

**Public Assessment Report**  
**Mutual Recognition Procedure**

**Arlevert 20mg/40mg Tablets**

**UK/H/984/01/MR**  
**UK licence no: PL 11249/0001**

**HENNIG ARZNEIMITTEL GmbH & Co. KG**

## LAY SUMMARY

The MHRA granted HENNIG ARZNEIMITTEL GmbH & Co. KG a Marketing Authorisation (licence) for the medicinal product Arlevert 20mg/40mg Tablets on 20<sup>th</sup> May 2005. This is a prescription-only medicine (POM) indicated for the treatment of vertigo symptoms of various origins.

Arlevert 20mg/40mg Tablets contain two active substances; cinnarizine and dimenhydrinate. The two substances belong to different groups of medicines. Cinnarizine is a part of a group called calcium antagonists. Dimenhydrinate belongs to a group called antihistamines. Both substances work by reducing symptoms of vertigo (a feeling of dizziness or “spinning”) and nausea (feeling sick). When these two substances are used together they are more effective than when each one is used on their own.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Arlevert 20mg/40mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

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## Module 1

<b>Product Name</b>	Arlevert 20mg/40mg Tablets
<b>Type of Application</b>	New Combinations, Article 10b
<b>Active Substance(s)</b>	Cinnarizine Dimenhydrinate
<b>Form</b>	Tablets
<b>Strength</b>	Cinnarizine 20mg/Dimenhydrinate 40mg
<b>MA Holder</b>	HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstrasse 1-2, D-65439 Flörsheim am Main, Germany
<b>Reference Member State (RMS)</b>	UK
<b>CMS</b>	Austria, Belgium, Denmark, Ireland, Italy, Luxembourg, The Netherlands, Poland, Slovenia, Sweden
<b>Procedure Number</b>	UK/H/0984/001/MR
<b>Timetable</b>	Day 90 – 3 <sup>rd</sup> April 2007

## Module 2

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Arlevert 20 mg/40 mg tablets

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg cinnarizine and 40 mg dimenhydrinate.  
For full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Tablet, round, biconvex white tablets embossed with 'A' on one side.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

Treatment of vertigo symptoms of various origins.

##### 4.2 Posology and method of 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:* Arlevert is not recommended in children and adolescents under the age of 18 years because there are no data available on the use of Arlevert in this age group.

*Elderly:* Dosage as for adults.

##### *Renal impairment:*

Arlevert 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  $\leq 25$  mL/min (severe renal impairment).

##### *Hepatic impairment:*

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

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

##### 4.3 Contraindications

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

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

Arlevert is contra-indicated in patients with known 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 urethroprostatic disorders.

##### 4.4 Special warnings and precautions for use

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, e.g. raised intra-ocular pressure, pyloro-duodenal obstruction, prostatic hypertrophy, hypertension, hyperthyroidism or severe coronary heart disease.

Caution should be exercised when administering Arlevert to patients with Parkinson's disease.

#### 4.5 Interaction with other medicinal products and other forms of interaction

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 ototoxic symptoms associated with amino glycosidic antibiotics and mask the response of the skin to allergic skin tests.

The concomitant administration of medicines that prolong the QT interval of the ECG (such as Class Ia and Class III anti-arrhythmics) should be avoided.

The information about potential pharmacokinetic interactions with cinnarizine and diphenhydramine and other medicinal products is limited. Diphenhydramine inhibits CYP2D6 mediated metabolism and caution is advised if Arlevert is combined with substrates of this enzyme, especially those with narrow therapeutic range

#### 4.6 Pregnancy and lactation

Pregnancy:

The safety of Arlevert in human pregnancy has not been established. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development and postnatal development (see Section 5.3). The teratogenic risk of the single actives dimenhydrinate/diphenhydramine and cinnarizine is low. No teratogenic effects were observed in animal studies.

Dimenhydrinate may have an oxytocic effect and may shorten labour. Arlevert should not be used during pregnancy.

Lactation:

Dimenhydrinate and cinnarizine are excreted in human breast milk. Arlevert should not be taken by women who are breast feeding.

#### 4.7 Effects on ability to drive and use machines

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

#### 4.8 Undesirable effects

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

Frequency of ADR	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000	Very rare <1/10,000
<b>Body system:</b>				
Blood and lymphatic system disorders				Leucopenia Thrombopenia Aplastic anaemia
Immune system disorders			Hypersensitivity reactions (eg cutaneous)	

Frequency of ADR	Common >1/100, <1/10	Uncommon >1/1,000, <1/100	Rare >1/10,000, <1/1,000	Very rare <1/10,000
			reactions)	
Nervous system disorders	Somnolence Headache	Paraesthesia Amnesia Tinnitus Tremor Nervousness Convulsions		
Eye disorders			Visual disorders	
Gastrointestinal disorders	Dry mouth Abdominal pain	Dyspepsia Nausea Diarrhoea		
Skin and subcutaneous tissue disorders		Perspiration Rash	Photosensitivity	
Renal and urinary disorders			Urinary hesitancy	

In addition the following adverse reactions are associated with dimenhydrinate and cinnarizine:

*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.

#### 4.9 Overdose

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

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

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

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cinnarizine combination; ATC code: N07CA52.

Dimenhydrinate, the chlorotheophylline salt of diphenhydramine, acts as antihistamine with anticholinergic (antimuscarinic) properties, exerting parasympatholytic and centrally-depressant effects. The substance exhibits anti-emetic and antivertiginous effects through influencing the chemoreceptor trigger zone in the region of the 4<sup>th</sup> ventricle. Dimenhydrinate thus acts predominantly on the central vestibular system.

Due to its calcium antagonistic properties, cinnarizine acts mainly as a vestibular sedative through inhibition of the calcium influx into the vestibular sensory cells. Cinnarizine thus acts predominantly on the peripheral vestibular system.

Both cinnarizine and dimenhydrinate are known to be effective in the treatment of vertigo. The combination product is more effective than the individual compounds in the population studied.

