All About Arlevert®
(cinnarizine 20mg/dimenhydrinate 40mg)

To view our animated video about Arlevert® please visit www.dizzycentre.com
Arlevert® is more effective and provides more rapid relief of vertigo symptoms than betahistine (12mg) and cinnarizine (50mg)\textsuperscript{1-9}

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INTRODUCTION

Vertigo is a common complaint reported by patients of all ages, and particularly in the elderly. In this particular age group it is associated with balance disorders, functional decline, social isolation, reduction in quality of life and falls.

Vertigo is associated with a wide spectrum of diseases comprising peripheral lesions, such as benign paroxysmal positional vertigo (BPPV) and acute vestibular neuritis and central lesions such as cerebellar infarction or cerebral blood flow disorders. Among the long list of potential diagnoses there are some uncommon but serious central causes such as a brainstem demyelination and stroke.

Establishing an accurate diagnosis is often a challenge in primary care due to the complexity and diversity of the underlying pathogenic mechanisms. Although positional testing techniques, such as the head impulse test (or head thrust test) and Hallpike test, are diagnostic of vestibular neuritis and BPPV, a survey of GPs with a special interest in vertigo suggests that fewer than 20% employ these diagnostic tests.

The gold standard treatment approach for BPPV is the use of vestibular rehabilitation techniques, such as the Epley and Semont manoeuvres, although many patients including the elderly and those with severe vertigo may not respond well to these techniques or are not compliant with therapy and will still require medication.

Many elderly patients using vestibular rehabilitation techniques are not compliant with therapy so still require medication.

Vertigo is often dismissed as a casual symptom, however it can pose considerable limitations on a patient’s ability to cope with daily activities, become chronic if left untreated. The availability of an effective vertigo treatment is therefore of particular importance.

Drugs of various classes have been used to treat vertigo, but there have been no new pharmaceutical treatments in the UK for vertigo since the mid-1970s.

This review focuses on Arlevert® (cinnarizine 20mg and dimenhydrinate 40mg) and its efficacy in treating vertigo of mixed origin.

DRUG BACKGROUND

Arlevert® is a combination of the specific calcium antagonist cinnarizine (20 mg) acting on the vestibular hair cells in the inner ear and the antihistamine dimenhydrinate (40 mg), and is taken three times daily (equivalent to 60 mg cinnarizine and 120 mg dimenhydrinate per day). Both components are known to be effective in the treatment of vertigo and this combination has been used widely in Germany for more than 30 years for the treatment of vertigo of various origins.

Arlevert® has been widely prescribed in Germany for over 30 years.

Cinnarizine is widely used as monotherapy in the treatment of vertigo in the UK and exerts its antivertigo effects primarily on the peripheral vestibular system. Dimenhydrinate acts mainly on the central vestibular system by inhibiting histamine- and cholinergic-receptor functions; in addition dimenhydrinate exerts antivertiginous and anti-emetic effects by influencing the chemoreceptor trigger zone. It is not available in the UK in any other presentation although there is extensive experience with its use in other countries. The differing modes of action of these two compounds provide the rationale for this combination therapy in treating vertigo originating from both central and peripheral vestibular regions (Figure 1). Arlevert® is licensed in the UK for the treatment of vertigo symptoms of various origins in adults. It is contraindicated in patients with severe renal or hepatic impairment and should not be taken in pregnancy.
KEY CLINICAL TRIALS
A number of randomised controlled studies with Arlevert® have demonstrated a favourable benefit-risk ratio when compared with other current therapies and placebo.1-8

Efficacy
Arlevert® has been shown to be particularly effective in treating a wide range of types of vertigo including acute vestibular vertigo,5 otogenic vertigo,1 vertigo in consequence of vertebrobasilar insufficiency6 and vertigo in patients suffering from Ménière’s disease.7

A 4-week randomised controlled pivotal study in 50 patients with acute vestibular vertigo compared the clinical efficacy of Arlevert® with its component parts (cinnarizine and dimenhydrinate).5 After 1 week of therapy, the fixed combination was statistically significantly more effective in reducing the intensity of vertigo symptoms than cinnarizine (p<0.001) and dimenhydrinate (p<0.01) alone. These benefits were still present at 4 weeks.

