yellow.

Table 5: Sponsor's proposed summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Risk in patients with angle-closure glaucoma	ü	–	ü	-
	Risk in patients with convulsions	ü	-	ü	–
	Risk in patients with suspicion of raised intracranial pressure	ü	-	ü	-
	Risk in patients with alcohol abuse	ü	-	ü	-
	Risk in patients with urine retention due to urethroprostatic disorders	ü	–	ü	-
Important potential risks	Risk in patients with conditions that might be aggravated by anticholinergic therapy: raised intra-ocular pressure, pyloro-duodenal obstruction, prostatic hypertrophy, hypertension, hyperthyroidism, severe	ü	–	ü	–

[20] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	coronary heart disease.				
	Risk in patients with Parkinson's disease	ü	–	ü	–
	Extrapyramidal effects[1]	ü	–	ü	–
	Drug/Drug interactions[1]	ü	-	ü	–
Missing information	Patients with severe hepatic impairment	ü	–	ü	–
	Patients with severe renal impairment	ü	-	ü	–
	Use in children	ü	-	ü	
	Use in pregnancy and lactation	ü	–	ü	–
	Use in patients beyond 4 weeks[1]	ü	–	ü	–
	Use in the elderly[1]	ü	–	ü	–
	Use in patients with Ménière's disease[1]	ü	–	ü	–

New and outstanding recommendations from second round evaluation

- This is a recommendation related to an original recommendation in the first round evaluation report: The evaluator has noted the updates to the 'Summary of the RMP' in the ASA. It is noted that other parts of the ASA, such as a table [not included here], have not been updated to rephrase the safety concerns. As this is not a critical issue, the inconsistency should be dealt with when the sponsor conducts the next RMP update.
- This is a recommendation to the TGA Delegate: 'Use in patients with Ménière's disease' is important missing information. It is recommended that the Delegate considers inclusion of advice on this missing information.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The Cizinate EU-RMP version 1.1 dated 10 April 2017 (data lock point 30 November 2015) with Australian Specific Annex version 02 dated March 2018, included with submission PM-2017-00806-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the periodic safety update report (PSUR) requirement:

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Introduction

This is a literature based submission by the sponsor to register a new fixed dose combination product (containing cinnarizine and dimenhydrinate) with the trade names Cizinate, Cizere and Citigo, proposed for new indication. Cinnarizine is not a previously approved active ingredient unlike dimenhydrinate, which is listed as a single ingredient product containing 50 mg of the medicine (Dramamine; ARTG AUST R 10270).

As per the clinical evaluation report (CER), it is noted in the Australian Therapeutic Guidelines that, vertigo is an illusion of motion, which is most often experienced as a rotatory sensation, although it may also be linear in quality (for example, a sensation of falling or pitching). It is frequently accompanied by autonomic symptoms such as nausea, retching, vomiting, pallor and sweating.

Vertigo is often a result of pathology in one of the inner ear balance organs. This may be due to hypofunction (for example, vestibular neuritis) or hyperfunction (for example, benign paroxysmal positional vertigo). It can also result from central neurological disorders affecting vestibular pathways in the brain stem, cerebellum and cortex (for example, migraine). Acoustic neuromas and acute middle ear infections seldom cause vertigo.

The following has been summarised, as per the clinical evaluator, from the information submitted by the sponsor.

Vertigo is a primary symptom of vestibular disease. It has a reported prevalence in the primary care setting of 5 to 7%. The prevalence increases with age, and may be as high as 50% in the population over 70 years. Vertigo is commonly associated with significant morbidity including falls, which may lead to immobilization and significant health costs.

Vertigo may arise from disease, injury or degenerative processes affecting either component of the vestibular system, or a combination of both.

The sponsor has noted that both cinnarizine and dimenhydrinate are known to be effective in the treatment of vertigo. At the time of submission, dimenhydrinate was listed on the ARTG) as a single ingredient product containing 50mg of the medicine (Dramamine, ARTG AUST R 10270). The approved indications were:

> *Prevention and relief of motion sickness and treatment of vertigo, nausea and vomiting associated with: electroshock therapy, anaesthesia and surgery, labyrinthine disturbances and radiation sickness. (Helps prevent travel sickness).*

Dimenhydrinate is in Schedule 2 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP);[21] when in primary packs of 10 doses or less for the prevention or treatment of motion sickness, except in preparations for the treatment of children under 2 years of age. It is in Schedule 3 when in oral preparations except when included in Schedule 2. Registration of dimenhydrinate 50 mg tablets (Dramamine) was cancelled by the sponsor on 30 June 2017, after acceptance of this submission for evaluation. The registrations of other products containing dimenhydrinate were cancelled in 2009.

The recommended dose regimen of the 50 mg dimenhydrinate product available in the UK for motion sickness is 50 mg three times daily. For other treatment, 4 hourly administration may be required. The maximum recommended total daily dose is 300 mg.

Currently cinnarizine is not listed on the ARTG. Cinnarizine 15 mg tablets (trade name: Stugeron) have been available in the UK since 1989 (date of first authorisation 14 September 1989). The European (SPC) indications are:

> *Control of vestibular disorders such as vertigo, tinnitus and vomiting such as is seen in Meniere's disease. Effective in the control of motion sickness.*

Cinnarizine is also accessed via the TGA's Special Access Scheme (SAS) to treat vertigo associated with various medical conditions, particularly Meniere's disease and motion sickness. Cinnarizine is not available in the USA or Canada. Stugeron appears to be available without prescription in the UK.

The proposed indication is the same as the approved indication for the FDC product that has a marketing authorisation in the EU, that is '*Treatment of vertigo symptoms of various origins*'. It is not clear whether a prescription is required for the FDC product, (trade name: Arlevert) in other countries.

Quality

The Delegate reiterated the quality findings as presented above (see Section II: *Quality findings*, above).

Quality summary and conclusions

The quality evaluator recommended the following; from a pharmaceutical chemistry perspective:

- Approval is recommended with regard to chemistry and quality controls aspect of the finished product. All outstanding issues for this aspect have been adequately resolved.
- The company has demonstrated that the proposed product under this application is bioequivalent to the product referenced in the literature based submission (Arlevert cinnarizine/dimenhydrinate 20/40 mg tablets, Germany, with efficacy and safety data).
- The bioequivalent study outcome has been referred to the clinical Delegate, in determining its suitability to extend the efficacy and safety of the overseas reference product 'Arlevert' (referenced in the literature-based submission) to the proposed product under this application.

[21] SUSMP is also known as the Poisons Standard.

Nonclinical

The Delegate reiterated the nonclinical findings as presented above (see Section III: *Nonclinical findings*, above).

Nonclinical summary and conclusions

- Modern pharmacological studies and consideration of the likely free therapeutic plasma levels of cinnarizine suggest that calcium channel blockade is not its main mechanism of action and that anti-histamine, anti-dopamine and blockade of pressure-sensitive potassium channel mechanisms may be involved.
- Individually, cinnarizine and diphenhydramine have been noted in the literature as undergoing pharmacodynamic interactions with various other drugs.
- Individually, cinnarizine and diphenhydramine have been noted in the literature as undergoing pharmacokinetic interactions with various other drugs.
- There are various concerns related to the use of a cinnarizine: dimenhydrinate combination, particularly the association of cinnarizine with drug-induced parkinsonism (DIP) with long-term use.
- The sponsor has proposed Pregnancy Category B3 for Cizinate; Cizere; and Citigo.[6] The minimal adverse effects seen in a very limited set of animal studies suggest that Pregnancy Category B2 is more appropriate.[7]
- While the nonclinical submission was limited in terms of primary, evaluable data, given the long-term clinical history of use there are no nonclinical objections to the registration of Cizinate; Cizere; and Citigo provided that the clinical data provides a favourable risk-benefit given the concerns with extrapyramidal adverse events with cinnarizine with long term use.
- If registration is approved, the draft PI should be amended as directed [beyond the scope of the AusPAR].

Clinical

Pharmacokinetics and pharmacodynamics

The Delegate reiterated the findings as summarised in Section V: *Clinical findings; Pharmacodynamics*, and *Pharmacokinetics*, as shown above.

Efficacy

As per the clinical evaluation report, there were two sections to the efficacy assessment. Firstly, the efficacy of cinnarizine in the treatment of vertigo in adults was examined. This was followed by a second section intended to:

- demonstrate that the FDC cinnarizine 20 mg and dimenhydrinate 40 mg is at least as safe and is more efficacious than either cinnarizine or dimenhydrinate alone as a treatment for vertigo of various origins in adults; and
- support the recommended dosage and administration regimen for FDC of one tablet three times daily.

There was no separate reappraisal of the efficacy of dimenhydrinate as monotherapy in the treatment of vertigo.

It should be noted that the proposed dosing of dimenhydrinate at 40 mg three times daily within the FDC tablet is lower than the over the counter dose recommendations for dimenhydrinate as monotherapy for adults (50 mg to 100 mg every 4 to 6 hours, no more than 400 mg in 24 hours.

Pivotal or main efficacy studies for cinnarizine monotherapy in the treatment of vertigo as per the clinical evaluation report

Bodla et al.[22]

This study compared the efficacy and tolerability of cinnarizine (25 mg tablet) with those of betahistine. The study can be considered pivotal because it compared the active ingredients in the proposed FDC with a product, betahistine, approved for the treatment of Meniere's syndrome in Australia. Betahistine is accepted internationally as a treatment of peripheral vestibular vertigo with recommended doses between 8 to 16 mg three times daily with a maximum of 48 mg daily. Cinnarizine is a selective calcium channel blocker.

Study subjects were randomly assigned to 4 weeks of treatment with either the cinnarizine 25mg three times daily, or betahistine 16 mg per tablet three times daily.

There were no restrictions on duration of disease, pre-treatment, and concomitant diseases, except those known to be contraindications to the medications used.