The product has not been evaluated in motion sickness.

## 5.2 Pharmacokinetic properties

### *Absorption and distribution:*

Dimenhydrinate rapidly releases its diphenhydramine moiety after oral administration.

Diphenhydramine and cinnarizine are rapidly absorbed from the gastro-intestinal tract. Maximum plasma concentrations ( $C_{max}$ ) of cinnarizine and diphenhydramine are reached in humans within 2 - 4 hours. The plasma elimination half-lives of both substances range from 4 to 5 hours, when given either alone or as the combination product.

### *Metabolism:*

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

### *Elimination:*

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

## 5.3 Preclinical safety data

Preclinical data revealed no specific hazard for humans based on repeated dose toxicity studies with the combination of cinnarizine and dimenhydrinate, fertility studies with cinnarizine or dimenhydrinate, and embryo/foetal development studies with dimenhydrinate. Doses were well in excess of the maximum human dose. Studies in dogs, rabbits and rats gave no evidence for teratogenic effects of cinnarizine. In one study in rats, cinnarizine decreased litter size, increased the number of resorbed fetuses and decreased the birth weight of pups.

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

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

cellulose, microcrystalline,  
maize starch,  
talc,  
hypromellose,  
silica, colloidal anhydrous,  
magnesium stearate,  
croscarmellose sodium

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Carton containing 20, 50, or 100 tablets.

Tablets are packed in PVC/PVDC/Aluminium blisters containing 20 or 25 tablets, as appropriate.

- 6.6 Special precautions for disposal**  
No special requirements
- 7 MARKETING AUTHORISATION HOLDER**  
HENNIG ARZNEIMITTEL GmbH & Co. KG  
Liebigstrasse 1-2  
D-65439 Flörsheim am Main/Germany
- 8 MARKETING AUTHORISATION NUMBER(S)**  
PL 11249/0001
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
May 2005
- 10 DATE OF REVISION OF THE TEXT**  
31/10/2007
- 11 DOSIMETRY (IF APPLICABLE)**
- 12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

# Module 3

## Patient Information Leaflet

### PACKAGE LEAFLET: INFORMATION FOR THE USER

Arlevert® 20 mg/40 mg tablets  
cinnarizine/dimenhydrinate

**Read all of this leaflet carefully before you start using this medicine.**

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

**In this leaflet:**

1. What Arlevert is and what it is used for
2. Before you use Arlevert
3. How to use Arlevert
4. Possible side effects
5. How to store Arlevert
6. Further information

**1. What Arlevert is and what it is used for**

Arlevert contains two active ingredients. One is cinnarizine and one is dimenhydrinate. The two substances belong to different groups of medicines. Cinnarizine is part of a group called calcium antagonists. Dimenhydrinate belongs to a group called antihistamines.

Both substances work by reducing symptoms of vertigo (a feeling of dizziness or 'spinning') and nausea (feeling sick). When these two substances are used together they are more effective than when each one is used on its own.

Arlevert is used for the treatment of various kinds of vertigo. Vertigo can have a number of different causes. Using Arlevert can help you carry on with daily activities that are difficult when you have vertigo.

**2. Before you use Arlevert**

**Do not use Arlevert if you:**

- are under the age of 18 years
- are allergic (hypersensitive) to cinnarizine, dimenhydrinate or diphenhydramine or any of the other ingredients. (Go to section 6. Further information, for a list of the other ingredients.)
- are allergic to any other antihistamines (such as astemizole, chlorpheniramine and terfenadine, used as allergy medicines). You should not take this medicine unless you have been told to by your doctor.
- suffer from angle-closure glaucoma (a specific type of eye disease)
- have epilepsy
- have increased pressure in the brain (e.g. due to a tumour)
- suffer from alcohol abuse
- have prostate problems which cause difficulty in urinating
- suffer from liver or kidney failure.

**Take special care with Arlevert**

**Tell your doctor if you suffer from:**

- low or high blood pressure
- raised pressure in the eye
- obstruction in the bowels
- enlarged prostate
- overactive thyroid
- severe heart disease
- Parkinson's disease.

The use of Arlevert may make these conditions worse. Arlevert may still be suitable for you but your doctor may need to take these facts into account.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription.

Arlevert may interact with other medicines that you are taking.

Arlevert can make you tired or sleepy when taken with the medicines listed below:

- barbiturates (medicines that are often taken to calm you down)
- narcotic analgesics (strong painkillers such as morphine)
- tranquillisers (a type of medicine used to treat depression and anxiety)
- monoamine oxidase inhibitors (used to treat depression and anxiety).

Arlevert may increase the effects of the following medicines:

- tricyclic antidepressants (used to treat depression and anxiety)
- atropine (a medicine that relaxes muscles and is often used to examine your eye)
- ephedrine (can be used to treat cough or blocked nose)
- procarbazine (a medicine used to treat some kinds of cancer)
- medicines taken to lower blood pressure.

Amino glycosides (a type of antibiotic) can damage the inner ear. If you take Arlevert you may not notice that this damage is happening.

You should not use Arlevert with drugs that are used to correct problems with your heart beat (anti-arrhythmics).

Arlevert may also change the way your skin reacts to allergy tests.

**Taking Arlevert with food and drink**

Take Arlevert after a meal. Arlevert can cause indigestion that can be reduced by taking the tablets after meals. Do not drink alcohol while using Arlevert because it may make you tired or sleepy.

**Pregnancy and breast feeding**

Do not take Arlevert if you are pregnant or are breast-feeding.

**Driving and using machines**

Arlevert may make you feel sleepy. If this occurs you should not drive or operate machinery.

**3. How to use Arlevert**

Always take Arlevert exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is: one tablet three times daily, with some liquid after meals. Swallow the tablet whole, do not chew.

Usually you will take Arlevert for up to 4 weeks. Your doctor will tell you if you need to take Arlevert for any longer.

**If you take more Arlevert than you should:**

If you accidentally take too many tablets or if a child takes some you should seek medical advice urgently.

