Vertigoheel®

PRODUCT MONOGRAPH

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Vertigoheel® Tablets
Composition: 1 tablet containing: Anamirta cocculus D4 210 mg; Conium maculatum D3, Ambra grisea D6, Petroleum rectificatum D8 30 mg each. **Indications:** Dizziness of various origins including motion sickness, arising from arteriosclerosis; insufficient cerebral circulation; tinnitus; geriatric polyneuropathy. **Contraindications:** None known. **Side effects:** None known. **Interactions with other medication:** None known. **Dosage:** In general, 3 tablets to be dissolved in the mouth 3 times daily; in sporadic dizziness and nausea initially 1 tablet every 15 minutes. **Package sizes:** Packs containing 50, 100 or 250 tablets. (9754)

Vertigoheel®

1. Vertigoheel®

Vertigoheel® is a combination medicine that has been established in the treatment of dizziness/vertigo of various origins for decades. Its components Anamirta cocculus (Indian berries), Conium maculatum (spotted hemlock), Ambra grisea (amber), and Petroleum rectificatum (mineral oil), have been known to be effective remedies for vertigo for a long time. Recent research has shown that the efficacy of Vertigoheel® is based on a mode of action that generally improves microcirculation, providing an excellent therapeutic approach particularly for the treatment of non-vestibular vertigo and associated symptoms.

Numerous scientific studies including randomized clinical trials, noninterventional studies reflecting use in day-to-day patient care, and meta-analyses of clinical trials confirm the efficacy of Vertigoheel® compared to conventional treatments.

Apart from the product's efficacy, the high safety profile and remarkable tolerability of Vertigoheel® is a particular benefit, especially in the long-term treatment that is often required for the management of vertigo.

2. Vestibular and Non-vestibular Vertigo

Vertigo is one of the most common symptoms with which patients present to their doctor, affecting almost one-third of people over 60. Dizziness is a common symptom of rotatory movement with difficulty in balance, gait and navigation within the environment. It has a considerable impact on the daily lives of a large percentage of affected individuals. Both patients with vestibular vertigo and those with nonvestibular dizziness have a significantly reduced health-related quality of life[2,3], and the associated risk of falling constitutes a hazard of daily living.

Types of Dizziness
According to Drachman & Hart[5], dizziness can be divided into four clinical sensations. "True" dizziness (vertigo) originates from the vestibular (central/peripheral) balance organ, and is experienced as systematic dizziness, including spinning dizziness/rotational vertigo (e.g., in vestibular neur(on)itis) and postural vertigo/dysequilibrium (e.g., in bilateral vestibulopathy). Diffuse forms of dizziness such as lightheadedness (e.g., from drug poisoning) are also described. Medical conditions, especially cardiac disorders, may lead to symptoms of presyncope which patients may also describe as dizziness.[4,6] A common feature shared by all diffuse forms of dizziness is that, unlike in true vertigo, symptoms are nonspecific. This is why the collective term "nonspecific dizziness" has been coined to describe these conditions.

Table 1. Classification of vertigo

Classification*	**Vestibular vertigo** (H 81–diagnosis†: disorders of vestibular function)	**Non-vestibular vertigo (dizziness and giddiness)** (R 42-diagnosis*: Dizziness and giddiness, including light-headedness and vertigo not otherwise specified; H82-diagnosis*: Vertiginous syndromes in diseases classified elsewhere)
Etiology	E.g. benign paroxysmal vertigo (BPPV); Meniere's disease; vestibular neuronitis	Multimodal with cerebral sclerosis, psychogenic, drug induced or cardiovascular
Symptoms	systematic	unsystematic

* International Classification of Diseases (ICD). 2011; http://www.who.int/classifications/icd/en/. Accessed 2011, November 2nd, 2011.

2.1 CLINICAL FEATURES

Dizziness is not a clinical entity *per se*, but comprises symptoms of various etiologies and pathogenetic origins. Suggested possible causes of the development of vertigo/dizziness include:

- Disorders of the vestibular organ of balance in the inner ear
- Diseases of the central nervous system
- Conflicting input from the various special senses (dysequilibrium)
- Cervical, thoracic, or lumbar/sacral spine diseases interfering with spatial proprioception
- Impaired blood flow
- Mental reactions and disorders
- Toxic environmental or drug exposures

The differential diagnosis of dizziness is based on a targeted evaluation by type of dizziness, attack duration, triggers, and associated symptoms, a vestibular and neurological examination, and knowledge of the most common dizziness/vertigo syndromes.[4]

Duration of Vertigo Attacks
Episodes of vertigo may last for seconds to minutes (e.g., in benign paroxysmal positional vertigo, vestibular paroxysm) or hours (e.g., in Menière's disease or vestibular migraine). Chronic dizziness, which may persist for days or even several weeks, is found in vestibular neuritis. Episodes of dysequilibrium may last for minutes to hours and can be triggered by transient ischemic attacks (TIAs) in the brain stem.[6]

Associated Symptoms
The following symptoms have been reported to be associated with vertigo: migraine headaches, increased sensitivity to light and noises (migraine vertigo), neck pain, hearing loss, tinnitus and pressure in the ears (Menière's disease or other peripheral vestibular disorders), breathlessness, hyperventilation, tremor, tachycardia, anxiety disorder, faintness (presyncope) and syncope (orthostatic hypotension, cardiac arrhythmia).[4]