Study subjects were outpatients of either sex, aged > 15 years, with otogenic vertigo with at least medium intensity of one or more vertigo symptoms. Patients who had Meniere's disease were excluded from participation, because treatment of this disease consists of long term prophylactic therapy, extending for a much longer period of time than the 4 week duration of this study.

Other exclusions were: vertigo due to unsolved organic primary disease (that is, non-vestibular origin), pregnancy, lactation, and women not using a safe method of contraception during the study were excluded.

Subjects were examined before the start of the treatment, after 7 ± 2 days during the study and at Day 28 ± 2 days:

- At each visit, vertigo symptoms, symptoms concomitant with vertigo and any other symptoms were recorded; vestibule spinal tests (Romberg's test) and vestibule-ocular tests (spontaneous, positional and caloric nystagmus) were also performed. In addition, hearing was tested by means of audiometry during the entry and final examinations.
- Efficacy evaluation was based on patients' assessments of the intensity of vertigo symptoms:
  - The primary efficacy variable was change in the 'mean vertigo score, (VSm), defined as the mean of the intensities of six vertigo symptoms and vertigo in consequence of six trigger factors (bowing; getting up; head movements; riding in car/train; and eye movements). It was evaluated using a Visual Analog Scale (VAS; severity was assessed on a 5-point scale from 0 to 4 with 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms, 4 = very severe symptoms):

    The vertigo symptoms assessed at each visits were: unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation and blackout. Vertigo following the six trigger factors: change in position; bowing; getting up; head movements; riding in car/train; and eye movements was also documented.

[22] Bodla R, et al Comparison of efficacy and tolerability of cinnarizine with betahistine in the treatment of otogenic vertigo. *International Journal of Pharmaceutical Research* 2011; 3: 36-40.

– The secondary efficacy variables assessed relate to the intensities of vegetative symptoms, that is, nausea, vomiting, sweating and palpitation, and concomitant symptoms of vertigo such as tinnitus and impaired hearing:

  Based on the scores of each symptom, a 'mean concomitant symptom score' (CSSM) was established. At the end of the mid study and final visits, the overall efficacy of treatments was evaluated with respect to vertigo symptoms, vegetative symptoms and concomitant symptoms based on a graded verbal rating scale: 1=very much improved, 2= much improved, 3= slightly improved, 4= not improved, and 5= deteriorated.

The study design was to show superiority of one treatment over the other.

Sample size calculation was based on the t-test model, and assumed a difference between the test medications in the reduction of VSm of d = 0.25 with an estimated standard deviation of s = 0.33. For a type 1 error of 0.05 and a type II error of 0.1 it was determined that a sample size of 30 subjects per group was required. Statistical analysis was performed on the original data on the basis of the intent- to-treat population, which was identical to the per-protocol population.

Confirmatory analysis of the primary efficacy variable VSm was based on change in this variable from baseline in hierarchical order:

1. 4 weeks after start of treatment and
2. 1 week after start of treatment.

Differences between medications were analysed by Student's t-test.

For baseline data, eighty outpatients were enrolled in the study and randomised to receive either cinnarizine (n = 40) or betahistine (n = 40). In these 80 patients, 3 patients from betahistine group terminated the study prematurely for unknown reasons after the entry examination and were lost to follow-up. All 77 patients who completed the study fulfilled the criteria for pre-protocol analysis and were included for the efficacy analysis. There were 27 (35.03%) males and 50 (64.97%) females. The minimum age was 25 years and 19 (64.67%) were aged ≥ 65 years. While no between groups comparison of demographic characteristics was included in the report, it was stated that there were no statistically significant differences with respect to demographic characteristics between the treatment groups. The distribution of diagnoses associated with vertigo within and between groups was not included in the report.

The clinical evaluator commented:

> 'This would generally be considered a negative study because it demonstrated statistical superiority of betahistine over cinnarizine in the management of symptoms of otogenic vertigo however; the following issues limit any conclusions regarding the relative efficacy of betahistine and cinnarizine in the management of otogenic vertigo:
>
> There was no placebo group with which to compare responses from both active treatment groups. This is a particularly important omission, given that for many causes of vertigo which were eligible for inclusion in the study, the vertigo is generally self-limiting for example viral labyrinthitis.
>
> The doses of betahistine are the maximum daily doses recommended in Australia for Meniere's syndrome.
>
> The mean VSm and CSSm were consistent, with the majority of subjects having mild or moderate vertigo and vegetative symptoms at baseline and thus, having limited scope to demonstrate improvements due to study treatments. The small between group differences in these efficacy parameter measures, are therefore not

unexpected. While the small differences between groups may have been statistically significant it is doubtful they were clinically significant.

There was no identification of the causes of vertigo, other than that they were otogenic vertigo, other than being due to Meniere's disease. This is important because, while the FDC product is intended to treat vertigo of various origins, vertigo due to Meniere's disease is likely to be a condition in which the product would be used, were it to be approved. Cinnarizine, under the trade name Stugeron is frequently used via the SAS for the management of Meniere's disease in Australia. It is approved for the control of vestibular disorders such as vertigo, tinnitus, nausea and vomiting such as is seen in Meniere's disease in the EU.'

The Delegate believes that as any confounder will equally affect both treatment arms to the same extent, the statistically significant finding of betahistine superiority over cinnarizine can be considered real. The sponsor is therefore not in a position to lay any claim of cinnarizine superiority over the currently marketed betahistine, for the management of vertigo in the PI.

Primary efficacy outcome

The results of the primary efficacy outcome are shown in Table 6, below.

Table 6: Changes in mean VSm over 4 week treatment period

	Cinnarizine	Betahistine
Baseline (Day 0)	1.56	1.7
After 1 week (Day 7)	1.27	0.95
After 4 weeks (Day 28)	1.09	0.72
Difference from baseline	0.47	0.98

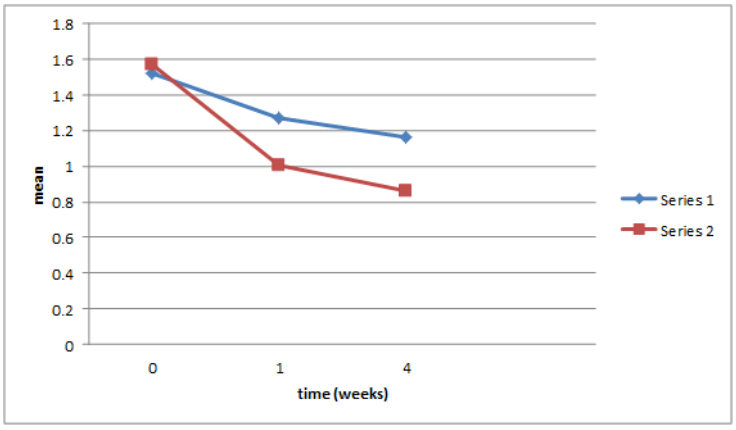
The mean VSm in both treatment groups improved during the 4 week treatment period with subjects given betahistine reporting a greater reduction in symptoms, and thus having a greater reduction in VSm. This difference, of 0.51 on a 5 point scale was statistically significant (p = 0.002). Additionally, at the end of treatment 9/30 (36.67%) of subjects given betahistine and 2/29 (6.9%) given cinnarizine reported no vertigo symptoms. CSSm scores over the course of the 4 week treatment period showed similar greater mean reduction in symptoms in the subjects given betahistine compared with those given cinnarizine as shown below.

Table 7: Changes in mean CSSm over 4 week treatment period

	Cinnarizine	Betahistine
Baseline (Day 0)	1.49	1.45
After 1 week (Day 7)	1.27	1.06
After 4 weeks (Day 28)	1.23	1.0
Difference from Baseline	0.26	0.45

The difference in reduction in mean CSSm between the groups was 0.19 on a 5 point scale. This was also statistically significant (p = 0.02). The overall efficacy evaluation, performed at the end of the study did not show superiority of betahistine over cinnarizine.

Figure 3: Mean CSSm scores versus time



Deering et al.[23]

For study treatment, subjects received either betahistine 24 mg or cinnarizine 15 mg three times daily for 3 months and then crossed over to the alternative treatment for a further 3 months, giving a total of 6 months treatment. There was no washout period between the active treatment periods.

For inclusion, subjects must be over 18 years and with at least two episodes of peripheral vertigo in the preceding 3 months.

Patients were excluded if their vertigo was identified as being due to epilepsy, tumour, trauma, ototoxic drugs, multiple sclerosis, systemic disease (such as thyroid dysfunction) and antihypertensive medicines. Those with pregnancy risk or receiving antihistamines, phenothiazines, barbiturates, vasodilators or tranquillizers were also excluded. Subjects were advised to avoid alcohol.

Regarding efficacy variables, subjects' details relating to their presenting complaint were recorded on entry, together with a clinical global impression of symptom severity on a 5 point scale (0 = normal, 1 = borderline, 2 = average, 3 = marked, and 4 = severe). Subjects were also issued with a diary and asked to record frequency and severity of attacks of dizziness. Subjects returned at 4-weekly intervals; compliance was checked, side-effects recorded and clinical global impression repeated.

[23] Deering RB, et al. A double-blind crossover study comparing betahistine and cinnarizine in the treatment of recurrent vertigo in patients in general practice. *Current Medical Research and Opinion* 1986; 10: 209-214.

The statistical method used was the analysis of variance of a crossover design with assessment of the drug-period interaction. Statistical significance was concluded if $p \leq 0.05$. Because of the lack of wash-out periods, it was stated that a comparison of the two treatments would only be calculated using data from the second and third months of each treatment.

For baseline data, the study population consisted of 88 subjects (34 males and 54 females) over 18years (mean age 61.5 years). Of the 88 subjects enrolled, 46 (52.2%) completed 6 months of treatment. Reasons for withdrawal are listed below in Table 8.