If you take too much Arlevert you may become very tired, dizzy and shaky. Your pupils might dilate and you may not be able to urinate. Your mouth may feel dry, your face flush, you may have a faster heart rate, fever, sweat and have a headache.

If you have taken a massive amount of Arlevert you could have fits, hallucinations, high blood pressure, feel shaky, get excited, and find it difficult to breathe. Coma could occur.

**If you forget to take a dose of Arlevert**

If you forget to take a tablet of Arlevert just miss out that tablet. Take the next tablet of Arlevert the next time when you would usually take it. Do not take twice as much to catch up on the tablet you missed.

**If you stop taking Arlevert**

Do not stop taking Arlevert before your doctor tells you to. You are likely to have the symptoms of vertigo again (dizziness and 'spinning') if you stop treatment too soon.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

**4. Possible side effects**

Like all medicines, Arlevert can cause side effects, although not everybody gets them.

Side effects which may commonly occur (less than 1 in 10 patients treated): drowsiness, dry mouth, headache, and stomach pain. These are usually mild and disappear within a few days even if you keep taking Arlevert.

Uncommon side effects (occurring in less than 1 in 100 patients treated): sweating, reddening of the skin, indigestion, nausea (feeling sick), diarrhoea, nervousness, cramps, forgetfulness, tinnitus (ringing in the ear), paraesthesia (tingling of the hands or feet), tremor (shaking).

Rare side effects (occurring in less than 1 in 1,000 patients treated): impaired vision, allergic reactions (e.g. skin reactions), light sensitivity, and difficulty in urinating.

Very rarely (occurring in less than 1 in 10,000 patients treated), white blood cell and platelet counts may be lowered, and blood cells may be severely reduced, which can cause weakness, bruising or make infections more likely.

In case of infections with fever and serious deterioration of your general condition, see your doctor and tell him about your medicine.

Other possible reactions which may occur with this type of medicine include: weight gain, constipation, tightness of the chest, jaundice (yellowing of the skin or whites of the eyes caused by liver or blood problems), worsening of an angle-closure glaucoma (an eye disease with increased pressure inside the eye), uncontrollable movements, unusual excitement and restlessness (especially in children), severe skin reactions.

If any of the above side effects gets serious or if you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

**5. How to store Arlevert**

Keep Arlevert out of the reach and sight of children.

Do not use the tablets after the expiry date printed on the box.

This medicinal product does not require any special storage conditions.

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

**6. Further information****What Arlevert contains**

The active substances of Arlevert are: cinnarizine 20 mg and dimenhydrinate 40 mg.

The other ingredients are: microcrystalline cellulose, maize starch, talc, hypromellose, colloidal anhydrous silica, magnesium stearate and croscarmellose sodium.

**What Arlevert looks like and contents of the pack**

Arlevert tablets are round white tablets marked with an 'A'. They are available in packs containing 20, 50 or 100 tablets. Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer:**

HENNIG ARZNEIMITTEL GmbH & Co. KG, Liebigstrasse 1-2, D-65439 Flörsheim am Main, Germany.

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Arlevert 20 mg/40 mg Tabletten
Belgium	Arlevertin ceeptin de 20 mg/40 mg
Belgium	Arlevert
Czech Republic	Arlevert
Denmark	Arlevert 20 mg/40 mg tablette
Germany	Arlevert
Hungary	Arleverttablett
Ireland	Arlevert 20 mg/40 mg tablet
Italy	Arlevertin 20 mg/40 mg compresse
Luxembourg	Arlevert 20 mg/40 mg Tabletten
Netherlands	Arlevert 20 mg/40 mg tabletten
Poland	Arlevert 20 mg + 40 mg tabletki
Romania	Arlevert
Slovakia	Arlevert
Slovenia	Arlevert 20 mg/40 mg tablete
Sweden	Arlevert 20 mg/40 mg tabletter
United Kingdom	Arlevert 20 mg/40 mg tablets

Is this leaflet hard to see or read?  
Phone 01604 882090. Ask for help.

This leaflet was last revised in  
10/2007.

# Module 4 Labelling

## Arlevert 20 mg/ 40mg tablets

### Pack size of 20 tablets



### Pack size of 50 tablets



Pack size of 100 tablets



Blister foil

20 mg/40 mg tablets dimenhydrinate embossment on rim embossment on rim HENNIG ARZNEIMITTEL GmbH & Co. KG	<b>Arlevert® 20 mg/40 mg tablets</b> Cinnarizine/Dimenhydrinate Expiry date: see embossment on rim Batch No: see embossment on rim HENNIG ARZNEIMITTEL GmbH & Co. KG
(xxx)	(yyy)
20 mg/40 mg tablets dimenhydrinate embossment on rim embossment on rim HENNIG ARZNEIMITTEL GmbH & Co. KG	<b>Arlevert® 20 mg/40 mg tablets</b> Cinnarizine/Dimenhydrinate Expiry date: see embossment on rim Batch No: see embossment on rim HENNIG ARZNEIMITTEL GmbH & Co. KG
20 mg/40 mg tablets Cinnarizine/Dimenhydrinate Expiry date: see embossment on rim	<b>Arlevert® 20 mg/40 mg tablets</b> Cinnarizine/Dimenhydrinate Expiry date: see embossment on rim

## Module 5

### Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Arlevert 20mg/40mg Tablets in the treatment of vertigo of various origins could be approved. A national marketing authorisation was granted on 20<sup>th</sup> May 2005.

This application was made under EC article 10.b (Fixed Combination) of the Directive 2001/83/EC as amended. Arlevert 20mg/40mg Tablets, containing the fixed combination of cinnarizine Ph Eur and dimenhydrinate Ph Eur (20 mg/40 mg), was first registered in Germany in 1977 and the product has been available on prescription in Germany since 1982.