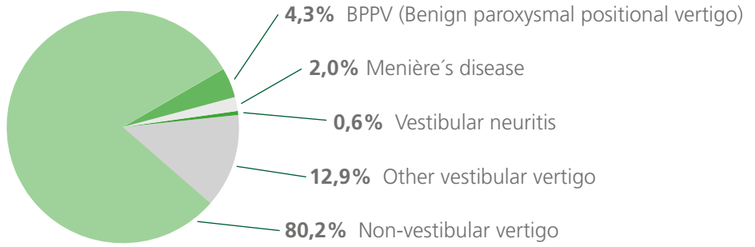
Triggers
Dizziness/vertigo attacks may occur spontaneously (Menière's disease, TIAs, cardiac arrhythmias, migraine) or be caused by standing up from a lying or sitting position (orthostatic lightheadedness), a change of head position (benign paroxysmal positional vertigo) or a pressure change in the head or auditory canal (perilymph fistula). Psychogenic dizziness may occur in specific environmental conditions precipitating an attack.[4]

2.2 EPIDEMIOLOGY

Dizziness/Vertigo is among the most common symptoms presenting in clinical practice, and it is one of the ten most frequent reasons for a neurological examination. Dizziness-related visits account for 2% of all visits to GPs' offices.[7-10]

Dizziness may occur in people of all ages. The lifetime prevalence is approximately 30%, and elderly people are affected more often than younger individuals. About 30% of 65-year-olds report recurrent episodes of dizziness.[6-13] Research shows that vertigo affects women more often than it does men.

Figure 1. Distribution of vertigo diagnoses in patients presenting to GPs with dizziness



A survey of the frequency of diagnoses and prescription orders for dizziness in a patient population served by a total of 138 GPs/family doctors (over 300,000 patients) documented dizziness as the presenting symptom in 3.4% of patients. A condition associated with vestibular vertigo was diagnosed in 19.8% of these patients, whereas in the majority of cases (80.2%, Figure 1) only the description of the symptom (ICD-10R 42, dizziness and giddiness) was documented.[14]

Epidemiology of Specific Conditions Associated with Vertigo
Specific conditions associated with dizziness are only rarely explored in epidemiological studies. The relative frequencies of the various vertigo syndromes, collected in a neurologic specialty clinic for vertigo and oculomotor disorders, are shown in Table 2.

Table 2. Frequencies of various vertigo syndromes diagnosed in a neurologic specialty clinic for vertigo and oculomotor disorders (from Strupp 2008)[6]

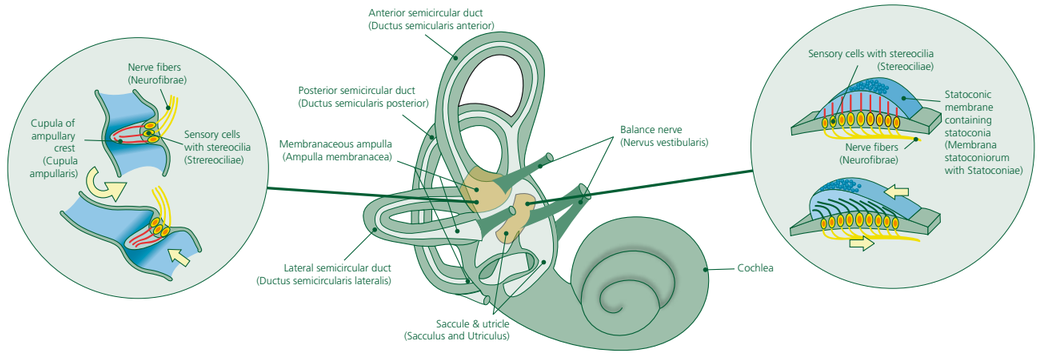
Diagnosis	n	%
Benign paroxysmal positional vertigo	1,336	18.6
Postural phobic vertigo	1,127	15.6
Central vestibular vertigo	893	12.4
Basilar/vestibular migraine	738	10.2
Menière's disease	677	9.4
Vestibular neur(on)itis	531	7.4
Bilateral vestibulopathy	367	5.1
Vestibular paroxysm	284	3.9
Psychogenic dizziness	228	3.2
Perilymph fistula	44	0.6
Unclear dizziness symptoms	239	3.3
Other	741	10.3
Total	**7,205**	**100%**

These data were collected in a specialty clinic and, therefore, cannot be ruled out to overestimate the prevalence of specific disorders associated with vertigo.[3]

2.3 SPECIFIC VESTIBULAR VERTIGO: SUBTYPES AND TREATMENT OPTIONS

Dizziness caused by disorders of the equilibrium system (Figure 3) is referred to as vestibular vertigo. Peripheral vestibular vertigo is a condition where the inner ear or the balance nerve is affected. Central vestibular vertigo is caused by disorders of the brain stem, cerebellum or cerebrum.

Figure 2: Vestibular system with enlarged sections showing the macula and cupola



The following three peripheral vestibular disorders with typical symptoms and clinical signs are the most prevalent: benign paroxysmal positional vertigo (BPPV), Menière's disease, and vestibular neuritis.[4]

2.3.1 BENIGN PAROXYSMAL POSITIONAL VERTIGO (BPPV)

BPPV is the most prevalent balance organ disorder and leads to brief episodes of spinning dizziness (typically lasting <20 seconds), repeatedly brought on by patients turning their head one particular way. Patients may occasionally experience associated symptoms such as nausea, vomiting, sweating, and anxiety.

The presumable underlying mechanical cause of BPPV is that calcium carbonate crystals known as otoliths become detached from the inner ear otolith organs. The loose otoliths float in the inner ear canals where their weight stimulates the inner ear sensory cells, resulting in the transmission of faulty body posture signals to the brain and hence conflicting input to the brain (vestibular mismatch) leading to vertigo and nystagmus.