Table 8: Reasons for withdrawal and/or non-inclusion in the analysis of results

Reason	Betahistine	Cinnarizine	Total
Side-effects	4	9	13
Better	5	3	8
Concurrent illness	3	-	3
Non-compliance	2	1	3
Inefficacy	2	1	3
Non-attendance	2	1	3
Missing data	4	5	9
Total	21	21	42

For efficacy outcome, analysis was performed on the 46 subjects who completed the study. Diary data were available from 39 subjects.

Table 9: Study population demographics and efficacy outcome data

Patients	Betahistine - cinnarizine	Cinnarizine - betahistine	Total
No. studied	22	24	24
Sex: Male	9	15	15
Sex: Female	13	9	9
Age (years): mean(SD)	62.1 (12.04)	61.0 (7.70)	61.0 (7.70)
Mean duration	5.14	4.96	5.04
Mean no. of attacks in 3 months prior to entry	28.5	26.1	27.3

Patients	Betahistine - cinnarizine	Cinnarizine - betahistine	Total
Mean typical length of attack (hours)	3.1	1.4	2.2
Severity of typical attack:			
Mild	3	7	10
Moderate	19	15	34
Severe	0	2	2

The frequency of attacks decreased during the first 3 months of treatment with either drug:

- During these months, the mean frequencies of attacks in patients taking cinnarizine were all higher than the patient's estimate of attack frequency pre-treatment.
- On betahistine treatment, all 3 months showed an improvement compared with pre-treatment.
- When subjects crossed over from betahistine to cinnarizine, they reported an increase in attacks during the first month. There was then a small decrease in the second and third months of treatment but the frequency was still double that achieved after 3 months on betahistine. However, when subjects crossed over from cinnarizine to betahistine treatment, the frequency of attacks continued to decrease.
- The results for the last 2 months of each treatment are compared below. A comparison of the last 2 months of each treatment by analysis of variance, showed that there were statistically significantly fewer vertigo attacks on betahistine than on cinnarizine ($p = 0.025$).

Table 10: Frequency of vertigo attacks: mean (± standard error) number of attacks per month

Month	Betahistine – cinnarizine (n=18)	Cinnarizine – betahistine (n=21)
1	8.7 ± 2.78 (n=17)	16.4 ± 4.21
2	5.9 ± 2.52	10.0 ± 2.90
3	4.3 ± 2.10	9.1 ± 2.55
4	10.3 ± 4.77	7.7 ± 2.21
5	8.6 ± 4.48	6.8 ± 2.67
6	9.1 ± 5.32 (n=17)	5.5 ± 2.16

The mean duration of attacks of vertigo showed little difference over the course of the study (may be a trend for decrease in mean duration with betahistine).

Table 11: Duration of vertigo attacks: mean hours (± standard error of the mean)

Month	Betahistine – cinnarizine (n=18)	Cinnarizine – betahistine (n=21)
1	1.26 ± 0.69 (n=17)	0.91 ± 0.21
2	1.19 ± 0.71	0.71 ± 0.17
3	0.57 ± 0.21	0.79 ± 0.23
4	1.18 ± 0.66	0.62 ± 0.14
5	0.44 ± 0.19	0.75 ± 0.19
6	0.87 ± 0.32 (n=17)	0.66 ± 0.15

Similarly, there were minor and not statistically significant differences in clinical global impression of symptom severity between treatments.

Table 12: Clinical Global Impression: mean (standard error of the mean) scores

Month	Betahistine – cinnarizine (n=22)	Cinnarizine – betahistine (n=24)
On entry	2.13 ±0.18	2.25 ± 0.18
1	1.68 ±0.18	1.38 ±0.18
2	1.27 ± 0.16	1.33 ±0.17
3	0.95 ±0.15	1.04 ± 0.17
4	1.18 ±0.15	1.09 ±0.17 (n=23)
5	0.71 ±0.17 (n=21)	1.17 ±0.16 (n=23)
6	0.95 ±0.15 (n=17)	1.17 ±0.20

It was concluded that the results of this study indicated a preference for betahistine over cinnarizine.

The clinical evaluator commented: The following factors contribute to limited utility of this study in determining the extent of efficacy of cinnarizine in the management of vertigo:

- There was no placebo control. This is important given the variability of vertigo symptom severity and its often episodic nature.
- It was a very small study suggesting low power to determine differences between treatments.
- The study used cinnarizine as a long term treatment when it is not proposed to be used continuously for longer than 4 weeks.
- The proposed dose of cinnarizine is 20 mg three times daily rather than the 15 mg three times daily used in this study.
- The dose of betahistine of 24 mg three times daily was higher than the currently recommended maximum daily dose of 48 mg.

- There was no clear statement of the primary objective or the primary efficacy endpoint.
- There was no clear hypothesis on which a sample size calculation or statistical plan was based.
- There was no clear statement on whether superiority of one product over the other had been determined. If the primary efficacy measure was Clinical Global Impression; then no difference in efficacy between the two treatments was seen. If, however it was difference in frequency of episodes in the last two months of each treatment period then it may have been reached but there was insufficient statistical information provided to determine if this was the case.
- The method for determining Clinical Global Impression was not included in the report.
- The discontinuation rate was quite high at approximately 50%, consequently the final assessment was based on only 46 subjects.
- The frequency of vertigo episodes prior to study appears to have been based on subject recall. This method is inherently inaccurate due to the limitations of recall, particularly over a long period of time as was required in this study.

Again, despite the limitations of the study, the Delegate believes that betahistine probably has an edge over cinnarizine in the management of vertigo.

Supportive studies for cinnarizine monotherapy in the treatment of vertigo as per the clinical evaluation report

- Mangabeira-Albernazet et al., (1978);[24] compared cinnarizine with another calcium antagonist, flunarizine, a derivative of cinnarizine which is not registered in Australia.
- Pianese et al.;[25] compared an active, which while registered in Australia is not approved for use in the treatment of vertigo, but rather in the treatment of ischaemic neurological deficits caused by cerebral vasospasm after subarachnoid haemorrhage.
- Gananca et al., (1988);[26] compared the efficacy of cinnarizine with that of oxpentifylline (Trental), an active which, while registered in Australia, is indicated for the treatment of intermittent claudication not vertigo. Note that oxypentifylline and pentoxifylline are synonyms.

Pivotal or main efficacy studies for cinnarizine/dimenhydrinate in the treatment of vertigo as per the clinical evaluation report

Hahn et al., (2011)[27]

Multicentre, double blind, randomised, three-arm, parallel-group study to compare the tolerability and efficacy of a FDC medicine, containing 20mg of cinnarizine and 40mg of dimenhydrinate to monotherapy with either 20mg cinnarizine or 40mg dimenhydrinate, in adult patients with vertigo of central, peripheral or mixed origin.

The objective of the study was to corroborate that the efficacy of the combination exceeds that of the single substances, without increasing the risk posed to the patients because of superimposition of adverse reactions.

[24] Mangabeira-Albernazet PL et al., Flunarizine and cinnarizine as vestibular depressants: A statistical study. *Journal for Oto-Rhino-Laryngology, Head and Neck Surgery*. 1978; 40: 92-100
[25] Pianese CP et al. Approaches to the management of peripheral vertigo: efficacy and safety of two calcium antagonists in a 12 week multinational double blind study. *Otology and Neurology* 2002; 23: 357-363
[26] Gananca MM et al. Controlled clinical trial of pentoxifylline versus cinnarizine in the treatment of labyrinthine disorders. *Pharmatherapeutica*. 1988; 5: 170-176
[27] Hahn A, et al. Comparison of cinnarizine/dimenhydrinate fixed combination with the respective monotherapies for vertigo of various origins. A randomized, double-blind, active-controlled, multicenter study. *Clinical Drug Investigation* 2011; 31: 371-383

Inclusion and exclusion criteria

Inclusion criteria:

- The study enrolled Caucasian male and female outpatients aged ≥ 30 years with vertigo due to peripheral, central or mixed peripheral/ central vestibular disorders.
- The diagnosis was established at the discretion of the investigators before subject's enrolment following usual neuro-otological criteria. Only subjects who assessed at least one (out of 6) vertigo symptoms as being of at least medium intensity (≥ 2) on a 5 point VAS and who had pathological vestibule-spinal movement patterns and/ or nystagmus reactions were eligible for participation.

Exclusion criteria:

- Patients with Meniere's disease, benign paroxysmal positional vertigo (BPPV), caloric areflexia or vertigo due to non-vestibular disorders were excluded from the study.
- Further exclusion criteria consisted mainly of known contraindications to the active substances (for example, convulsions, suspected compressive intracranial processes, angle-closure glaucoma, urine retention due to prostatic adenoma with residual urine, severe renal insufficiency, Parkinson's disease).
- Pregnant and nursing women were also excluded.
- The following medicines were contraindicated: monoamine oxidase inhibitors, tricyclic antidepressants, parasympatholytics, corticosteroids, antihistamines, and heparin.
- Other anti-vertiginous agents (other than study drugs) and/or drugs with cerebrovascular activity were also not permitted.

Study treatments

Regarding study treatments, patients received the fixed-dose combination of cinnarizine 20 mg/ dimenhydrinate 40 mg (Arlevert) or monotherapy with cinnarizine 20 mg or dimenhydrinate 40 mg. Patients who had been taking anti-vertiginous drugs before enrolment underwent a 7 day washout before the start of study treatment. The tablets were indistinguishable in appearance, taste, weight, shape and packaging to ensure blind conditions. At randomisation, each patient was allocated a unique patient number in chronological order that served as an identifier for the distribution of blinded medication. The investigators were supplied with sealed envelopes that contained the decoding information for each patient separately, in case of emergency.