The drug substance cinnarizine is a piperazine derivative and a selective calcium antagonist. It has weak antihistamine and sedative activity, and is used for symptomatic treatment of motion sickness, nausea, vertigo and other vestibular disorders. The usual dose for vertigo and vestibular disorders is 30 mg three times daily by mouth.

The drug substance dimenhydrinate is an ethanolamine derivative and is a sedating antihistamine with antimuscarinic and significant sedative effects. It is used mainly as an antiemetic in the prevention and treatment of motion sickness, nausea, vertigo and other vestibular disorders. The usual dose for vertigo and vestibular disorders is 50 to 100 mg, given two or three times daily by mouth.

No new preclinical studies were submitted and none were required. In view of the extensive toxicology data available on both the known active substances the pre-clinical section of the application was based on published bibliography and was found to be satisfactory. No new toxicological problems for this product were found.

Clinical studies on Arlevert 20mg/40mg Tablets were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that Arlevert 20mg/40mg Tablets provide satisfactory clinical benefits.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

**II. ABOUT THE PRODUCT**

Name of the product in the Reference Member State	Arlevert 20mg/40mg Tablets
Name(s) of the active substance(s) (INN)	Cinnarizine 20mg Dimenhydrinate 40mg
Pharmacotherapeutic classification (ATC code)	Histamine (5HT1) antagonists (N07C A52)
Pharmaceutical form and strength(s)	Tablets, Cinnarizine 20mg/Dimenhydrinate 40mg
Reference numbers for the Mutual Recognition Procedure	UK/H/984/001/MR
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Denmark, Ireland, Italy, Luxembourg, The Netherlands, Poland, Slovenia, Sweden
Marketing Authorisation Number(s)	PL 11249/0001
Name and address of the authorisation holder	HENNIG ARZNEIMITTEL GmbH & Co. KG Liebigstrasse 1-2, D-65439 Flörsheim am Main, Germany

### III SCIENTIFIC OVERVIEW AND DISCUSSION

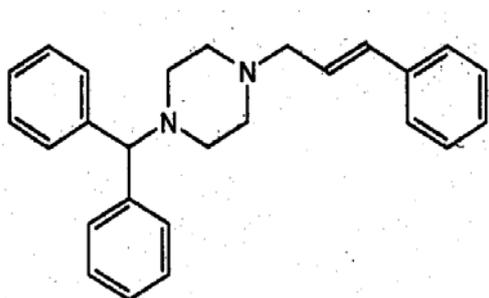
#### III.1 QUALITY ASPECTS

##### S. Drug substance (1)

INN/Ph Eur name: Cinnarizine

Chemical name: 1-benzhydryl-4-cinnamyl-piperazine

Structural formula



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

Molecular weight: 368.5

##### General Properties

Characters: White or almost white powder.

Solubility: Practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, slightly soluble in alcohol and methanol.

Cinnarizine is the subject of a European Pharmacopoeia monograph.

A Certificate of Suitability has been provided covering the manufacture and control of the drug substance cinnarizine. The drug substance specification complies with the Ph Eur monograph.

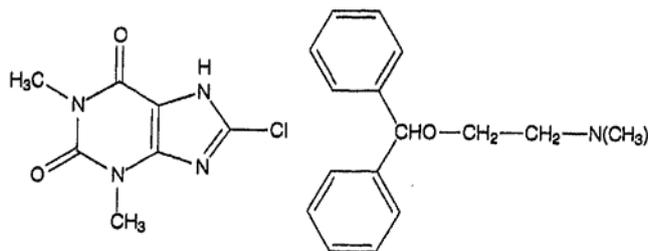
The Certificate of Suitability specifies a re-test date for the drug substance of 6 years when stored in container-closure comprising of double polyethylene bags inside a cardboard box.

##### S. Drug substance (2)

INN/Ph Eur name: Dimenhydrinate

Chemical name: 2-benzhydryloxyethyl-dimethyl-ammonium; 8-chloro-1,3-dimethyl-2-oxo-purin-6-olate

Structural formula:



Molecular formula:  $C_{17}H_{21}NO, C_7H_7ClN_4O_2$

Molecular weight: 470.0

### General Properties

Characters: White, crystalline powder or colourless crystals

Solubility: Slightly soluble in water, freely soluble in alcohol and sparingly soluble in ether.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate drug substance specification based on the European Pharmacopoeia has been provided. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies. Batch analysis data are provided and comply with the proposed specification.

Active dimenhydrinate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Appropriate stability data have been generated supporting a shelf life of 60 months when stored at 25°C.

### P. Medicinal Product

#### Other Ingredients

Other ingredients consist of pharmaceutical excipients cellulose microcrystalline, maize starch, talc, hypermellose, colloidal anhydrous silica, magnesium stearate and croscarmellose sodium.

All excipients comply with their respective European Pharmacopoeial monographs. Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph/specifications.

None of the excipients used contain material of animal or human origin.

**Pharmaceutical development**

The objective of the development programme was to establish a beneficial risk/benefit for Arlevert 20mg/40mg Tablets compared to co-administered cinnarizine 20 mg and dimenhydrinate 40 mg. To this end HENNIG ARZNEIMITTEL GmbH & Co. KG has conducted clinical safety and efficacy as well as pharmacokinetic studies comparing Arlevert 20mg/40mg Tablets versus co-administered cinnarizine 20 mg and dimenhydrinate 40 mg tablets.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development was stated and is satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

*In vitro* dissolution profiles have been generated for the proposed product with satisfactory results. Impurity studies have also been undertaken. Two new impurities were identified and are both controlled satisfactorily.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results at commercial-scale.

**Finished Product Specification**

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container-Closure System**

All strengths of the tablet are packaged in polyvinylchloride/polyvinylidene aluminium/blister strips in pack sizes of 20, 50 and 100 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations regarding materials for use in contact with food.

**Stability of the product**

Stability studies were performed on ten production-scale batches of the finished product, in accordance with current guidelines and in the packaging proposed for marketing. All results from stability studies were within specified limits. These data support a shelf-life of 36 months with no storage conditions.