The diagnosis is confirmed by provoking spinning dizziness by asking patients to rotate and position their head a particular way, and by observing the patient for the development of nystagmus typical of BPPV. The Dix-Hallpike Maneuver is the classical test used to trigger BPPV and to identify the affected side.[15]

BPPV occurs mainly in elderly people. By age 70, one in three adults at some point of their lifetime will have experienced this harmless (except for the risk of falling associated with it) yet initially serious-seeming form of dizziness.Treatment consists of the use of liberatory maneuvers: The clinician rapidly turns the patient's head to different positions to flush out the agglomerate of particles from the semicircular duct which, therefore, will no longer produce positional vertigo. Maneuvers of first choice for BPPV of the posterior semicircular duct are the Epley and Semont maneuvers. Most patients can perform these maneuvers on their own after a brief training session.

Both maneuvers are equally effective, and the cure rate is greater than 95% within a few days, as shown in various clinical trials and meta-analyses. The annual recurrence rate of BPPV is approximately 15% to 30%, and approximately 50% of patients go on to experience recurrence at some point which can be successfully treated by performing the same maneuver.[4,6,17]

2.3.2 MENIÈRE'S DISEASE

Menière's disease is an inner ear disorder characterized by episodic vertigo, unilateral low frequency hearing loss, and ringing noises in the ears (tinnitus). The combined occurrence of these three symptoms is referred to as Menière's triad.

The most likely cause of the disease is increased inner ear fluid production and the resultant pressure increase (endolymphatic hydrops). Suggested precipitating factors include physical and mental stress, an exaggerated response of the immune system, and circulatory disturbances.

The disease may be chronic in some patients, typically occurs between 40 and 60 years of age, and affects men more often than it does women.

During an acute attack, spinning dizziness and nausea can be controlled with antivertigo medication. High-dose, long-term betahistine prophylaxis significantly reduces the number of attacks. Patients experiencing frequent and severe vertigo attacks over a prolonged period of time may benefit from gentamicin instillation into the middle ear to purposefully damage the affected vestibular organ.[4,6,17]

2.3.3 VESTIBULAR NEURITIS (NEURONITIS)

This condition typically comes on suddenly manifesting as severe, sustained spinning dizziness, nausea, vomiting, and unsteadiness of gait. These symptoms are particularly intense in unilateral vestibular neuronitis.

The cause of the persistent rotational vertigo is an inflammation of the balance nerve which is presumably triggered by infection with reactivated herpesviruses.[4]

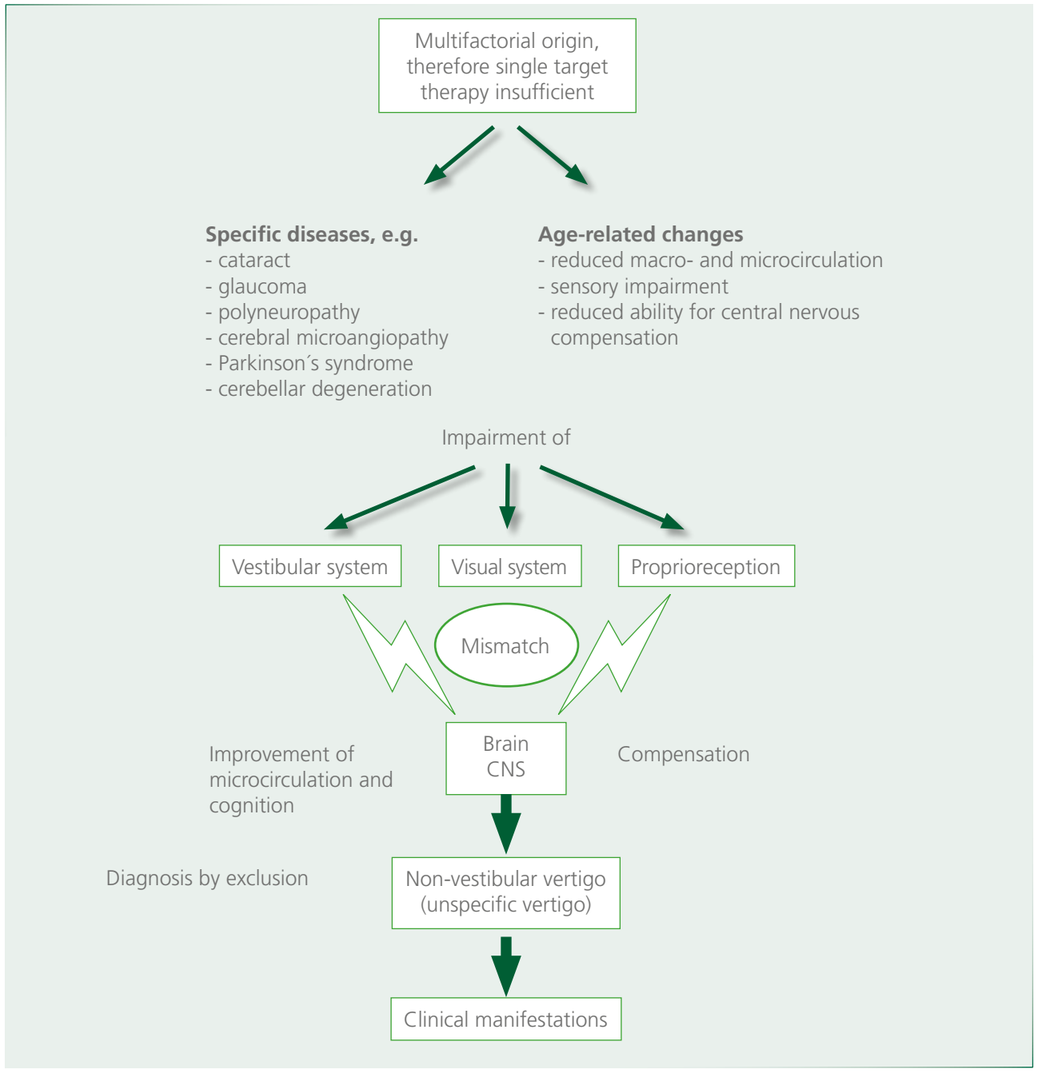
The condition is most prevalent among adults between 50 and 60 years of age, with women being affected more often than are men.