In the study, patients underwent assessments at entry (Baseline), after 1 week and after 4 weeks of treatment. At each visit, the intensity of 12 vertigo symptoms was rated by the patients on a 5-point VAS (0 = not present, more than or equal to 2 = medium intensity and 4 = very strong). The symptoms were:

- dystasia and walking unsteadiness
- vertigo on change of position, bowing, getting up, and travelling by car or train, head movement, eye movement
- A mean vertigo score (MVS) served as a measure of vertigo intensity and was calculated by adding the scores on all 12 vertigo symptoms and dividing by 12. Possible values of the resulting mean score ranged from 0 to 4

Efficacy variables

The primary efficacy variable was the change in MVS at the end of Week 4. The secondary efficacy variables included:

- change in the severity of vegetative symptoms (nausea, vomiting, sweating, tachycardia) as rated by patients on the same 5-point VAS
- the assessment of several neuro-otological variables. The latter were:
  - vestibulospinal (Unterberger and Romberg) tests, which were recorded photo-optically. The evaluation parameters for Romberg test were anterior-posterior and lateral deviation while they were lateral and angular deviation for Unterberger test.
  - caloric test with electronystagmography (ENG) measurement (performed according to standard procedures (that is, irrigation of each ear with 20 mL of water at 30°C and 44°C for 30 seconds each)). The evaluation was based on nystagmus frequency.
  - standard pure tone audiometry was performed at baseline and the end of Week 4.

The tertiary efficacy variable was the patients and investigators rating of the overall efficacy of study treatment at the end of Weeks 1 and 4 using a 5-point verbal rating scale (very good, good, moderate or poor).

Analysis populations

For efficacy analyses, the intent-to-treat (ITT) group was defined as all randomised patients who received at least one dose of study medication and provided at least one post-randomisation efficacy value. A per-protocol (PP) analysis was not performed because the ITT and PP groups were identical that is, all study patients were compliant with study protocol.

Sample size

No information on sample size was included in the published report.

Statistical methods

Missing data were imputed by last observation carried forward (LOCF). The comparability of demographic and baseline clinical variables between treatment groups, was assessed at 10% significance level by analysis of variance (ANOVA) for quantitative data and by Kruskal-Wallis test for ordinal data. Qualitative (categorical) data were analysed using the chi-squared test. In cases of insufficient homogeneity of demographic or baseline clinical variables, analysis of covariance (ANCOVA) was performed using the relevant baseline values as covariates.

Analysis of efficacy variables was based on changes from baseline to the end of Weeks 1 and 4. Differences between the groups were analysed non-parametrically using the Mann-Whitney U test at a global significance level of $\alpha = 0.05$. Odds ratios and 95% confidence intervals were calculated for differential responder analysis. Supportive assessment of effect size, standardised differences and 95% CI were calculated based on the Student's t-test model. The reliability of the composite MVS was controlled by testing the consistency of the individual symptom scores with respect to the MVS using Cronback's α coefficient (SAS CORR procedure). Possible centre-by-treatment effects were determined using ANCOVA with the centre and interaction term as covariates.

Major protocol deviations

There were no significant protocol violations or deviations and thus no PP analysis.

Baseline data

A total of 182 patients were randomised. Five of these patients had no post-randomisation efficacy data at the end of week 1 and were not included in the efficacy analysis. Thus, the efficacy evaluation was based on data from 177 patients.

177 patients: 105 women and 72 men with a mean (SD) age of 52 (12.3) years were included in the efficacy analysis. There were no significant differences in demographic or clinical characteristics between the 3 treatment groups. There was a slightly higher age in the fixed-combination group than in the monotherapy groups.

Table 13: Demographic and clinical characteristics

Characteristic	Cinnarizine 20 mg/ dimenhydrinate 40 mg (n = 59)	Cinnarizine 20 mg (n = 60)	Dimenhydrinate 40 mg (n = 58)	p-Value
Sex [no. (%)]				
male	26 (44.1)	26 (43.3)	20 (34.5)	0.502[a]
female	33 (55.9)	34 (56.7)	38 (65.5)	
Age (y)				
mean ± SD	54.6 ± 11.5	49.7 ± 12.6	51.9 ± 12.4	0.090[b]
range	31–83	30–79	30–72	
Height (cm)				
mean ± SD	167.9 ± 8.7	170.3 ± 8.3	168.8 ± 8.3	0.304[b]
range	152–195	154–188	150–192	
Weight (kg)				
mean ± SD	73.3 ± 11.8	72.3 ± 13.8	73.0 ± 14.3	0.914[b]
range	51–107	46–100	48–110	
Body mass index (kg/m^2)				
mean ± SD	26.0 ± 3.9	24.8 ± 3.8	25.5 ± 3.6	0.235[b]
range	20.1– 40.6	17.9– 34.6	18.1– 36.3	
Duration of illness				
median (mo)	24.0	20.0	24.0	0.247[b]
patients [no. (%)]				
<1 y	20 (33.9)	18 (30.9)	15 (25.9)	
1–10 y	30 (50.8)	31 (51.7)	29 (50.0)	
≥10 y	9 (15.3)	11 (18.3)	14 (24.1)	
Type of vertigo [no. (%)]				
paroxysmal	33 (55.9)	40 (66.7)	36 (62.1)	0.483[a]
continuous	26 (44.1)	20 (33.3)	22 (37.9)	
Pre-treatment of vertigo [no. (%)]	35 (59.3)	42 (70.0)	42 (72.4)	0.274[a]

a Chi-squared (χ^2) test.

b ANOVA.

Of the randomised patients, 53 (29.1%) were diagnosed with vertigo of peripheral origin caused by labyrinthine apoplexy or vestibule-cochlear dysfunction and 30 (16.5%) with vertigo of central origin (for example, due to brainstem or cerebellar ischemia or cerebral concussion). The remaining 99 (54.4%) presented with signs of combined peripheral and central vestibular dysfunction (for example, due to vertebrobasilar insufficiency or trauma). The mean disease duration was approximately 4 years with a median duration of 2 years. Approximately 2/3 of the patients had received drug therapy for their vertigo prior to enrolment. 77 (43.4%) had concomitant disease, of which hypertension was the most common (34 patients; 19.2%).

Primary efficacy outcomes

Primary efficacy outcomes as per the clinical evaluator:

- MVS during the 4-week study period are shown in Figure 4. Baseline MVS were similar in the 3 treatment groups.
- Patients receiving the fixed combination showed the greatest improvement during the course of therapy. At Week 4, the MVS had decreased by >80% in the fixed combination group and by around 60% in each of the comparator groups. The differences between the fixed combination and the comparators were statistically significant, both at Week 1 and at Week 4.

Figure 4: Mean vertigo score (MVS) at Week 4

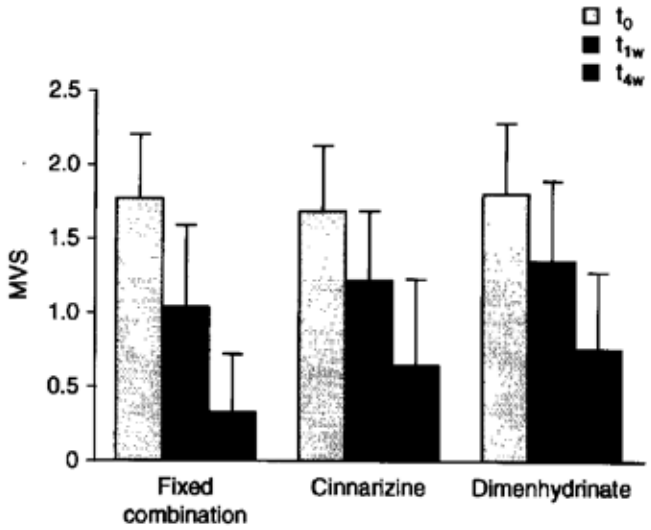


Fig. 2. Mean vertigo score (MVS) during 4-week treatment with cinnarizine 20 mg/dimenhydrinate 40 mg as a fixed combination (n = 59), cinnarizine 20 mg (n = 60) or dimenhydrinate 40 mg (n = 58), three times daily. Values are presented as mean ± SD of the assessments at baseline (t_0), after 1 week (t_{1w}) and after 4 weeks (t_{4w}) of treatment.

Table 14: Change in mean vertigo score (MVS) during the Week 4 treatment period

Time point/variable	Cinnarizine 20 mg/ dimenhydrinate 40 mg (n = 59)	Cinnarizine 20 mg (n = 60)	Dimenhydrinate 40 mg (n = 58)
Baseline (t_0)			
MVS (mean ± SD)	1.77 ± 0.44	1.69 ± 0.44	1.81 ± 0.48
After 1 week (t_{1w})			
Change from t_0 (mean ± SD)	−0.73 ± 0.45	−0.47 ± 0.37*	−0.44 ± 0.40*
After 4 weeks (t_{4w})			
Change from t_0 (mean ± SD)	−1.44 ± 0.56	−1.04 ± 0.53*	−1.06 ± 0.56*
Difference in LS mean (95% CI)[a]		0.35 (0.18, 0.52)	0.41 (0.24, 0.57)
Cohen's standardized difference [d (95% CI)]		0.74 (0.37, 1.12)	0.69 (0.31, 1.06)

a Comparator vs fixed combination.

LS = least squares; * p < 0.001 vs fixed combination (Mann-Whitney U test).

The clinical relevance of the differences in MVS reduction was evaluated by analysis of effect sizes using Cohen's standardised difference. The mean differences between the fixed combination and either cinnarizine or dimenhydrinate were both above the limit of medium effect size (d = 0.5), which, according to Cohen is considered sufficient to demonstrate clinical relevance. The reliability of the composite variable of MVS as a measure of vertigo was confirmed by Cronback's α coefficients (raw and standardised variance) at baseline, end of Week 1 and the end of Week 4.