**SPC, PIL, Labels**

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

## Conclusion

The grant of this marketing authorisation is recommended.

## III.2 PRE-CLINICAL ASPECTS

### INTRODUCTION

Arlevert 20mg/40mg Tablets are indicated for treatment of vertigo symptoms of various origins. Each Arlevert 20mg/40mg Tablet contains 20 mg cinnarizine in combination with 40 mg dimenhydrinate for oral administration. The proposed therapeutic dose is one Arlevert 20mg/40mg Tablet three times daily i.e. equivalent to 60 mg cinnarizine and 120 mg dimenhydrinate per day (1 mg cinnarizine/kg/day and 2 mg dimenhydrinate/kg/day for a 60 kg person). This application is based on published bibliography and a number of preclinical bridging toxicity studies with the formulation intended for marketing. After initial assessment by the Pharmaceutical Assessor, an Expert Comment on the toxicity and safety of benzhydrol was provided. The rationale for combining cinnarizine and dimenhydrinate is that synergism at low doses of the two actives, which act at the peripheral and central vestibular system, respectively, will lower the incidence of side-effects and increase therapeutic efficacy.

### PHARMACODYNAMICS

Cinnarizine is a selective calcium antagonist (blocks L-, T- and N-type voltage- and receptor-operated channels) inhibiting the influx of extracellular  $Ca^{2+}$ . Cinnarizine also has antihistamine properties blocking histamine  $H_1$  receptors ( $K_i=60nM$ ).

Dimenhydrinate is the 8chloro-theophylline salt of diphenhydramine. The drug substance diphenhydramine is an ethanolamine class antihistamine that acts predominantly as a competitive (reversible) inhibitor of histamine  $H_1$  receptors with additional sedative, anticholinergic and local anaesthetic activity.

The rationale for using Arlevert 20mg/40mg Tablets in treatment of vertigo is that vertigo, in the majority of cases, originates from both central and peripheral vestibular regions. The labyrinth-depressive effect of cinnarizine and central effect of dimenhydrinate on vestibular nuclei can be used in combination for treatment of vertigo of various origins.

Considering the wealth of clinical data and absence of suitable animal models correlating with vertigo in man, the absence of preclinical data with the proposed combination seems justified.

*In vitro*, cinnarizine and its major metabolite 4-hydroxy-cinnarizine (C-2) inhibit binding of specific ligands to D2-receptors ( $K_i$  13nM and 4nM, respectively). Given the plasma cinnarizine and C-2 concentrations observed after repeat oral administration of cinnarizine (7 mg/kg daily for 10-15 consecutive days) to rats, inhibition of D2-receptors and consequential parkinsonian symptoms are possible at therapeutic doses. Use of cinnarizine in patients with manifest Parkinson's disease should be considered with caution. The antimuscarinic activity of dimenhydrinate (25-50 mg, 3 times daily) can apparently be used in treatment of Parkinson's disease. The combination of cinnarizine with dimenhydrinate may counteract the occurrence of cinnarizine-induced parkinsonism. A precautionary warning of use of Arlevert 20mg/40mg Tablets in patients with Parkinson's disease is included under section 4.4 of the SmPC.

Side-effects associated with clinical use of Arlevert 20mg/40mg Tablets are discussed in Module 2.6.2.4. In view of the extensive clinical data on potential side-effects of Arlevert

20mg/40mg Tablets, absence of preclinical data is acceptable. Symptoms of overdosage are also adequately discussed in Module 2.6.2.4.

Cinnarizine, in contrast to other calcium antagonists, has no significant effects on blood pressure but regular monitoring of blood pressure is recommended when cinnarizine is used in combination with hyper/hypotensive medicines.

No preclinical safety pharmacology studies with the formulation proposed for marketing are provided.

Cinnarizine was shown to inhibit the *in vitro* binding of other calcium antagonists such as diltiazem ( $K_i = 0.2 \mu\text{M}$ ) by allosteric modulation.

Side-effects associated with the anticholinergic activity of diphenhydramine (e.g. narrow angle glaucoma and urinary retention) may increase, when used concomitantly with tricyclic antidepressants, parasympatholytics and MAOIs.

### PHARMACOKINETICS

No preclinical pharmacokinetic (PK) data on cinnarizine or Arlevert 20mg/40mg Tablets in animals are provided. In monkeys benzhydrol apparently accounts for 1-2% of the dose excreted in urine, but it has been suggested that benzhydrol may arise from decomposition of diphenylmethoxyacetic acid or its glucuronide which is acid labile. Evidence of benzhydrol being a metabolite in man is discussed below. Pharmacokinetics of single oral dose of individual actives and Arlevert 20mg/40mg Tablets in humans are presented. Absence of preclinical PK studies with Arlevert 20mg/40mg Tablets is considered acceptable as such data will be superseded with clinical PK data.

### TOXICOLOGY

#### Acute and chronic toxicity

The acute oral toxicity of combination of 20 mg cinnarizine with 40 mg dimenhydrinate ( $\text{LD}_{50}$ , mouse: 1600 mg/kg; rat: 5760 mg/kg) in rodents appears to be lower than those of cinnarizine ( $\text{LD}_{50}$  mouse: >1000 mg/kg; rat: >2500 mg/kg) or dimenhydrinate ( $\text{LD}_{50}$  mouse: 203 mg/kg; rat: 1320 mg/kg).

In a study by Heisler (1986), rats fed with combination of cinnarizine and dimenhydrinate (*ca* 250, 333 and 416 mg/kg/day) for up to 9 months, slight increase in body weight gain was seen at mid- (females only) and high-doses (males only). The increase in weights of liver (high-dose males) and adrenal gland (high-dose females) were apparently not accompanied with histopathological changes and were not considered dose related.

#### Reproductive toxicity

Oral doses of cinnarizine had no effects on fertility of male and female rats. In rats, cinnarizine (320 mg/kg/day, GD6-15) decreased litter size, increased number of resorbed fetuses and decreased birth weight of pups.