Single-agent glucocorticoid therapy significantly speeds recovery of peripheral vestibular function. Targeted balance retraining exercises speed and improve central vestibular compensation of the tone imbalance between the intact and compromised labyrinth.[17]

2.4 NON-VESTIBULAR VERTIGO: SUBTYPES AND TREATMENT OPTIONS

Non-vestibular vertigo may have a variety of causes. Triggers may include cardiovascular diseases such as hypotension, hypertension or cardiac arrhythmias, psychiatric disorders (depression, anxiety, psychoses), and medications and drugs of abuse.[4]

Figure 3. Aetiology of non-vestibular vertigo



2.4.1 PSYCHOGENIC VERTIGO

Psychogenic vertigo is often preceded by an organic condition with attacks of dizziness, triggering mental insecurity and a secondary anxiety disorder. Apprehension of the next attack facilitates the development of postural phobic vertigo which often persists after the underlying physical cause has been treated (thus becoming a chronic condition).

Psychogenic vertigo typically comes on as a result of great mental stresses associated with problems in a relationship or on the job. Affected patients often have depressive or anxiety disorders at the same time.
Psychogenic dizziness preferentially develops in women between 30 and 40 years of age, and in men between 40 and 50 years of age. As with all anxiety disorders, the most important treatment modality is behavioral therapy. Antidepressants with anxiolytic activity may also provide relief.[4]

2.4.2 MULTIFACTORIAL NON-VESTIBULAR VERTIGO

Unsteadiness of gait/postural imbalance (dysequilibrium) is associated with a tendency for falling, but not with nystagmus. Nausea and vomiting are comparatively rare in this type of dizziness.

Presumable causes include age-related changes in vestibular, somatosensory, and visual functions, as well as other multifactorial causes that lead to impairment of the sensory and motor system and hence to imbalance. Non-vestibular vertigo is often associated with cataract, glaucoma, polyneuropathy, cervical myelopathy, cerebral microangiopathy, parkinsonian syndrome, cerebellar degeneration, and osteoarthritis of the hip and knee, and total joint replacement.[4]

Conflicting inputs from the (visual, labyrinthine, proprioceptive) balance systems are a frequent cause of diffuse dysequilibrium especially in elderly patients, which is often chronic and has an unclear prognosis. The unsteadiness is due to age-related input conflict or inadequate input to the brain about the body's position in space. Dysequilibrium is frequently due to many different factors including pseudoparkinsonian syndrome, peripheral neuropathy, loss of vision, and poorly compensated peripheral vestibular disorders. This type of dizziness is usually an exclusion diagnosis.

Dizziness may have many different causes and, therefore, cannot be managed with the isolated treatment approaches typically used for specific types of dizziness. As a result, consideration should be given to a treatment that leverages a multitarget mode of action.

Vertigoheel® is a combination medication indicated for the symptomatic relief of dizziness/vertigo of various origins. The substances of plant, animal, and mineral origin used in Vertigoheel® are used in low to intermediate potencies (D3 to D8) and, in this substance concentration, are directed against various symptoms of dizziness among other symptoms.

The multitarget mode of action of this product has been increasingly characterized in recent years and is presented in chapter 3.

3. Vertigoheel®: Mechanism of Action in Vertigo of Various Origins

3.1 VERTIGOHEEL® – A NATURAL MULTITARGET AND MULTICOMPONENT MEDICINE

Vertigoheel® is a multicomponent medicine containing the pharmacologically active ingredients *Anamirta cocculus* (Indian berries), *Conium maculatum* (spotted hemlock), *Ambra grisea* (amber), and *Petroleum rectificatum* (mineral oil). Intense research into the mode of action of Vertigoheel® suggests multitarget activity impacting vasodilation of small blood vessels and thereby improving microcirculation.