Differential responder analysis further supported the clinical relevance of the improvements in vertigo with the fixed combination. Approximately 80% of the patients treated with the fixed combination had no or only minor vertigo symptoms (MVS ≤ 0.5) at Week 4 and about 25% were completely symptom-free. In comparison, only 1 patient in the comparator groups (the dimenhydrinate group) was symptom-free at Week 4 and only half the patients receiving a comparator had an MVS ≤ 0.5 at the end of Week 4.

Other efficacy outcomes

Other efficacy outcomes as per the clinical evaluator:

- The initial mean scores of the 4 vegetative symptoms of nausea, vomiting, sweating and tachycardia in the 3 groups were comparable.
- In the fixed combination and dimenhydrinate groups, vegetative symptoms progressively and markedly improved from baseline to Week 4 with no significant differences between the 2 medications. Cinnarizine was significantly less effective in reducing vegetative symptoms compared with the fixed combination.
- In the routine test of balance (the Unterberger stepping test), the parameters of lateral sway and angular deviation both improved moderately during therapy. Statistical evaluation indicated significantly greater improvements in lateral sway with the fixed combination in comparison with the single substances at Week 1 but not at Week 4. For angular deviation, the baseline values in the fixed combination group decreased to a significantly greater extent compared with the cinnarizine group at Week 4.
- Nystagmus frequencies in the caloric test showed no relevant changes during the study period in all groups.
- Similarly, pure tone audiometry showed only marginal changes between baseline and Week 4.
- Patients' and investigators' ratings of efficacy were similar. At end of both Weeks 1 and 4, the ratings were best for the fixed combination, followed by cinnarizine and worst for dimenhydrinate. By the end of the treatment, 74.6% of the fixed combination patients judged the efficacy as much improved or very much improved, as opposed to 63.4% of patients treated with cinnarizine and 48.3% treated with dimenhydrinate. Statistical analysis showed significantly better ratings for the fixed combination product compared with dimenhydrinate at both Weeks 1 and 4 assessments.

Table 15: Changes in selected secondary efficacy variables in the course of treatment

Variable	Cinnarizine 20 mg/ dimenhydrinate 40 mg (n=59)	Cinnarizine 20 mg (n=60)	Dimenhydrinate 40 mg (n=58)
Vegetative symptoms			
Mean vegetative score[a] (mean ± SD[b])			
baseline (t_0)	1.35 ± 0.82	1.33 ± 0.97	1.47 ± 0.77
change from baseline at t_{1w}	−0.86 ± 0.73	−0.57 ± 0.58*	−0.81 ± 0.71
change from baseline at t_{4w}	−1.23 ± 0.82	−0.81 ± 0.66**	−1.17 ± 0.72
Unterberger stepping test			
Lateral sway (cm) [mean ± SD]			
baseline (t_0)	16.5 ± 6.8	15.2 ± 6.6	15.3 ± 5.6
change from baseline at t_{1w}	−3.6 ± 4.8	−1.4 ± 4.0**	−1.8 ± 4.0*
change from baseline at t_{4w}	−4.7 ± 4.5	−3.9 ± 4.8	−2.9 ± 4.8
Angular deviation (°) [mean ± SD]			
baseline (t_0)	50.4 ± 47.9	34.4 ± 31.2	38.9 ± 34.4
change from baseline at t_{1w}	−20.3 ± 47.5	−6.1 ± 37.5	−11.1 ± 38.8
change from baseline at t_{4w}	−22.6 ± 56.7	−6.4 ± 38.8*	−16.1 ± 36.4

a Mean of the scores for the symptoms nausea, vomiting, sweating and tachycardia for each patient.

b Mean ± SD of the mean vegetative scores for all patients.

t_{1w} = after 1 week of treatment; t_{4w} = after 4 weeks of treatment; * $p < 0.05$, ** $p < 0.01$ vs fixed combination (Mann-Whitney U test).

The clinical evaluator commented:

- Given the poor evidence provided to support cinnarizine monotherapy in the treatment of vertigo, it is reassuring to see a reasonably well conducted study showing

a benefit from the fixed dose combination, when given at the proposed dose regimen compared with each of the component actives, given as monotherapy.

- Ideally, there would have been a placebo arm included. However, as the majority of patients were already taking treatment for vertigo, it may have been difficult to recruit patients to a study with a placebo arm. Nevertheless, the increased efficacy shown when cinnarizine is given in combination with dimenhydrinate over dimenhydrinate alone, shows that cinnarizine has some efficacy in the treatment of vertigo.
- As in the cinnarizine monotherapy studies, there were relatively small changes in the composite vertigo efficacy measure and the majority of patients, had fairly low levels of vertigo severity at baseline. This does limit the ability of any medications to demonstrate efficacy. The differences have been considered to be clinically relevant and this is acceptable.
- There were multiple secondary efficacy endpoints and no information on how multiplicity effects were managed. Thus, the validity of many of the statistical results reported for these endpoints is suspect. That does not alter the validity of the primary efficacy endpoint. Clinically meaningful and statistically significant superiority of the fixed dose combination of cinnarizine and dimenhydrinate, when given using the proposed dose regimen, over each of the component actives have been demonstrated.

Pytel et al., (2007)[28]

A prospective, multicentre, randomised, double-blind active and placebo-controlled parallel-group outpatient study in men and women (age > 30 years) with central, peripheral, or combined central/ peripheral vestibular vertigo.

Inclusion and exclusion criteria

Inclusion criteria:

- Only patients who assessed ≥ 1 vertigo symptom as being of medium intensity (≥ 2) on a 5-point VAS and who had abnormal vestibulospinal movement patterns on craniocorpography (CCG) were eligible for participation.

Exclusion criteria:

- Patients with Meniere's disease, benign paroxysmal positional vertigo, bilateral caloric inexcitability (areflexia), or vertigo caused by nonvestibular disorders (for example, psychogenic vertigo), as well as patients who were pregnant or nursing were excluded from the study.
- Additional exclusion criteria consisted mainly of known contraindications to the active substances, cinnarizine and dimenhydrinate. These exclusions and contraindicated medications were as for the larger study above (Hahn). There was a 7-day washout period for patients taking those medications prior to commencement of the study.

Study treatments

For study treatments, patients received either the fixed-dose combination of cinnarizine 20 mg + dimenhydrinate 40 mg or cinnarizine 50 mg or dimenhydrinate 100 mg or placebo. Each patient took 1 tablet of study medication 3 times daily for 4 weeks. As in the study reported by Hahn, the tablets were indistinguishable.

[28] Pytel J, et al Efficacy and tolerability of a fixed low-dose combination of cinnarizine and dimenhydrinate in the treatment of vertigo: A 4-week, randomized, double-blind, active- and placebo-controlled, parallel-group, outpatient trial. *Clinical Therapeutics* 2007; 29: 84-98

Efficacy outcomes

The primary efficacy outcome measure was the change in MVS after 4 weeks of treatment. The MVS was calculated using the same methods as for the Hahn et al. study, above.

The secondary efficacy variables were also similar to those of the Hahn study.

Unlike the Hahn study, this study included ITT and PP analyses.

Analysis of the primary and secondary efficacy variables was based on change from Baseline at 1 and 4 weeks after the start of treatment, with a focus on the change in MVS as a measure of the intensity of vertigo symptoms. Confirmatory analysis was limited to the change in MVS after 4 weeks of therapy, assessed non-parametrically using the Mann-Whitney U test at a global significance level of 0 approximately equal to 0.05.

Baseline criteria

Two hundred and forty-six (246) patients were randomly assigned to treatment: FDC cinnarizine 20 mg+ dimenhydrinate 40 mg (n=61), cinnarizine 50 mg (n=61), dimenhydrinate 100 mg (n=64), and placebo (n=60). Seven patients discontinued the study before the week-1 examination, and 7 patients discontinued after that examination. Thus, the ITT population consisted of 239 patients. Of these 231 patients were included in the PP population.

The study population was approximately two thirds female and one third male, with mean (SD) age of 51.3 (10.6) years. The mean duration of vertigo was 2.6 years. Approximately half of the patients in each group reported vertigo of an episodic nature. The remaining patients reported having continuous vertigo. Between 4 and 8 patients in each group reported having both episodic and continuous vertigo symptoms.

Based on the medical findings and results of neuro-otologic testing at the beginning of the study, 38 of the randomised patients were diagnosed with peripheral vertigo (for example, caused by vestibular neuropathy, labyrinthitis, labyrinth contusion), 49 were diagnosed with central vertigo (for example, caused by vertebrobasilar ischemia, vascular encephalopathy, basilar impression, cerebral contusion), and the remaining 159 were diagnosed with combined central/peripheral vertigo.

The 3 types of vertigo were distributed similarly among the 4 treatment groups. Approximately 40% of patients in each group had received anti-vertigo drug treatment before the start of the study; the most frequently used single agent was betahistine (38 patients).

Across all treatment groups, nausea and headache were the most frequently reported and most severe concomitant symptoms of vertigo before the start of treatment (around 75% of patients; mean initial symptom scores, 1.6 to 2.0), followed by sweating and tinnitus (around 68% of patients; mean initial symptom scores, 1.4 to 1.8).

One hundred and fifty-six (166, (63.4%)) patients had concomitant diseases at study entry and 153 (62.2%) received concomitant medication. Cardiovascular diseases constituted around 40% of the concomitant conditions, followed by disorders of the locomotor apparatus (20%). Accordingly, around 40% of concomitant medications were cardiovascular drugs, around 13% were drugs acting on the central nervous system, and around 9% were analgesics and anti-rheumatics.

Results

The primary efficacy outcomes (as per the clinical evaluator):

- As shown below, there is superiority of the FDC over either of the monotherapy treatments and over placebo.