Another randomised controlled study in 61 patients with otogenic (peripheral) vertigo demonstrated Arlevert® to be more efficient than betahistine (12 mg betahistine dimesylate) in reducing symptoms of vertigo (including unsteadiness, staggering, rotary sensation and tendency to fall) after both 1 week (p=0.002) and 4 weeks (p=0.001) of therapy.5 The study authors recommended the combination therapy as first line therapy for the treatment of otogenic vertigo.5

A large randomised controlled pivotal study in a broad population of 246 patients with central, peripheral or mixed central-peripheral vertigo compared the efficacy of Arlevert® with the individual components at higher doses (50mg cinnarizine and 100mg dimenhydrinate, respectively) and placebo treatment.5 The combination therapy was significantly more effective than the individual components and placebo in reducing vertigo symptoms after 4 weeks (p<0.001) and was particularly more effective in reducing symptoms of nausea when compared with the comparators.

Arlevert® has also been recommended as an effective option in treating patients with vertigo associated with cerebrovascular disease (vertebrobasilar insufficiency; VBI).6 A study in 37 patients with vertigo associated with VBI demonstrated significant benefit for Arlevert® therapy when compared with betahistine (12 mg betahistine dimesylate) or placebo.6 At week 1 Arlevert® reduced the vertigo symptoms significantly when compared to betahistine (p<0.05) and placebo (p<0.01). After 4 weeks of treatment Arlevert® reduced the vertigo symptoms scores 2.5-fold when compared to betahistine (p<0.01).

In a 12-week study in 82 patients with Ménière’s disease, Arlevert® demonstrated similar efficacy and safety as the standard therapy, betahistine, with an 80% reduction in vertigo symptoms, a 60% reduction in tinnitus and almost complete elimination of nausea, vomiting, sweating and tachycardia.7 The study authors recommended the use of Arlevert® for treatment of acute episodes and in long-term therapy of vertigo in patients with Ménière’s disease.

ARLEVERT® IS SIGNIFICANTLY MORE EFFECTIVE THAN BETAHISTINE IN REDUCING SYMPTOMS OF VERTIGO1,3,6,7

Before Treatment After 1 Week After 4 Weeks
Mean vertigo scores
Betahistine dimesylate (12mg tds) (n=29) Arlevert® (tds) (n=30)
2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2 0.0

Cirek 2005

ARLEVERT® IS SIGNIFICANTLY MORE EFFECTIVE IN REDUCING VERTIGO SYMPTOMS THAN CINNARIZINE2

Before Treatment After 4 Weeks
Mean vertigo scores
Cinnarizine (50mg tds) (n=61) Arlevert® (tds) (n=61)
2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2 0.0

Pytel 2007
To request copies of Arlevert® clinical papers discussed in the review please visit www.dizzycentre.com

Arlevert® is the only dual action treatment for vertigo symptoms of various origins - both central and/or peripheral.¹⁹

The Arlevert® dual action treatment results in the reduction of vertigo symptoms and concomitant nausea and vomiting.¹⁻⁷

Arlevert® does not appear to interfere with the normal compensation recovery process.¹
Do you see patients with reoccurring vertigo?

Don't send them home dizzy

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RECOVERY FROM VERTIGO SYMPTOMS
In 2012, Scholtz et al published a study comparing the therapeutic efficacy of Arlevert® to betahistine (12 mg betahistine dimesylate) in 62 patients with vestibular neuritis.1 The study endpoints evaluated improvements in vertigo symptoms, concomitant vegetative symptoms and activities of daily living (ADL) at weeks 1 & 4 of therapy.