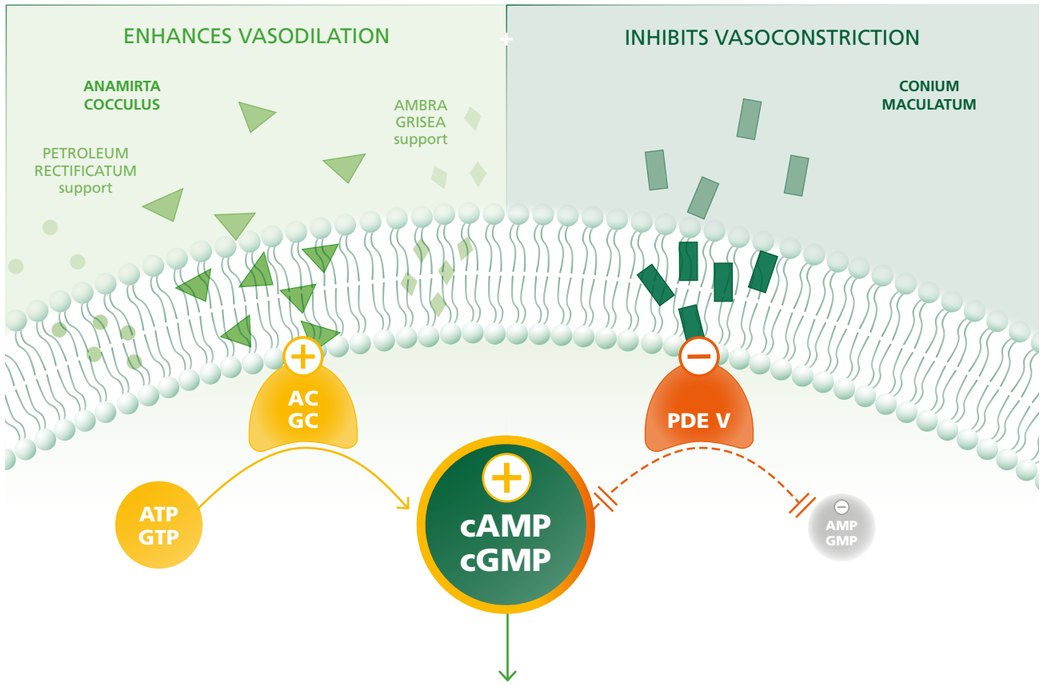
3.1.1 DUAL MECHANISM OF ACTION FOR THE IMPROVEMENT OF MICROCIRCULATION

Impaired blood flow in the smallest vessels (microcirculation disorders) play a major role in conditions such as hypertension, arteriosclerosis (atherosclerosis), myocardial infarction, diabetes mellitus, edema as well as a vertigo.

The endothelium with its exocrine, paracrine, and metabolic functions is crucial for regulating blood pressure and maintaining microcirculation. Vasorelaxation is characteristically mediated via cyclic nucleotide signalling in vascular smooth muscle cells, i.e. by stimulation of the second messengers cAMP and cGMP via adenylate cyclase (AC), guanylate cyclase (GC) and the phosphodiesterases V (PDE V).[20]

In vitro studies performed with cell cultures demonstrate the dual mechanism of action of the active ingredients in Vertigoheel® (*Anamirta cocculus, Conium maculatum, Ambra grisea, and Petroleum rectificatum*) on adenylate cyclase (AC) and phosphodiesterase V (PDE V).[20] *Anamirta cocculus* induces dose-related stimulation of the *in vitro* activity of adenylate cyclase (AC), a membrane-bound enzyme which forms cAMP from ATP after suitable activation. *Conium maculatum* induces dose-related inhibition of the *in vitro* activity of the enzyme phosphodiesterase V, an enzyme that cleaves phosphodiester bonds and breaks down cGMP to GMP (Figure 5).

Figure 4. Second messenger activity improves vestibular microcirculation[20, 21]



THE REGULATION OF SECOND MESSENGER ACTIVITY IMPROVES MICROCIRCULATION

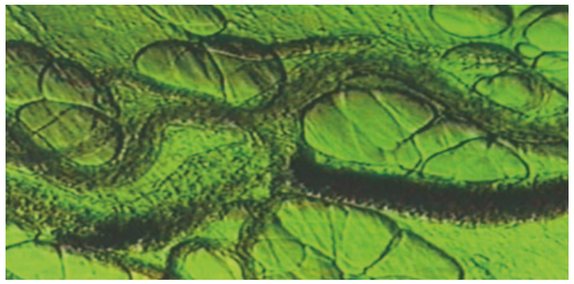
AC Adenylate cyclase
GC Guanylate cyclase
PDE Phosphodiesterase
ATP Adenosine triphosphate
GTP Guanosine triphosphate
cAMP Cyclic adenosine monophosphate
cGMP Cyclic guanosine monophosphate
AMP Adenosine monophosphate
GMP Guanosine monophosphate

3.1.2 MICROCIRCULATORY EFFECTS OF VERTIGOHEEL® IN HUMANS

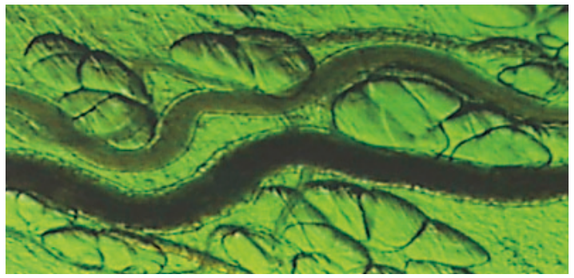
The microcirculatory effects of Vertigoheel® were established in an intravital microscopic study in patients with mild vertigo. In this study, an intravital microscope equipped with a combined reflected/transmitted light system was used to observe the microcirculation in accurately defined areas of the subcutis. The images for evaluation were provided by a computer-assisted image construction and processing system.[21]
Compared to the control group, Vertigoheel®-treated patients showed significant improvements in relevant microcirculatory parameters in the test areas as early as four weeks after starting therapy.[21]

Figure 5. Improved microcirculation

HIGH-SPEED CAMERA IMAGES OF MICROCIRCULATION IN PRECISELY DEFINED LOCATIONS DEMONSTRATE EFFECT ON MICROCIRCULATION



Vascular network at baseline.



Vascular network after 12 weeks.

After 12 weeks' treatment, arteriolar and venular erythrocyte flow rates were substantially increased (Figure 5). In addition, the following favorable effects were observed:

- Increase in perfused junctions in the network of microvessels
- Slight decrease in hematocrit
- Increase in partial pressure of oxygen
- Increase in vasomotion
- Increase in the number of leukocytes adhering to the venular wall
- Increase in the local concentration of intracellular adhesion molecule 1 (ICAM-1)

This intravital microscopic study shows the favorable impact of Vertigoheel® on microcirculatory parameters in patients with mild vertigo.[21]

4. Clinical Efficacy

Numerous scientific studies including randomized clinical trials, noninterventional studies reflecting use in day-to-day patient care, and meta-analysis of clinical trials have evaluated the clinical efficacy of Vertigoheel®.