Oral doses of dimenhydrinate administered to rats (75 mg/kg/day from 3 days pre-mating to end of gestation period) or rabbits (50 and 100 mg/kg/day, GD8-16) were not potentially teratogenic. Clinically, however, the incidence of cleft palate and clefts with other defects was higher in children whose mothers had taken diphenhydramine (active ingredient of dimenhydrinate) in the first trimester of pregnancy. The review by Leatham, however, concluded that teratogenic risk of dimenhydrinate and diphenhydramine is low and that dimenhydrinate may have a relaxing or a stimulating effect on the uterus depending on the

stage of pregnancy at which it is given (for example at term dimenhydrinate may have an oxytocic effect and may shorten labour).

Diphenhydramine crosses the placenta and also enters human milk. In the absence of peripost-natal studies with Arlevert 20mg/40mg Tablets this medicine should not be taken by women who are breast-feeding.

### **Mutagenicity and carcinogenicity**

An Ames test performed in 1985 by Safeparm Laboratories (UK) with the combination of cinnarizine and dimenhydrinate (1:2 ratio) was negative at concentrations up to 0.5 mg/plate. During assessment of the National application the MHRA asked for justification for absence of a full genotoxicity package.

The applicant provided additional data from an *in vitro* chromosome aberration test in hamster V79 cells with cinnarizine. The conclusions of this GLP compliant study are that cinnarizine is non-clastogenic in the assay both with and without S9 mix. Dimenhydrinate was not included in the study.

The applicant also refers to a paper published as part of the National Toxicology Program (NTP) in the USA, in which dimenhydrinate was tested for its ability to induce mutations in a number of Salmonella strains. A positive result was recorded in one strain (TA 1535), although when the experiment was repeated by a separate team the results were negative. Equivocal results were recorded in a second strain (TA 100) and negative results in three others (TA 1537, TA 97 and TA 98).

In the applicant's own bacterial mutagenicity tests the combination product produced negative results in five Salmonella strains (including TA 1535 and TA 100). It is noteworthy that the top concentrations of dimenhydrinate used in the NTP study were greater (at least three fold) than those used in the applicant's study, although even at the doses used in the applicant's study some equivocal results were seen in the NTP study.

The applicant concluded that the absence of a full genotoxicity package is justified for the following reasons:

1. The individual pharmaceutical ingredients have been available for adults and children as prescription and OTC medicines for many years
2. Arlevert 20mg/40mg Tablets has been available in Germany for 20 years and in various other countries for 5 to 10 years without serious adverse effects being reported
3. The lack of published data indicate that safety concerns have not arisen
4. The paucity of published data indicates the lack of molecular structural concerns
5. The limited data available on the individual drug substances and the combination product do not indicate the potential for genotoxicity
6. No new impurities were formed during stability studies with the combination product.

While some additional data have been provided, including *in vivo* genotoxicity testing (micronucleus assay in bone marrow) of the combination product, a full genotoxicity package is still lacking. The strongest justification for this is the extent of clinical experience, both

with the individual actives (across Europe) and with the combination (particularly in Germany).

Cinnarizine has been licensed in the UK as Stugeron since 1973, and as Stugeron Forte since 1977. Dimenhydrinate has been licensed in the UK as Dramamine/Gravol since 1972; and the proposed combination product has been available in Germany for over 20 years.

The note for guidance on fixed combination medicinal products states that "safety studies in animals should be performed with the active substances of the fixed combination in the proportion present in the product. Such studies will not be required where all the substances have been extensively and safely used in humans in identical or very similar combinations for a long period and the safety of such combinations is well documented".

Since the proposed product has been available in Germany for over 20 years it may be considered that further preclinical studies including genotoxicity and carcinogenicity studies are not required.

### **Drug substance and drug product**

Sources of cinnarizine and dimenhydrinate are of Ph Eur specification. Drugs substance specification limits for potential related substance/impurities of cinnarizine and dimenhydrinate comply with current Ph Eur requirements and are of no safety concern.

An Expert Comment on potential toxicity and safety of benzhydrol was provided. It stated that benzhydrol and benzophenone are potential metabolites of dimenhydrinate in both animals and humans and as such they may be considered qualified. The applicant was asked to provide evidence that benzhydrol and benzophenone are metabolites formed in humans to justify their finished product limits.

Evidence for the presence of benzhydrol and benzophenone as metabolites of dimenhydrinate in man is indirect and as yet to be fully confirmed.

The applicant reports that benzhydrol has been identified as a metabolite in *in vitro* studies and refers to published data that show low levels of benzhydrol isolated from the urine of Rhesus Monkeys treated with diphenhydramine. It is possible, however, that the benzhydrol arose during the acidic extractions used during sample preparation. The applicant reports that further evidence for the formation of benzhydrol and benzophenone comes from studies reported by Pfeifer *et al*, in Rhesus Monkeys and other animal models.

The applicant was not able to provide the evidence requested but reduced the proposed release and shelf-life specification limits for benzhydrol and benzophenone in line with the relevant guideline (ICH Q3B).

All excipients of the proposed formulation are routinely used in pharmaceutical formulations and are not of safety concern at the proposed levels and dose regimen.

### **Summary of Product Characteristics and Patient Information Leaflet**

These are satisfactory.

### **CONCLUSIONS**

A Marketing Authorisation may be granted.

### III.3 CLINICAL ASPECTS

#### INDICATIONS

Treatment of vertigo symptoms of various origins.

#### DOSE AND DOSE SCHEDULE

*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.

#### *Renal impairment:*

Arlevert 20mg/40mg Tablets should be used with caution in patients with mild to moderate renal impairment. Arlevert 20mg/40mg Tablets should not be used by patients with a creatinine clearance of  $\leq 25$  mL/min (severe renal impairment).

#### *Hepatic impairment:*

No studies in patients with hepatic impairment are available. Arlevert 20mg/40mg Tablets should not be used by patients with severe hepatic impairment.