Table 16: Change in mean vertigo score (MVS) after 4 weeks treatment (ITT)

Variable	Cinnarizine 20 mg+ Dimenhydrinate 40 mg (n = 61)	Cinnarizine 50 mg (n = 61)	Dimenhydrinate 100 mg (n = 59)	Placebo (n = 58)
Vertigo score, mean (SD)				
Baseline	1.85 (0.54)	1.72 (0.52)†	1.69 (0.57)†	1.74 (0.63)
After 4 wk	0.45 (0.51)	0.81 (0.58)	0.87 (0.58)	1.01 (0.69)
Change from baseline	1.37 (0.66)	0.87 (0.53)*	0.83 (0.66)*	0.76 (0.48)*
Adjusted LS mean after 4 wk (95% CI)§	0.43 (0.30-0.56)	0.86 (0.73-1.00)‖	0.90 (0.76-1.03)‖	0.99 (0.86-1.13)‖
Difference in LS mean, combination vs comparator (95% CI)		0.43 (0.25-0.62)	0.47 (0.28-0.66)	0.56 (0.38-0.75)
Cohen's standardized difference (95% CI)		0.84 (0.47-1.21)	0.83 (0.45-1.20)	1.06 (0.67-1.45)
Mann-Whitney estimator (95% CI)		0.72 (0.63-0.80)	0.72 (0.62-0.80)	0.77 (0.68-0.84)

LS = least squares.
* Range from O = no symptoms to 4 = *very* severe symptoms. † Imbalance at 20% level between fixed-dose combination and both cinnarizine (P = 0.087) and dimenhydrinate (P = 0.122). * $P < 0.001$, fixed-dose combination versus comparator (Mann-Whitney *U* test). § Analysis of covariance. ‖ $P < 0.001$ for the probability that the LS mean for the fixed-dose combination was equal to the LS mean for the comparator.

The responder analysis showed that at the end of Week 4, there were 38 (62.3) patients given cinnarizine + dimenhydrinate with a MVS ≤ 0.5 compared with 18 (29.5%) given cinnarizine, 18 (30.5%) given dimenhydrinate and 14 (24.1%) given placebo. All comparisons of the FDC with other treatments were statistically significant for responder (all with p< 0.001).

Other efficacy outcomes (as per the clinical evaluator):

- None of the secondary efficacy outcome comparisons of the FDC with the other treatment groups were statistically significant.

Table 17: Change in selected secondary efficacy variables at end of Week 4

Variable Change from baseline at Wk4	Cinnarizine 20 mg + Dimenhydrinate 40 mg (n=61)	Cinnarizine 50 mg (n=61)	Dimenhydrinate 100 mg (n=59)	Placebo (n=58)
Nausea	1.61	1.02	1.09	1.01
Headache	0.90	0.86	0.58	0.78
Sweating	0.93	0.76	0.81	0.91
Tinnitus	0.51	0.51	0.41	0.68
Unterberger's stepping test: Lateral sway Angular deviation	3.47 39.84	2.25 25.33	2.34 26.68	1.21 31.93

The clinical evaluator commented:

- A major benefit from this study was the inclusion of a placebo control group. Given the variability of vertigo symptoms over time within an individual, the placebo inclusion allowed for an estimate of the absolute effect of the proposed FDC on vertigo, rather than only the comparative effect seen in the previous study by Hahn.
- The difference from baseline in mean MVS between the FDC and each of the actives and between the FDC and placebo was around the 0.5 difference that was previously considered as being clinically relevant.
- While no statistical comparison between placebo and cinnarizine was performed, this study at least showed a trend towards benefit in the management of vertigo for cinnarizine.
- The higher monotherapy dose of dimenhydrinate (100 mg three times daily) was inferior to the FDC suggesting that a lower dose of dimenhydrinate is required to achieve the same reduction in vertigo severity. Thus, fewer or less intense dose-related side effects may be anticipated with the combination product compared with dimenhydrinate.

The Delegate notes the higher dose (x 2.5) of the individual active compared to the corresponding dose of each active in the FDC, for the study. Yet the FDC is comparatively better.

Other efficacy studies for fixed combination cinnarizine/dimenhydrinate therapy in the treatment of vertigo as per the clinical evaluation report

Scholtz study (2004)[29]

A randomised, parallel group trial of 50 adults to compare the efficacy and tolerability of a fixed combination of cinnarizine 20 mg + dimenhydrinate 40 mg versus monotherapy with its respective components in the treatment of acute vertigo symptoms due to acute unilateral vestibular loss.

All patients received a 15% mannitol infusion as standard therapy during the first 6 days of treatment.

Efficacy was determined by the patients' assessments of vertigo symptoms after 1 and 4 weeks of treatment using a verbal rating scale (vertigo score) and by vestibulo-ocular and vestibulospinal tests.

The primary efficacy criterion was defined as the relief of vertigo symptoms after 1 week of treatment.

After 1 week of treatment, the fixed combination was significantly more effective than 20 mg cinnarizine ($p < 0.001$) and 40 mg dimenhydrinate ($p < 0.01$). After 4 weeks, the fixed combination was still significantly more effective than cinnarizine in reducing vertigo symptoms ($p < 0.01$) and significantly more effective than dimenhydrinate in improving the patients' balance while standing ($p < 0.05$).

The clinical evaluator commented that this study can only be supportive because it assessed vertigo due to a single cause and all patients received mannitol, in addition to the other study treatments. It nevertheless showed at least an additive effect of the combination over each of the components of the proposed FDC product.

[29] Scholtz AW, et al. Treatment of vertigo due to acute vestibular loss with a fixed combination of cinnarizine and dimenhydrinate: A double-blind, randomized, parallelgroup clinical study. *Clinical Therapeutics* 2004; 26: 866-877

Novotny study (1999)[30]

A comparative, randomised, double-blind, multicentre, parallel group study. Patients with vertigo and tinnitus of peripheral or central origin, excluding Meniere's disease and BPPV were randomised to receive either one of the following drugs, 3 times daily for 4 weeks:

- Cinnarizine 20 mg/ dimenhydrinate 40 mg (n = 40)
- Dimenhydrinate 40 mg (n = 41)
- Cinnarizine 20 mg (n = 41)

Efficacy was evaluated by assessment of:

- vertigo symptoms (dysstasia, unsteadiness while walking, staggering, rotary sensations, tendency to fall, lift sensations and scotodinia)
- concomitant vegetative symptoms (nausea, moving, sweating, tachycardia, tinnitus and impaired hearing)
- CCG (craniocorpography)
- nystagmus tests
- frenzel glasses
- electronystagmography
- a caloric test
- threshold audiometry
- factors that give rise to vertigo, including change of position, bowing, rising from bed, and driving by car or other motor vehicle

The primary efficacy parameter was not identified and there were insufficient details on the study protocol to consider this study further. However, it was reported that vertigo symptoms were reduced to a greater extent with the combination therapy than with either of the actives, given alone.

The clinical evaluator commented on the other efficacy studies that the supportive efficacy studies in all cases showed at least a trend towards greater efficacy with a FDC of cinnarizine/ dimenhydrinate given at the proposed dose than with either active, given as monotherapy at the doses used in those studies.

Analyses performed across studies: pooled and meta-analyses

Schremmer (1999)[31]

This paper presented an analysis of a series of controlled clinical studies to evaluate the efficacy and tolerability of the FDC product (Arlevert cinnarizine 20 mg/ dimenhydrinate 40 mg) in the treatment of central, peripheral or combined central/peripheral vestibular vertigo.

Five randomised, controlled, double-blind studies were included in the analysis with a total of 635 patients.

Patients were randomised to receive either one of the following 7 treatments at three times daily for 4 weeks (cinnarizine 20 mg/ dimenhydrinate 40 mg; cinnarizine 20 mg;

[30] Novotny M, et al. The efficacy of Arlevert for vertigo and tinnitus. International *Tinnitus Journal* 1999; 5; 60-62.
[31] Schremmer D, et al. Efficacy and tolerability of a fixed combination of cinnarizine and dimenhydrinate in treatment of vertigo. Analysis of data from five randomized, double-blind clinical studies. *Clinical drug Investigation* 1999; 18: 355-368.

cinnarizine 50 mg; dimenhydrinate 40 mg, dimenhydrinate 100 mg, betahistine 12 mg or placebo).

The studies used the same main methods of examination (vertigo score, craniocorpography, electronystagmography) and the same primary criterion of efficacy.

Study subjects were adult patients with vertigo. Symptom intensity was evaluating using a rating scale from 0 (no symptoms) to 4 (very strong symptoms). Symptoms assessed in each of the 5 studies and considered in the combined analysis were:

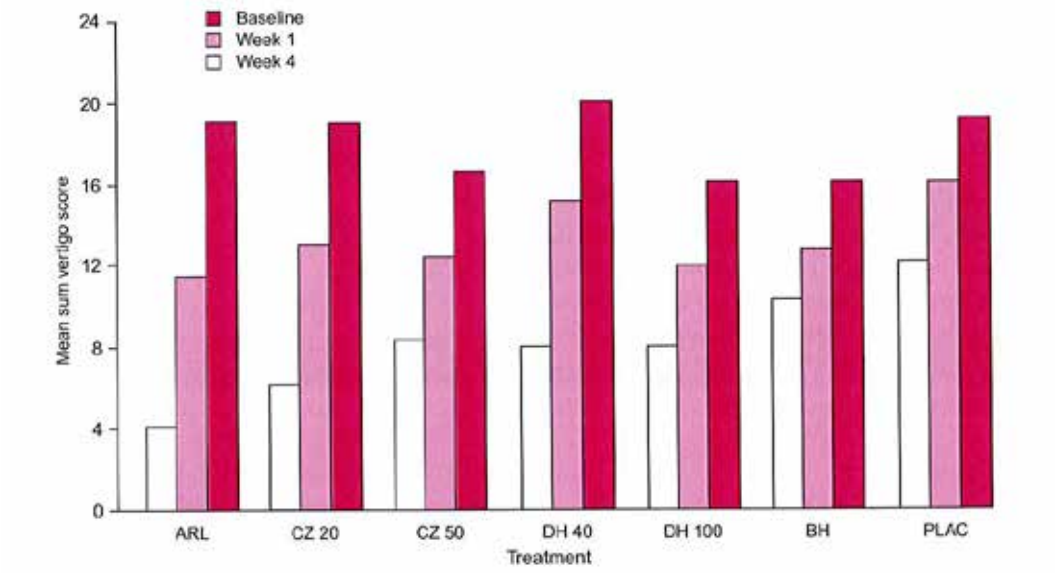
- vertigo symptoms (dysstasia and walking unsureness, staggering, rotary sensation, tendency to fall and lift sensation
- vertigo following trigger factors (change of position, bowing, getting up, head movements and eye movements)
- vegetative symptoms (nausea, vomiting, sweating and tachycardia
- further concomitant symptoms (tinnitus, impaired hearing and pressure sensation in the ear).