Table 3. Main Vertigoheel® comparative clinical studies

Author	Comparator	Design	Result
Weiser et al. 1998[22]	Betahistine	Randomized double-blind	Proven therapeutic equivalence with betahistine Significant improvement of quality of life
Weiser et al. 2000[23]	Betahistine	Open	Proven therapeutic equivalence with betahistine
Issing et al. 2005[24]	Ginkgo biloba	Randomized double-blind	Proven therapeutic equivalence with *Ginkgo biloba* in atherosclerosis-related vertigo
Wolschner et al. 2001[25]	Dimenhydrinate	Open	Proven therapeutic equivalence with dimenhydrinate
Schneider et al. 2005[26]	Various	Metaanalysis	Results of individual studies confirmed

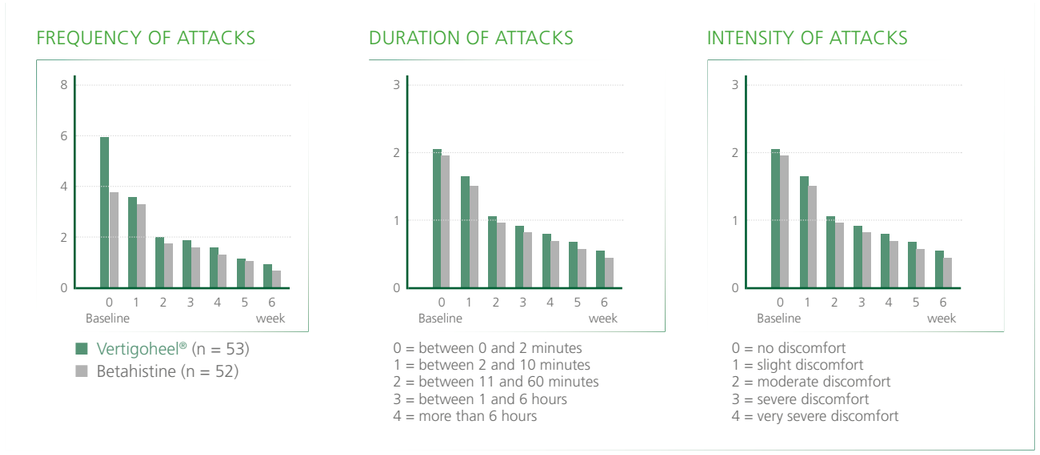
4.1 VERTIGOHEEL® VS. BETAHISTINE

A randomized, double-blind, controlled trial compared the efficacy and safety of Vertigoheel® with those of betahistine.[22]

The trial enrolled 119 patients with vestibular vertigo including rotational vertigo, positional vertigo, height vertigo or post-concussion vertigo, and/or vasomotor dizziness, caused by impaired blood flow. Patients took either 15 drops of Vertigoheel® three times daily or betahistine 18 mg/day taken in 3 divided doses, for 42 days.

Primary efficacy was assessed in terms of the observed reduction in the frequency, duration, and intensity of vertigo attacks scored using a 5-point rating scale (from 1 = no symptoms to 5 = worsened) at 3, 7, 14, and 42 days. Secondary efficacy was assessed using a dizziness-specific quality-of-life questionnaire at baseline and at 42 days.

Figure 6. Efficacy of Vertigoheel® vs. betahistine



The efficacy-related therapeutic equivalence of Vertigoheel® to betahistine was established. Both treatments reduced the frequency, duration, and intensity of vertigo attacks over the 6-week study period (Figure 6). Ninety percent of patients reported good or excellent tolerability of Vertigoheel®. In both treatment groups more than 70% of the patients experienced a significant improvement of their quality of life.

4.2 VERTIGOHEEL® VS. BETAHISTINE

Two noninterventional studies evaluated the efficacy and tolerability of Vertigoheel® versus betahistine.[23]

A total of 112 physicians (mostly GPs and otolaryngologists) participated and documented treatment data from 229 Vertigoheel® patients and 292 betahistine patients. Key causes of dizziness/vertigo in both studies were arteriosclerosis, degenerative spine disease, hypertension, hypotension, and heart failure.

Both treatments achieved significant and clinically relevant reductions in the frequency, duration, and intensity of vertigo attacks. In the treating doctors' judgment, 89% of all Vertigoheel® patients and 90% of betahistine patients felt much better or were free from symptoms upon completion of treatment.

4.3 VERTIGOHEEL® VS. *GINKGO BILOBA* EXTRACT

A prospective, randomized, double-blind parallel-group study compared the effect of Vertigoheel® with that of *Ginkgo biloba* extract in 170 elderly patients from 60 to 80 years of age suffering from atherosclerosis-related vertigo.[24]

Patients received 2 Vertigoheel® tablets three times daily or 1 *Ginkgo biloba* extract tablet plus 1 placebo tablet three times daily for 8 weeks. The combined primary endpoint assessed changes from baseline to week 6 in overall quality of life and mean daily frequency, intensity, and duration of vertigo episodes.

Over a treatment period of 6 weeks symptoms improved in both treatment groups. Efficacy was rated as "very good" by 24.1% of the patients in the Vertigoheel® group and 16.0% in the *Ginkgo biloba* group. Tolerability was rated as "very good" by 88.5% of the patients in the Vertigoheel® group and 79% in the *Ginkgo biloba* group.

The study established the therapeutic equivalence of Vertigoheel® to *Ginkgo biloba* extract in the treatment of atherosclerosis-related vertigo.