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

The dose and dose schedule is satisfactory.

#### TOXICOLOGY

See preclinical section above.

#### CLINICAL PHARMACOLOGY

No new clinical pharmacology data on either the individual actives or the combination have been generated.

#### PHARMACODYNAMICS

See preclinical section above.

#### PHARMACOKINETICS

The pharmacokinetic study was an open, single-dose, randomised, three-period, and crossover study to compare the rate and extent of absorption in healthy male volunteers. A dose of 20 mg of cinnarizine and 40 mg of dimenhydrinate was administered separately or simultaneously.

The following tablets were used in the pharmacokinetic studies:

- Arlevert 20mg/40mg Tablets, HENNIG ARZNEIMITTEL
- Cinnarizine 20 mg tablets, HENNIG ARZNEIMITTEL
- Dimenhydrinate 40 mg tablets, HENNIG ARZNEIMITTEL

The study comprised three periods of single-dose administration, separated by a washout period of 1 week. Blood samples were collected pre-dose and up to 12 hours post-dose after administration of either Arlevert 20mg/40mg Tablets or cinnarizine. Blood samples were collected pre-dose and up to 14 hours post-dose after administration of dimenhydrinate.

Primary parameters of  $AUC_{0-\infty}$  or  $AUC_{exp}$ ,  $C_{max}$ ,  $t_{max}$  were determined as well as the mean body residence time to infinity ( $MRT_{0-\infty}$  or  $MRT_{exp}$ ) and the elimination half-life ( $t_{1/2}$ ) for both cinnarizine and dimenhydrinate.

**Cinnarizine Pharmacokinetic Parameters (Mean  $\pm$  s.e.m., n = 11)**

Parameter	Units	Cinnarizine	Arlevert 20mg/40mg Tablets
$C_{max}$	ng/ml	38.58 $\pm$ 6.16	37.36 $\pm$ 4.46
$T_{max}$	h	2.05 $\pm$ 0.42	2.27 $\pm$ 0.22
$AUC_{exp}$	ng/ml.h	225.22 $\pm$ 49.70	238.26 $\pm$ 38.61
$MRT_{exp}$	h	7.89 $\pm$ 1.39	7.03 $\pm$ 0.54
$T_{1/2}$	h	4.94 $\pm$ 1.00	4.10 $\pm$ 0.35

**Diphenhydramine Pharmacokinetic Parameters (Mean  $\pm$  s.e.m., n = 12)**

Parameter	Units	Dimenhydrinate	Arlevert 20mg/40mg Tablets
$C_{max}$	ng/ml	40.91 $\pm$ 3.45	37.36 $\pm$ 4.46
$T_{max}$	h	1.71 $\pm$ 0.19	1.88 $\pm$ 0.27
$AUC_{exp}$	ng/ml.h	265.14 $\pm$ 25.19	240.94 $\pm$ 23.63
$MRT_{exp}$	h	7.81 $\pm$ 0.40	7.65 $\pm$ 0.37
$T_{1/2}$	h	4.76 $\pm$ 0.22	4.52 $\pm$ 0.20

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

The Westlake 95% confidence intervals for the  $AUC_{exp}$  of dimenhydrinate are reported as  $\pm 25.14\%$  (power 70.17%). The figure is outside the  $\pm 20\%$  range, therefore the 90% confidence intervals (as per ICH guideline) were calculated and a figure of  $\pm 21.43\%$  was obtained.

For cinnarizine, the study could not exclude that a difference in bioavailability exists between cinnarizine administered alone and as Arlevert 20mg/40mg Tablets. Even the 90% confidence intervals were  $\pm 30.51\%$  (power 30.23%).

The applicant concludes that the study results were close to showing bioequivalence for dimenhydrinate administered alone and as Arlevert 20mg/40mg Tablets. A difference in bioavailability between cinnarizine administered alone and as Arlevert 20mg/40mg Tablets cannot be excluded. This might be due to the large interindividual variability or less than optimal dissolution of the cinnarizine reference product.

**EFFICACY****Clinical Studies**

This assessment considers the evidence of efficacy for Arlevert 20mg/40mg Tablets, a fixed combination of cinnarizine 20mg and dimenhydrinate 40mg.

The objectives of the clinical studies were to demonstrate the efficacy of Arlevert 20mg/40mg Tablets in the therapy of vertigo of various origins; to establish its possible superiority over the single substances at the same or higher doses, as well as over betahistine and placebo; and to establish whether Arlevert 20mg/40mg Tablets was associated with a better safety profile. A summary of these studies is presented below.

Study	Purpose of the study	Formulation used in the clinical study	Control groups	Patient population
<b>I</b>	Central and/or peripheral vertigo	Arlevert tablets Cinnarizine 50 mg tablets Dimenhydrinate 100 mg tablets Placebo tablets	Cinnarizine 50 mg Dimenhydrinate 100 mg Placebo	Outpatients with central and / or peripheral vertigo
<b>II</b>	Vertigo due to vertebrobasilar insufficiency	Arlevert tablets Betahistine 12 mg tablets Placebo tablets	Betahistine 12 mg Placebo	Outpatients with symptomatic vertebrobasilar insufficiency
<b>III</b>	Acute vertigo of peripheral origin	Arlevert tablets Cinnarizine 20 mg tablets Dimenhydrinate 40 mg tablets	Cinnarizine 20 mg Dimenhydrinate 40 mg	Inpatients with acute vertigo of peripheral origin
<b>IV</b>	Central and/or peripheral vertigo	Arlevert tablets Cinnarizine 20 mg tablets Dimenhydrinate 40 mg tablets	Cinnarizine 20 mg Dimenhydrinate 40 mg	Outpatients with central and / or peripheral vertigo
<b>V</b>	Central and/or peripheral vertigo	Arlevert tablets Cinnarizine 50 mg tablets Dimenhydrinate 100 mg tablets	Cinnarizine 50 mg Dimenhydrinate 100 mg	Outpatients with central and / or peripheral vertigo
<b>VI</b>	Otogenic (peripheral) vertigo	Arlevert tablets Betahistine 12 mg tablets	Betahistine 12 mg	Outpatients with otogenic (peripheral) vertigo
<b>VII</b>	Acute vestibular disorders	Arlevert tablets Betahistine 12 mg tablets	Betahistine 12 mg	Outpatients with vertigo as a consequence of acute vestibular disorders
<b>VIII</b>	Menière's disease	Arlevert tablets Betahistine 12 mg tablets	Betahistine 12 mg	Outpatients with Menière's disease