Arlevert® demonstrated a significant improvement (p<0.001) in vertigo symptoms, concomitant vegetative symptoms and ADL over betahistine at week 1. However, more importantly at week 4 nearly all patients taking Arlevert® (87%) showed complete recovery from their vertigo symptoms versus 50% of those taking betahistine.1

87% of vertigo patients treated with Arlevert® are able to return to daily living activities within four weeks.5

In 2016, Scholtz et al published research comparing Arlevert® to betahistine (16 mg betahistine dihydrochloride) in patients with peripheral-vestibular vertigo associated with Meniere’s syndrome. Arlevert® showed to be significantly superior in reducing the intensity of vertigo symptoms after both 1 week (p= 0.003) and 4 weeks (p= 0.035) of therapy.3

Safety
In all clinical trials to date, Arlevert® is described consistently as well tolerated in patients with vertigo.1,9 Since its introduction in Germany in 1982 and subsequent prescription of over 1.3 billion tablets (equivalent to 15.5 million 4-week treatments) only 5 serious drug reactions, that have not even been clearly assignable to Arlevert®, have been reported.20 Two studies have also confirmed that there is no significant impairment to performance when healthy volunteers are taking Arlevert®.21,22 The most frequently occurring adverse events are somnolence and dry mouth.19 These events are usually mild and disappear spontaneously within a few days, even if treatment is continued19 making Arlevert a beneficial treatment in comparison to prochlorperazine, a strong sedative which has also other and more severe adverse reactions.23

Arlevert® demonstrated a similar tolerability profile to its individual components cinnarizine and dimenhydrinate24,5,24 One study showed Arlevert® to be associated with fewer adverse events than its individual components (9.8% vs 19.7% and 15.6%, respectively).2 Points

The tolerability of Arlevert® was rated either as ‘good’ or ‘very good’ by almost all patients taking Arlevert® in the 2004 and 2016 Scholtz et al. studies.5,8

Arlevert® tolerability was similar or superior to betahistine in 4 studies3,6,7,8 with patients and investigators rating Arlevert® tolerability as ‘good’ or ‘very good’ after both 1 and 4 weeks treatment.3,7

In one of these trials, the rate of adverse events associated with Arlevert® was much lower than that with betahistine (18.2 % vs 38.5%, respectively).6

Arlevert® does not appear to interfere with the normal compensation recovery process.1

The use of antiemetics and in particular prochlorperazine in the acute stage of peripheral vestibular disease if often limited to the first few days assuming that a more prolonged intake may delay compensation due to sedation.1 In both the Scholtz 2004 and 2012 study patients taking Arlevert® at the recommended clinical dosage of three times daily does not exert sedative effects.1,5

ROLE IN CLINICAL PRACTICE
It is clear that the majority of patients receive treatment for vertigo symptoms in primary care.17 However, accurate diagnosis remains a major challenge. Besides various vestibular rehabilitation techniques, pharmacotherapy plays an essential role in the treatment of vertigo. In a survey, over 75% of GPs with a special interest in vertigo felt that an effective combination therapy such as Arlevert® would be of significant benefit to patients with vertigo of mixed origins.17

A survey showed that GPs commonly treat patients with severe vertigo symptoms with a powerful sedative to reduce initial nausea and vomiting and then switch patients with vertigo to a milder sedative for the recovery phase.17

For GPs, Arlevert® provides a very effective and well-tolerated alternative treatment option for patients with severe vertigo symptoms.1,4,5,8

Arlevert® has proven efficacy and safety based on 30 years’ experience in Germany and numerous European countries and is available as a treatment option in the UK since 2006. This combination therapy is highly effective and well tolerated in treating both central and peripheral vertigo owing to its dual mechanism of action.19 The fixed combination of cinnarizine and dimenhydrinate is more effective than using higher doses of the individual components, with similar or better tolerability.12,4,24
KEY POINTS