4.4 VERTIGOHEEL® VS. DIMENHYDRINATE

A reference-controlled cohort study with 774 patients compared the efficacy and tolerability of Vertigoheel® with that of dimenhydrinate in dizziness/vertigo of various origins.[25]

The patients received Vertigoheel® (typically 2 to 3 tablets three times daily) or dimenhydrinate (50 mg two or three times daily) for a maximum of 8 weeks. Most patients had non-vestibular dizziness (visual/somatosensory or psychosomatic dizziness). Presenting symptoms included unsteadiness and staggering, along with a tendency to fall. A second main group was comprised of patients with vestibular vertigo (systematic dizziness) with sensations of spinning dizziness, Menière's disease or dysequilibrium.

The mean number per day, intensity, and duration of vertigo episodes per day was reduced significantly in both treatment groups. At the end of treatment, patients in both groups were essentially free from associated symptoms of nausea, vomiting or sweating. Outcome was rated "good" or "excellent" for 88% of all Vertigoheel® patients (dimenhydrinate, 87%). Tolerability was rated "good" or "excellent" for 99% of Vertigoheel® patients (dimenhydrinate, 98%).

The study showed the therapeutic equivalence of Vertigoheel® to dimenhydrinate-containing products in the management of dizziness/vertigo of various origins.

4.5 META-ANALYSIS OF STUDIES IN SUPPORT OF THE EFFICACY OF VERTIGOHEEL® VS. OTHER ANTIVERTIGO MEDICATIONS

The discussion below presents the results of a meta-analysis of two randomized, controlled trials and two noninterventional studies of the efficacy and tolerability of Vertigoheel® compared to other commonly used drugs.[26] The meta-analysis includes the results of the studies by Weiser,[22] Issing,[24] and Wolschner [25] presented above, as well as another noninterventional study by Weiser.[23]

Table 3. Studies included in the meta-analysis

	Study 1	Study 2	Study 3	Study 4
Study type	Clinical study N = 105	Clinical study N = 154	Cohort study N = 477	Cohort study N = 652
Design	Double-blind randomized	Double-blind randomized	Open Propen score	Open Propen score
Reference	Betahistine	*Gingko biloba*	Betahistine	Dimenhydrinate
Indication	Dizziness of various origins	Senile dizziness	Dizziness of various origins	Dizziness of various origins
Treatment duration	6 weeks	8 weeks	8 weeks	8 weeks
Response criteria	Number, duration and intensity of dizzy spells	Ditto	Ditto	Ditto

A total of 1,388 patients participated in those studies, and 635 of these patients were treated with Vertigoheel® and 753 with a comparator medication (betahistine, dimenhydrinate, *Ginkgo biloba* extract). Primary efficacy endpoints across all studies were improvements in the number, intensity, and duration of daily dizziness/vertigo attacks. The duration of treatment (6 to 8 weeks) and dosage are considered similar across studies.

Studies differed in terms of patient age and baseline characteristics (number of daily attacks). To allow for these differences, individual changes in the number, intensity, and duration of attacks were adjusted to the same age and identical baseline data (grand mean across studies) for the meta-analysis. ANOVA (with studies as the random factor) revealed neither a significant impact of study on adjusted changes nor a study-by-treatment effect interaction. The studies were thus considered as comparable.

Table 4. Results of the meta-analysis of 4 clinical studies

+ = Equivalence of Vertigoheel® ++ = Superiority of Vertigoheel®	Number of dizzy spells	Duration	Intensity
Study 1 / Betahistine	+	+	+
Study 2 / *Ginko biloba*	+	+ +	+
Study 3 / Betahistine	+	+	+
Study 4 / Dimenhydrinate	+	+	+
Meta-analysis	+	+ +	+

Equivalent improvement with Vertigoheel® and the respective comparator treatment was established on all three outcome measures (reduction in mean number of episodes, reduction in mean duration, and reduction in mean intensity).

The meta-analysis confirmed the results of the individual studies showing clinically significant efficacy and tolerability for Vertigoheel® in patients with dizziness/vertigo.

4.6 QUALITY OF LIFE IN PATIENTS WITH NON-VESTIBULAR VERTIGO

The observations described above support the results of a randomized, double-blind study of the quality of life of patients with acute or chronic vertigo/dizziness of various origins. [29]

A total of 119 patients were enrolled in the trial and received 15 drops of Vertigoheel® or 6 mg of betahistine three times daily for 6 weeks.

Quality of life was assessed using the SF-36 Health Survey. This patient questionnaire captures patient outcomes relating to health-related quality of life and comprises the following categories:

- Physical function
- Role physical
- Role emotional
- Social function
- Bodily pain
- Mental health
- Vitality
- General health

Patients completed the SF-36 Health Survey and a vertigo-specific patient questionnaire capturing vertigo symptoms and associated symptoms (such as tinnitus, headache, tachycardia, nausea) and dizziness-related impairment of daily living on the first and last days of treatment.

In addition, each patient used a 5-point rating scale to keep daily records of the frequency, duration, and intensity of their vertigo episodes. The SF-36 Health Survey-captured quality-of-life data showed significant improvement in general and mental health in both treatment groups. The dizziness questionnaire demonstrated improvement in direct vertigo symptoms and associated symptoms with Vertigoheel®

5. Prescription Frequency and Safety

Vertigoheel® has been used for the treatment of dizziness/vertigo of various origins for over 40 years worldwide. Approximately 160 million daily doses sold worldwide during the period from 2004 to 2009 make Vertigoheel® one of the most frequently used vertigo medications.