Assessment of efficacy was performed using the following ratings: 1= very much improved, 2 = much improved, 3 = slightly improved and 4 = not improved.

Results

Efficacy results are summarised in the figure below.

Figure 5: Intensity of vertigo symptoms in the course of treatment



The clinical evaluator commented:

- This combined analysis is supportive only due to the lack of inclusion of subsequent studies and the lack of identification of the individual studies.
- The studies, while not being individually identified are likely to have included some of the previously evaluated studies.
- The primary efficacy endpoint was not specifically stated in the combined analysis, but appears to be the Clinical Global Impression score. The latter was a secondary variable in some of the studies.
- The combined analysis has shown efficacy of the combined product, though the statistical management and selection of efficacy criteria is unlikely to be consistent with current practice.

Clinical evaluator's conclusions on clinical efficacy

- The submission contained one study in which, when the proposed FDC product was given at the proposed dose regimen to patients with various causes for vertigo, was superior to both placebo and constituent active monotherapies, given at higher doses than contained in the proposed FDC product. Additionally, 2 studies comparing the FDC with constituent active monotherapies, given at the same doses as contained in the FDC product, also showed superiority of the FDC with respect to reduction in vertigo symptoms.
- MVS was the primary efficacy measure in most studies. This is a composite endpoint, derived from a set of symptoms associated with vertigo. While it is subjective, so is the sensation of vertigo.
- Various objective measures were also assessed as secondary efficacy outcomes although, the statistical management of these secondary efficacy outcomes may not have met current requirements. This evaluator considers however, that given that the primary efficacy outcome consistently demonstrated superiority of the FDC over the individual active constituents, given as monotherapy, that the efficacy of the FDC has been demonstrated for its proposed indication.
- The evaluator notes that patients with Meniere's disease were generally excluded from the pivotal efficacy studies. This is acceptable given the long term nature of symptoms in Meniere's disease. The evaluator's do not consider that exclusion from these studies is sufficient for the FDC to be specifically not recommended for management of vertigo associated with Meniere's disease.
- This is a symptomatic treatment for vertigo, not a treatment of the underlying disease. Efficacy of continuous use for longer than 4 weeks has not been adequately assessed and given the known safety concerns of long term use of either component, it will be important to note that the FDC should not be taken continuously in the long term.
- Assessment of the cinnarizine efficacy as monotherapy in the treatment of vertigo was quite limited. This was due to the age and design of the clinical trial evidence available. Study results suggested that cinnarizine is inferior to betahistine in the treatment for vertigo associated with Meniere's disease. The use of a cinnarizine monotherapy arm in the study by Pytel et al.[28] showed that a 50 mg dose of cinnarizine had efficacy in the management of vertigo compared with placebo, though a statistical comparison of that effect was not performed. Efficacy of the proposed dose of cinnarizine used in conjunction with dimenhydrinate in the FDC, relies primarily on the increase in efficacy seen when the FDC was compared with dimenhydrinate alone (Hahn et al.).[27]

The Delegate commented that the FDC is not superior to betahistine.

Safety

Regarding the overall conclusions on clinical safety, the clinical evaluator stated that:

- The adverse events most frequently associated with cinnarizine/ dimenhydrinate combination are sedation and dry mouth. Although it wasn't clear from the clinical trial reporting data, the sedation reduces over time in many patients as is the case, with the other centrally acting antihistamines.
- Dimenhydrinate has been abused for its delirium-inducing effects in the past and this product, would also have the potential for abuse.
- The potential side effect that I consider as not being adequately highlighted in the submission or in the SPC for Arlevert is the propensity for cinnarizine to cause extrapyramidal symptoms, particularly parkinsonian symptoms, which may be permanent. They are more likely to occur in older adults, with higher doses and with

long term exposure. These effects are most likely due to the demonstrated dopamine D_2 receptor blockade by cinnarizine. Extrapyramidal symptoms can occur within weeks of commencement of treatment or after many years of treatment. While many cases resolve on ceasing treatment, some cases have resulted in permanent parkinsonian movement disorders or other extrapyramidal symptoms such as other dystonias and akathisia.

- If this product is approved for registration, the risk of developing extrapyramidal signs and symptoms should be adequately highlighted in the PI. Prescribers and the public should be advised that cinnarizine/ dimenhydrinate should be taken at the lowest dose and for the shortest time period, consistent with adequate symptom control. Treatment should be ceased if any extrapyramidal signs or symptoms occur. Ideally, this treatment would be prescribed only after the failure of currently available treatments for vertigo such as betahistine.

Clinical evaluator's recommendation

At the first round of evaluation, the clinical evaluator recommended Cizinate/ Cizere/ Cizigo (cinnarizine 20 mg/ dimenhydrinate 20 mg) be approved; however, they recommended modification of the proposed indication as follows:

> *Short-term treatment, of vertigo symptoms of various origins, in adults who have not responded to alternative treatments.*

Approval should also be subject to satisfactory negotiation of the PI and CMI. Additionally, the cinnarizine component requires entry onto the SUSMP prior to marketing.

At the second round of evaluation, the proposed indication had now been amended as requested and cinnarizine is now on the SUSMP. The clinical evaluator recommended that Cizinate/Cizere/Citigo containing cinnarizine 20 mg/ dimenhydrinate 40 mg be approved for registration.

Risk management plan

The Delegate had no additional comments. Please see Section VI: *Pharmacovigilance Findings* above.

Risk-benefit analysis

Delegate's considerations

Delegate's discussion

Vertigo is often a result of pathology in one of the inner ear balance organs. The latter may result from hypofunction as in vestibular neuritis, hyperfunction as in benign paroxysmal positional vertigo or due to central neurological disorders affecting vestibular pathways in the brain stem, cerebellum and cortex.

Vertigo is commonly associated with significant morbidity including falls, which may lead to immobilisation and significant health costs.

The sponsor has demonstrated that the proposed product under this application is bioequivalent to the product referenced in the literature based submission (Arlevert cinnarizine/dimenhydrinate 20/40mg tablets, Germany, with efficacy and safety data).

That bioequivalence study outcome has been referred to the Delegate, in determining its suitability to extend the efficacy and safety of the overseas reference product Arlevert

(referenced in this literature-based submission) to the proposed product under this application. This Delegate believes that the bioequivalent study outcome is sufficient for extrapolating the efficacy and safety of the overseas reference product, Arlevert, to that the proposed product in this application.

There is sufficient clinical data set suggesting that the FDC product is better than each constituent monotherapy active, in relieving the symptoms of Vertigo. The FDC is not superior to betahistine.

The use of the FDC has a potential risk for the development of extrapyramidal symptoms, particularly parkinsonian symptoms. The latter may be more associated with older age, higher doses and long term exposure.

Proposed indication

Initially proposed by the sponsor:

> *Treatment of vertigo symptoms of various origins*

Later modified by the sponsor (as per the clinical evaluator's recommendation) to:

> *Short-term treatment of vertigo symptoms of various origins, in adults who have not responded to alternative treatments*

The Delegate agreed with the modifications given that the:

- study duration was between 4 weeks to 3 months;
- studied population was mostly adults;
- betahistine, currently registered for vertigo, appeared to yield better efficacy outcome compared to cinnarizine in head to head trial; and
- extra-pyramidal symptoms are associated with the proposed FDC of cinnarizine and dimenhydrinate.

Deficiencies of the data

Despite the evidence that the two actives together work synergistically towards better efficacy outcome compared to each active monotherapy, there is;

- no clinical study assessing whether or not the pharmacokinetics of either active component is affected by the presence of the other.

Conditions of registration, if contemplated

Compliance with the nonclinical, clinical and RMP evaluators' recommendations to the draft PI. The Delegate believes that the sponsor is in compliance with the bulk of the latter.

Proposed regulatory action

Approvability of the submission.

Conclusion

There is sufficient level of efficacy and safety data to consider the approvability of the cinnarizine/dimenhydrinate FDC product for the modified indication as stated above. The Delegate is of the opinion, that the bioequivalence study provided is sufficient to bridge the safety and efficacy of the overseas reference product, Arlevert, (in the literature based submission) to the proposed product under this application.

Proposed action

The Delegate was not in a position to say, at the time, that the application for Cizinate/Cizere/Cizigo should not be approved for registration.

Request for ACM advice

1. Adequacy of the provided bioequivalence study to bridge the issue of efficacy and safety of the proposed product under this application, with reference to that of the overseas reference product, Arlevert, used in the literature based submission.
2. Approvability of the submission as mentioned under 'Proposed regulatory action' below and provision of advice as appropriate, based on the available evidence

Response from sponsor

The sponsor appreciated the opportunity to comment on some outstanding issues which are the subject of the Delegate's request for advice, noting that the Delegate's proposed regulatory action is 'Approvability of the submission'.

The sponsor endorsed the Delegate's proposed regulatory action. The sponsor believes that this medicine has demonstrated a favourable benefit risk profile in the indication proposed, and consequently this medicine will provide prescribers and patients with an effective treatment option to assist with the management of this debilitating condition.