- Arlevert® is the only dual action treatment for vertigo symptoms of various origins – both central and/or peripheral.19
- When compared to dimenhydrinate (100 mg tds, or 40 mg tds) or cinnarizine (50 mg tds or 20 mg tds), Arlevert® provides more rapid and effective relief from vertigo symptoms in patients suffering from central, peripheral or mixed vertigo.23,24
- Arlevert® is significantly more effective than betahistine (12 mg tds) in reducing vertigo symptoms within the first week of treatment.1,3
- After 4 weeks of continuous treatment, 87% of patients taking Arlevert® make an almost complete recovery from their vertigo symptoms compared to betahistine (50%).1
- Arlevert® does not appear to interfere with the normal compensation recovery process.1

REFERENCES


UK PRESCRIBING INFORMATION

Arlevert® (cinnarizine 20mg / dimenhydrinate 40mg)

Prescribing Information (refer to Summary of Product Characteristics for full information). Presentation: Round, biconvex white tablets embossed with ‘A’ on one side, with a diameter of 8.1 mm, containing 20mg cinnarizine and 40mg dimenhydrinate. Indications: Treatment of vertigo symptoms of various origins. Arlevert is indicated in adults. Dosage and Administration: Adults: 1 tablet three times daily, to be taken unchewed with some liquid after meals. Children and adolescents under the age of 18 years: not recommended. Elderly: Dosage as for adults. The duration of treatment should generally not exceed four weeks, but can be longer as determined by the physician. Contraindications: Arlevert is contra-indicated in patients with hypersensitivity to the active substances, diphenhydramine or other antihistamines of similar structure or to any of the excipients. Arlevert should not be used in patients with angle-closure glaucoma, convulsions, suspicion of raised intracranial pressure, alcohol abuse or urine retention due to urethropaetic disorders. Arlevert should not be used by patients with severe hepatic or renal impairment. Arlevert is not recommended during pregnancy and should not be used during breast-feeding. Warnings and precautions: Arlevert does not reduce blood pressure significantly; however, it should be used with caution in hypotensive patients. Arlevert should be taken after meals to minimise any gastric irritation. Arlevert should be used with caution in patients with conditions that might be aggravated by anticholinergic therapy. Caution should be exercised when administering Arlevert to patients with Parkinson’s disease. Side effects: The most frequently occurring ADRs are somnolence (including drowsiness, tiredness, fatigue, daze) occurring in about 8% of patients and dry mouth occurring in about 5% of patients in clinical studies. These reactions are usually mild and disappear within a few days even if treatment is continued. Consult the SmPC in relation to other side effects. Drug Interactions: The anticholinergic and sedative effects of Arlevert may be potentiated by monoamine oxidase inhibitors. Procarbazine may enhance the effect of Arlevert. In common with other antihistamines, Arlevert may potentiate the sedative effects of CNS depressants including alcohol, barbiturates, narcotic analgesics and tranquillisers. Patients should be advised to avoid alcoholic drinks. Arlevert may also enhance the effects of antihypertensives, ephedrine and anticholinergics such as atropine and tricyclic antidepressants. Arlevert may mask otoxic symptoms associated with amino glycoside antibiotics and mask the response of the skin to allergic skin tests. The concomitant administration of medicines that prolong the QT interval of the ECG (such as Class IA and Class III anti-arrhythmics) should be avoided. Diphenhydramine inhibits CYP2D6 mediated metabolism and caution is advised if Arlevert is combined with substrates of this enzyme, especially those with narrow therapeutic range. Presentation and Basic NHS Cost: Arlevert (100 tablets, presented as 4 blister strips of 25 tablets) £24.00. Legal Category: POM. Marketing Authorisation Holder: Hennig Arzneimittel GmbH & Co. KG, Liebigstrasse 1-2 D-65439 Rößheim am Main/Germany. Marketing Authorisation Number: PL 11249/0001. Further information is available from: Hennig Arzneimittel GmbH & Co. KG, Liebigstrasse 1-2 D-65439 Rößheim am Main/Germany (0844 504 0866). Arlevert is a registered trademark of Hennig Arzneimittel, Germany. Date of Preparation: January 2016.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Cambridge Regulatory Services Ltd. on pv@cambreg.co.uk or +44(0) 1480 465755.

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