Numerous scientific studies including randomized clinical trials, reference-controlled cohort studies, and meta-analyses of clinical trials confirm the efficacy and high safety profile of Vertigoheel®.[22-29]

Excellent tolerability
- No known interactions
- No sedative effects
- High acceptance across all patient populations studied

Supported by a broad evidence base and an excellent safety profile, Vertigoheel® is an established alternative to conventional therapy with synthetic chemical drugs.

Given its safety profile, Vertigoheel® appears to be particularly suitable for the treatment of vertigo of various origins, also in elderly patients.

Vertigoheel®

6. Vertigo & Risk of Falling – a Major Challenge of Aging Societies

Vertigo of various origins, a problem experienced by almost one in three over-60-year-olds, is associated with a significant risk of falling.[3, 30-33] Elderly patients in particular tend to keep their activities of daily living to a minimum for fear of falling and the associated risk of injury, resulting in significant impairment of quality of life.[31-38]

Elderly people are afraid of falling for a reason: Almost one-third of over-65-year-olds and half of those over 80 suffer at least one fall per year. In nursing homes in Germany alone, there are about one million falls each year, affecting one in two nursing home residents. Ten to 20% of all falls cause injuries, 5% result in fractures including hip fractures in 2%. Fourteen to 34% of patients suffering a hip fracture will die within one year, and 20% go on to require nursing home care.[31]

Falls among the elderly are due to numerous factors rather than to a single medical condition or functional deficit (Table 5).

Table 5. Causes of age-related fall

Age-related physiological changes	• Overall slowing of bodily functions • Reduced flexibility of the musculoskeletal system • Muscular atrophy • Loss of vision and hearing • Balance organ disorders
Diseases	• Impaired cerebral blood flow • Cerebral dysfunction • Cardiac arrhythmias • Vestibular and non-vestibular vertigo • Sensibility disorders • Paralysis • Parkinson's disease • Diseases of the musculoskeletal system
Longer reaction times	• Cognitive impairment • Decreased situation awareness • Decreased hazard awareness • Peculiarity • Misjudgments

Interventions aimed at preventing falls include psychotherapy (patient encouragement), balance retraining exercises, the treatment of a possible underlying organic disease, and the use of symptomatic drug treatments and walking aids.[31]

7. Vertigoheel® Tablets Product Information

7.1 COMPOSITION

Each tablet contains: *Anamirta cocculus* D4 210 mg
Conium maculatum D3 30 mg
Ambra grisea D6 30 mg
Petroleum rectificatum D8 30 mg
Other ingredients: Magnesium Stearate 1.5 mg
Contains lactose

7.2 INDICATIONS & USAGE

Dizziness of various origins, particularly arising from insufficient cerebral circulation (e.g. arteriosclerosis); motion sickness; tinnitus.

7.3 CONTRAINDICATIONS

Known allergy (hypersensitivity) to one or more of the ingredients. Do not use during pregnancy and lactation.

7.4 PRECAUTIONS FOR USE

No cases of overdose have been reported, and none are expected due to the homeopathic dilutions.

7.5 WARNINGS

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Do not use during pregnancy and lactation.
No effects on the ability to drive and use machines have been reported, and none are expected due to the homeopathic dilutions.

7.6 SIDE EFFECTS

Allergic (hypersensitivity) skin reactions may occur in very rare cases (i.e. affects less than 1 in 10,000 users).

7.7 DRUG-DRUG INTERACTIONS

No interactions have been reported, and none are expected due to the homeopathic dilutions.

7.8 DOSAGE & ADMINISTRATION

Unless otherwise prescribed:
Standard Dosage:
Adults:
1 tablet 3x daily.
Paediatric:
12–18 yrs.: 1 tablet 3x daily.

Acute or Initial Dosage:
Adults (and children 12 yrs. and older):
1 tablet every 1/2 to1 hr., up to 12x daily, and then continue with standard dosage.
Paediatric:
12–18 yrs.: 1 tablet every 1/2 to1 hr., up to 12x daily, and then continue with standard dosage.

Method of Administration:
Preferably allow the tablet to dissolve in the mouth, and then swallow. For children it is possible to crush the tablet and add to a small amount of water. This medicine should be taken away from meals.

7.9 HOW SUPPLIED & PACKAGE SIZES

Package Sizes:
Packs containing 50, 100 and 250 tablets

8. Summary

Vertigoheel® is a medicinal product that has been established in the treatment of dizziness/vertigo of various origins for decades.

Vertigoheel® is a multicomponent medicine containing the pharmacologically active ingredients Anamirta cocculus (Indian berries), Conium maculatum (spotted hemlock), Ambra grisea (amber), and Petroleum rectificatum (mineral oil).

Intense research into the mode of action of Vertigoheel® suggests multitarget activity for this complex homeopathic remedy. Vertigoheel® has a direct effect on the signaling pathways of vascular smooth muscle cells, thus impacting on small vessel bioregulation.

In vitro studies performed with cell cultures demonstrate the dual mechanism of action of the active ingredients in Vertigoheel® on adenylate cyclase (AC) and phosphodiesterase V (PDE 5).

Vertigoheel® is safe and effective in the treatment of dizziness/vertigo of various origins, as evidenced by numerous scientific studies including randomized clinical trials, noninterventional studies reflecting use in day-to-day patient care, and meta-analysis of clinical trials. The therapeutic equivalence of the effect of Vertigoheel® has been established in clinical trials versus alternative treatments (*Ginkgo biloba* extract) and conventional treatments (betahistine, dimenhydrinate).

The management of patients with non-vestibular vertigo tends to be a particular clinical challenge where the high safety profile of this complex remedy is especially appreciated by clinicians. Thus, there are no known interactions between Vertigoheel® and other drugs, a critical benefit in the management of elderly patients who typically need to take comedications for chronic conditions.

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