Response to Delegate's advice sought

1. Adequacy of the provided bioequivalence study to bridge the issue of efficacy and safety of the proposed product under this application, with reference to that of the overseas reference product, Arlevert, used in the literature based submission

Sponsor's response

The sponsor draws attention of the Advisory Committee on Medicines (ACM) to the following comments provided in the Delegate's summary and request for advice dated 25 June 2018, relating to this study.

> 'The sponsor has demonstrated that the proposed product under this application is bioequivalent to the product referenced in the literature based submission (Arlevert cinnarizine/dimenhydrinate 20/40mg tablets, Germany, with efficacy and safety data). That bioequivalent study outcome has been referred to the clinical Delegate, in determining its suitability to extend the efficacy and safety of the overseas reference product Arlevert (referenced in the literature based submission) to the proposed product under this application. The Delegate believe that the bioequivalent study outcome is sufficient for extrapolating the efficacy and safety of the overseas reference product, Arlevert, to that the proposed product in this application.'

The sponsor therefore considers that this issue should not be an impediment to the approval of the medicine.

Response to Delegate's overview

In the summary of issues of the request the Delegate noted that:

Despite the evidence that the two actives together work synergistically towards better efficacy outcome compared to each active monotherapy, there is no clinical study assessing whether or not the pharmacokinetics of either active component is affected by the presence of the other.

Sponsor's response

We draw attention of the Committee to the following comments provided in Delegate's summary and request for advice dated 25 June 2018, relating to the first round questions and the sponsor's reply.

> *Question 1*

> *Is the sponsor able to provide an assurance that no clinical PK study is needed to verify that the PK of cinnarizine and dimenhydrinate in the product proposed for registration is the same as the PK of cinnarizine and dimenhydrinate in alternative oral formulations?*

The sponsor responded in 5 parts. The most reassuring part of the response was to identify summary results of a study comparing the PK of cinnarizine and dimenhydrinate alone and in combination. This study summary was included in the EPAR published in 2007 after a mutual recognition procedure, Arlevert 20 mg/40 mg tablets having been authorised in the UK in 2005.

The clinical evaluator's comment was as follows:

> 'These responses are satisfactory. The results in the EPAR are particularly reassuring, though it appears this study was somewhat underpowered to determine bioequivalence of the active components given alone and in the proposed FDC.'

It should be noted that part of the sponsor's response also summarised the efficacy and safety outcomes of a well-designed multicentre, double blind, randomised, four arm, parallel-group trial which compared the tolerability and efficacy of a fixed dose combination (FDC) medicine containing 20 mg of cinnarizine and 40 mg of dimenhydrinate to monotherapy with 50 mg cinnarizine or 100 mg dimenhydrinate, or placebo, in adult patients with vertigo of central, peripheral or mixed origin.

Observations included:

- The decrease in MVS at Week 4 was significantly greater in the FDC treatment group (1.37 ± 0.66) compared to 50mg cinnarizine (0.87 ± 0.53; $p < 0.001$) or 100mg dimenhydrinate alone (0.83 ± 0.66; $p < 0.001$).
- The percentage of participants rating overall tolerability as good or very good at Week 4 were 96.6% in FDC, 93.1% in cinnarizine group, 72.4% in dimenhydrinate group and 87.7% in placebo.
- The FDC was more efficacious and better tolerated than both cinnarizine or dimenhydrinate even when the single doses were administered at 2.5 times the FDC dose, supports the conclusion than a clinically relevant detrimental interaction between cinnarizine and dimenhydrinate is unlikely to occur in practice.
- The sponsor therefore considers that this issue should not be an impediment to the approval of the medicine.

Comments on indication

In the Delegate's Overview/request for ACM advice, the Delegate notes that:

- There are no further comments on the PI.
- No further amendments are recommended (to the CMI).
- There are no further clinical evaluator comments (on the RMP).

Sponsor's response

The sponsor concludes that there are no outstanding issues preventing a favourable recommendation from the ACM supporting the registration of the FDC medicine. Therefore, there are no further changes proposed to the PI, CMI or RMP.

We note however that the indication proposed in the request is inconsistent with our understanding of the agreed indication.

In the Delegate's request for advice, the Delegate states the proposed indication as:

> *Short-term treatment of vertigo symptoms of various origins, in adults who have not responded to alternative treatments.*

We understand that the indication remains:

> *Treatment of vertigo in adults with symptoms of various origins*

In response to comments from the clinical evaluator in the first round evaluation report, the sponsor agreed to adopt the recommendation that the term 'adults' be added to the original indication, but proposed that the terms 'short term' and 'not responded to alternative treatments' not be added to the indication. The rationale for this position was based on the following information, provided in the application, and summarised in our reply to the first round questions.

Short term: As proposed by the evaluator, we have included the following statement in the *Dosage and Administration* section of the PI:

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

We consider the inclusion of the term 'short term' in the indication is therefore no longer necessary.

Not responded to alternative treatments:

We submitted the following summary information in reply to the first round questions in support of our proposal not to include the above statement in the indication for the FDC.

> *Hahn (2011);[27] and Pytel (2007);[28] the two pivotal safety and efficacy studies submitted in the LBS application, included a significant proportion of subjects treated who were treatment niave. In Hahn (2011), 59% of subjects randomised to the FDC were treatment niave, whilst in Pytel (2007_ the proportion was 41%.*
>
> *The supporting study by Schremmer (1999);[31] provided the results of five separate randomised controlled trials comparing the safety and efficacy of FDC to placebo, betahistine and monocomponent cinnarizine or dimenhydrinate. Overall, 230 of the 601 (38%) subjects evaluated in this trial were treatment naive. Of the 196 subjects randomised to FDC, 79 (40.3%) received no prior treatments.*
>
> *Across all nine studies submitted in the application, around 300 had not received prior treatment for their vertigo.*

In the second round comments on the draft PI, the clinical evaluator noted that 'Clinical changes requested in the initial evaluation have been implemented where they didn't conflict with those of the nonclinical evaluator. Additionally, the format of the PI has been amended to comply with the revised recommendations. There are no further comments on the PI'. Therefore, our understanding is that the following indication has been accepted by the clinical evaluator:

> *Treatment of vertigo in adults with symptoms of various origins*

When prescribed and taken according to the agreed PI and CMI cinnarizine 20 mg/ dimenhydrinate 40 mg FDC tablets provide an acceptable benefit risk profile for the treatment of vertigo in adults with symptoms of various origins.

Conclusion

We support the Delegate's proposed regulatory action 'Approvability of the submission'.

Advisory Committee Considerations[32]

The Advisory Committee on Medicines (ACM) taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Cizinate / Ciziere / Cizigo tablet containing cinnarizine 20 mg /dimenhydrinate 40 mg to have an overall positive benefit-risk profile for the amended indication:

> *Short-term, symptomatic treatment of vertigo of various causes, in adults who have not responded to alternative treatments.*

As compared to the sponsor's proposed indication:

> *Treatment of vertigo in adults with symptoms of various origins.*

The ACM agreed with the modifications proposed by the clinical evaluator and agreed to by the Delegate, namely: 'short term' and 'who have not responded to alternative treatments'.

In providing this advice the ACM noted the following:

- Dimenhydrinate 50mg (Dramamine) was previously registered in Australia but withdrawn in 2017.
- Dimenhydrinate is currently registered in Australia as fixed dose combination product (FDC) Travacalm Original (available over the counter).
- Cinnarizine is available in Australia via the Special Access Scheme.
- Cinnarizine is registered in UK (Stugeron) for 'Control of vestibular disorders such as vertigo, tinnitus and vomiting such as is seen in Meniere's disease. Effective in the control of motion sickness'.
- A similar formulation (Arlevert) is registered in EU (2005) for the same indication requested and available on prescription in Germany since 1982.
- The data submitted by the sponsor demonstrates statistically significant and clinically meaningful efficacy.
- Fixed dose Cinnarizine 20 mg /Dimenhydrinate 40 mg is overall well tolerated with a well-known safety profile that is manageable within an appropriate risk management framework, which is accommodated in the proposed Australia-specific RMP.
- The risk of extrapyramidal symptoms (EPS) requires additional management because of its prevalence, predictability and impact, in the settings of longer term use, particularly in higher doses, in elderly patients (for whom vertigo is a more prevalent problem) and in some drug-drug and drug-disease interactions.

Specific advice

The ACM advised the following in response to the delegate's specific questions on the submission:

[32] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

1. *Adequacy of the provided bioequivalence study to bridge the issue of efficacy and safety of the proposed product under this application, with reference to that of the overseas reference product, Arlevert, used in the literature based submission*.

The active ingredients in the proposed product are identical and the excipients are, for practical purposes, the same as those in the long-approved Arlevert. The bioequivalence data submitted are acceptable to the chemistry and quality evaluator and the clinical evaluator. As such, accepting this as adequate evidence of bioequivalence is recommended.

2. *Approvability of the submission as mentioned under 'Proposed regulatory action' below and provision of advice as appropriate, based on the available evidence.*

The ACM recommended the specific amendments described above to the wording of the indications.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Cizigo cinnarizine 20 mg / dimenhydrinate 40 mg uncoated tablets blister pack; Cizinate cinnarizine 20 mg / dimenhydrinate 40 mg uncoated tablets blister pack; and Cizere cinnarizine 20 mg / dimenhydrinate 40 mg uncoated tablets blister pack, indicated for:

> *Short-term, symptomatic treatment of vertigo of various causes, in adults who have not responded to alternative treatments.*

Specific conditions of registration applying to these goods

The Cizinate EU-RMP version 1.1 dated 10 April 2017 (data lock point 30 November 2015) with Australian Specific Annex version 02 dated March 2018, included with submission PM-2017-00806-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Cizigo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>. The PI for other tradenames is identical except for the product name.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au