All eight clinical studies (Studies I-VIII) were conducted in patients and employed randomised, double-blind, parallel-group designs and were carried out in accordance with the guidelines of Good Clinical Practice (GCP). Possible bias was avoided by means of double-blind design and randomisation. In addition to these studies, two crossover studies were performed in healthy volunteers and the results of several open-label studies are available. The investigational drug Arlevert 20mg/40mg Tablets and the reference products were manufactured in accordance with the guidelines of Good Manufacturing Practice (GMP).

The treatment period of the patients usually extended to 4 weeks, including a follow-up examination after 1 week and a final examination after 4 weeks of therapy. No long-term studies were carried out, since the combination preparation Arlevert 20mg/40mg Tablets has

been marketed in Germany for more than 20 years and a large amount of data on post marketing experience concerning the efficacy and safety of the drug is available.

The patient's subjective evaluation of reduction of the vertigo symptoms, quantified by the decrease of the variable “Mean Vertigo Score” (MVS), was used as the primary efficacy criterion in all studies. In each case, it represents six vertigo symptoms (dysstasia and walking unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation, and swaying resp. blackout), and the intensity of vertigo in consequence of six different triggering factors (change of position, bowing, getting-up, walking resp. driving by car/train, head movement, and eye movement). These 12 criteria were rated and quantified by the patient using either a visual analogue scale (VAS) or a verbal rating scale (VRS). The results of this evaluation were combined in the Mean Vertigo Score. Thus, the Mean Vertigo Score is a method of measuring vertigo based on an assessment of symptoms and their intensity.

Studies I, III, IV and V are considered to be pivotal to this application. This is because the active controls in these studies allow a risk:benefit assessment of the combination product against its individual components, as required by the CPMP *Note for guidance on fixed combination medicinal products*. Note that Studies I and V compare with higher doses of each component therapy. Satisfactory certificates of analysis have been provided for the test and reference batches used in the clinical studies.

The results from Studies I, III, IV and V are presented below.

**Effect Sizes (Cohen's d) and their 95%-Confidence Intervals  
for Studies I, III, IV, and V**

Study	Arlevert vs Cinnarizine			Arlevert vs Dimenhydrinate			Arlevert vs Placebo		
	Cohen's d	95%-Confidence Limits		Cohen's d	95%-Confidence Limits		Cohen's d	95%-Confidence Limits	
		Lower	Upper		Lower	Upper		Lower	Upper
I	0.863	0.479	1.243	0.885	0.500	1.266	1.178	0.776	1.575
III <sup>1</sup>	1.251	0.459	2.025	1.244	0.464	2.007			
IV	0.744	0.368	1.117	0.687	0.310	1.062			
V	0.682	0.281	1.079	0.692	0.287	1.094			

<sup>1</sup> Study III: 1-week treatment

Clinical relevance is further supported by the result that between 60 and 80% of the patients treated with the combination reported either no or only mild symptoms of vertigo after the end of treatment. To further corroborate the clinical relevance of Arlevert 20mg/40mg Tablets, responder rates have been calculated. A responder is defined as any patient with a change from baseline of at least 50 percent. There is a distinct and statistically high significant difference between Arlevert 20mg/40mg Tablets and placebo. Not only has Arlevert 20mg/40mg Tablets been demonstrated to be more effective than placebo, but it has also been demonstrated to be more effective than both active treatments. This demonstrates the clinical benefit of treatment with Arlevert 20mg/40mg Tablets.

In conclusion, the clinical relevance of the therapeutic success achieved with Arlevert 20mg/40mg Tablets has been demonstrated by a large effect size in comparison to placebo and at least medium effect sizes in comparison to the single components.

## SAFETY

In the clinical programme described above there were no serious and/or unexpected adverse events.

## CLINICAL OVERVIEW

The clinical overview was written by an appropriately qualified Doctor and is a suitable summary of the clinical aspects of the dossier.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

This SPC is medically satisfactory.

**PATIENT INFORMATION LEAFLET (PIL)**

The PIL is medically satisfactory and consistent with the information in the SPC.

**LABELLING**

The labels are medically satisfactory.

**APPLICATION FORM (MAA)**

The MAA form is medically satisfactory.

**MEDICAL CONCLUSION**

The grant of a marketing authorisation is recommended.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT  
QUALITY**

The important quality characteristics of Arlevert 20mg/40mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**PRECLINICAL**

The preclinical sections of this application are based on published bibliographic data and no new preclinical pharmacodynamic studies with the formulation intended for marketing have been provided.

Absence of preclinical pharmacokinetics studies with Arlevert 20mg/40mg Tablets is considered acceptable, as such data will be superseded with clinical pharmacokinetics data. This is satisfactory.

The presented bibliographic data on acute and chronic toxicology, reproductive toxicology and genotoxicity and carcinogenicity for both actives has been supplemented with bridging studies with the combination preparation intended for marketing.

**EFFICACY**

Arlevert 20mg/40mg Tablets was consistently superior to its components on the primary endpoints of each pivotal study, both at doses similar to those used in the combination product and at higher doses. Evidence of efficacy therefore appears to have been robustly demonstrated.

In the clinical programme there were no serious and/or unexpected adverse events. The most frequent events were tiredness, dryness of mouth and headache. These adverse events did not occur more frequently with the combination. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

**RISK BENEFIT ASSESSMENT**

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

## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome