

1 Clinical benefit (efficacy and effectiveness)

Numerous scientific studies including randomized clinical trials, non-interventional studies reflecting use in day-today patient care, and meta-analysis of clinical trials have evaluated the clinical benefit of Vertigoheel® (Table 7).

Table 7. Main Vertigoheel® comparative clinical studies

Author	Comparator	Design	Results
Weiser et al. 1998 ⁴¹	betahistine	Randomized Double-blind	Proven therapeutic equivalence with betahistine. Significant improvement of quality of life
Weiser et al. 2000 ⁴²	betahistine	Non-interventional	Therapeutic equivalence with betahistine demonstrated
Issing et al. 2005 ⁴³	Ginkgo biloba	Randomized Double-blind	Proven therapeutic equivalence with Ginkgo biloba in atherosclerosis-related vertigo
Wolschner et al. 2001 ⁴⁴	dimenhydrinate	Non-interventional	Therapeutic equivalence with dimenhydrinate demonstrated
Schneider et al. 2005 ⁴⁵	Various	Meta-analysis	Results of individual studies confirmed

1.1 Vertigoheel® vs. betahistine

A randomized, double-blind, controlled trial compared the efficacy and safety of Vertigoheel® with betahistine.⁴¹

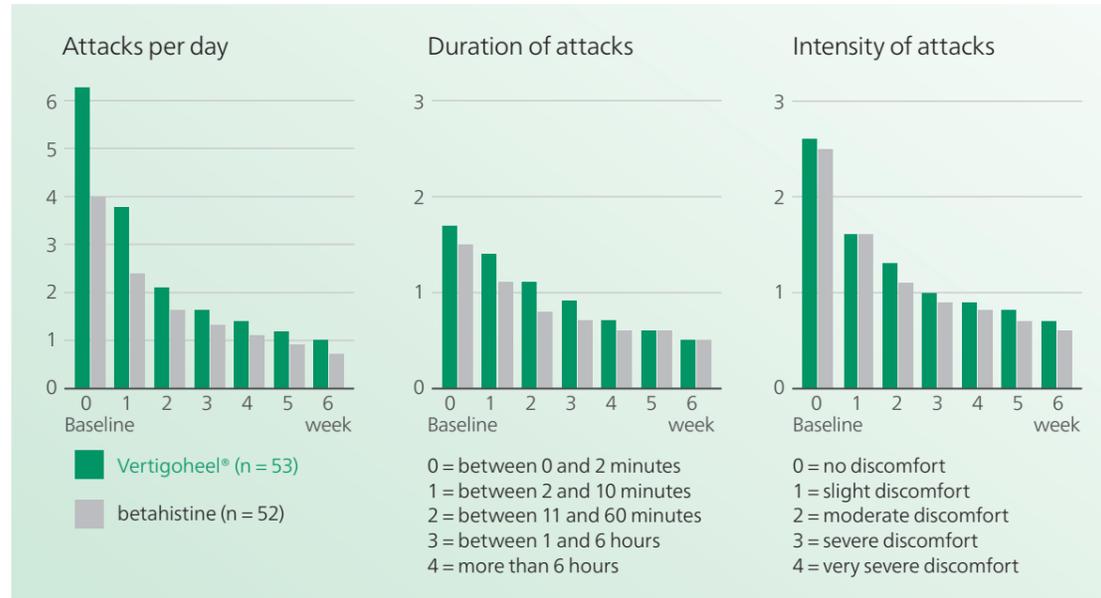
The trial enrolled 119 patients with vestibular vertigo including rotational vertigo, positional vertigo, height vertigo or post-concussion vertigo, and/or vasomotor dizziness, caused by impaired blood flow. Patients took either 15 drops of Vertigoheel® three times daily or betahistine 18 mg/day taken 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 at 3, 7, 14, and 42 days (Figure 6). Secondary efficacy was assessed using a dizziness-specific quality-of-life questionnaire at baseline and at 42 days.

Key Fact

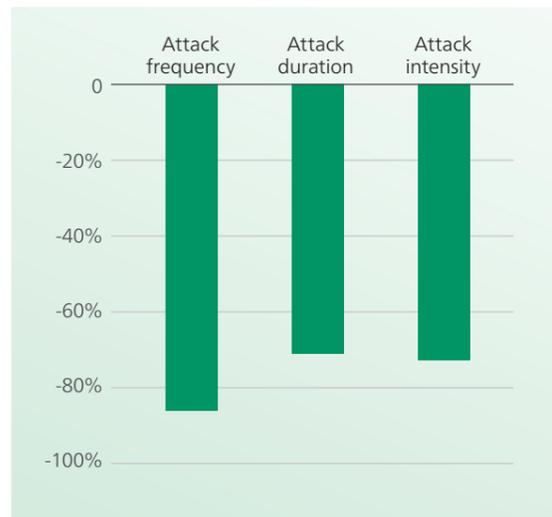
Numerous scientific studies have evaluated the clinical benefit of Vertigoheel®

Figure 5. Efficacy of Vertigoheel® vs. betahistine (graph adapted from Weiser 1998)⁴¹



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 5). More than 90% of patients reported good or excellent tolerability of Vertigoheel® and betahistine. In both treatment groups more than 70% of the patients experienced a significant improvement of their quality of life (Figure 6).

Figure 6. Reduction of attacks of vertigo of various origins by Vertigoheel® (graph adapted from Weiser 1998, data at 6 weeks)⁴¹



1.2 Vertigoheel® vs. betahistine

Two non-interventional studies in parallel evaluated the effectiveness and tolerability of Vertigoheel® versus betahistine.⁴²

A total of 112 physicians (mostly GPs and otolaryngologists) participated and documented treatment data of 229 Vertigoheel® patients and 292 betahistine patients. The patients suffered from peripheral or central vestibular vertigo or non-vestibular vertigo.

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. The compliance of the patients were rated by the physicians as good or very good in more than 90% of the patients for Vertigoheel® and betahistine.

1.3 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.⁴³

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. The reduction in frequency, intensity, and duration is shown in figure 7 below.

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.

Key Fact

Vertigoheel® reduces the frequency, duration and intensity of vertigo attacks by >70%

Figure 7. Average frequency, duration and intensity of vertigo episodes as rated over six weeks treatment with Vertigoheel® or Ginkgo biloba⁴³



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

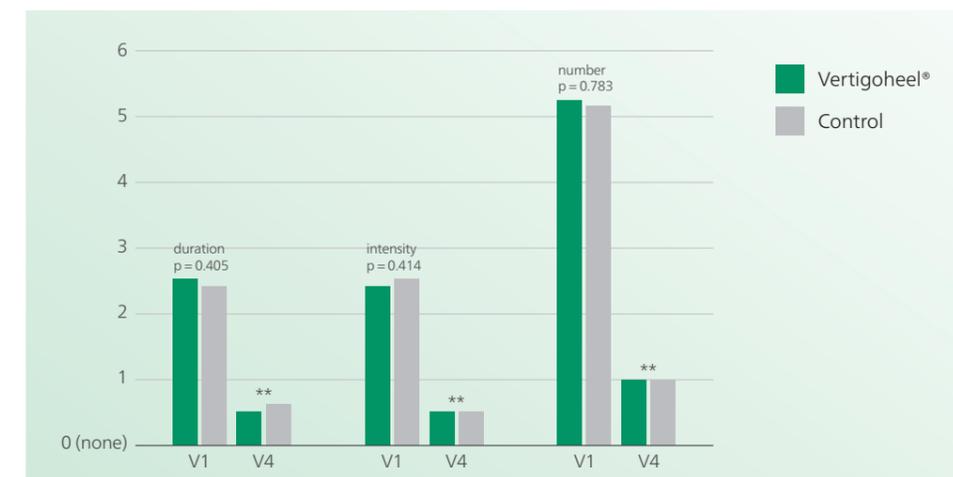
1.4 Vertigoheel® vs. dimenhydrinate

A reference-controlled cohort study with 774 patients compared the effectiveness and tolerability of Vertigoheel® with that of dimenhydrinate in vestibular or non-vestibular vertigo of various origins.⁴⁴

The patients received Vertigoheel® (typically 2 to 3 tablets three times daily) or dimenhydrinate (mostly 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 with sensations of spinning vertigo or postural vertigo. Roughly 1/3 of the patients with vestibular vertigo were diagnosed for Menière’s disease.

The mean number of vertigo attacks per day, intensity, and duration of vertigo episodes per day was reduced significantly in both treatment groups at the end of treatment (approx. 80 % for number of vertigo attacks and more than 70 % for intensity and duration, see figure 8). Within the first week of treatment roughly half of the patients reported an improvement. 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%).

Figure 8. Average frequency, duration and intensity of vertigo episodes as rated over a maximum of 8 weeks treatment with Vertigoheel® or dimenhydrinate (V1 baseline V4 final visit)



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

Key Fact

Vertigoheel® has been shown to be therapeutically equivalent to existing therapies

1.5 Meta-analysis of studies in support of the clinical benefit (efficacy & effectiveness) of Vertigoheel® vs. other antivertigo medications

The discussion below presents the results of a meta-analysis of two randomized controlled trials and two non-interventional studies of the efficacy, effectiveness and tolerability of Vertigoheel® compared to other commonly used drugs.⁴⁵ The meta-analysis includes the results of the studies by Weiser et al. 1998; Issing et al. 2005; Wolschner et al. 2001 presented above, as well as another non-interventional study by Weiser & Strösser 2000 (Table 8).⁴¹⁻⁴⁴

Table 8. Studies included in the meta-analysis

	Study 1 Weiser 1998 ⁴¹	Study 2 Issing 2005 ⁴³	Study 3 Weiser & Strösser 2000 ⁴²	Study 4 Wolschner et al. 2001 ⁴⁴
Study type	Clinical trial N = 105	Clinical trial N = 154	Non-interventional study N = 477	Non-interventional study N = 477
Design	Double-blind randomized	Double-blind randomized	Open	Open
Reference	betahistine	Ginkgo biloba	betahistine	dimenhydrinate
Indication	Vertigo of various origins	Atherosclerosis related-vertigo	Dizziness of various origins	Vestibular and non-vestibular vertigo
Treatment duration	6 weeks	8 weeks	8 weeks (mean)	8 weeks (maximum)
Response criteria	Number, duration and intensity of daily vertigo episodes			

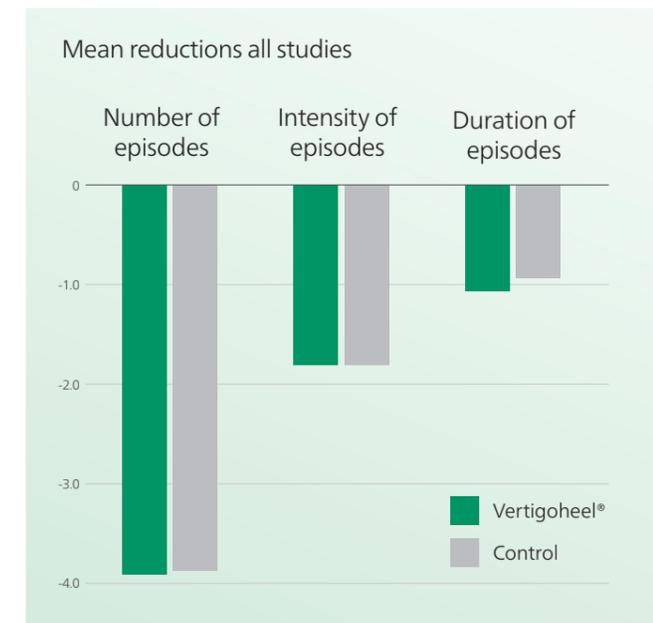
A total of 1,388 patients participated in those studies, and 635 of these patients were treated with Vertigoheel® and 753 with a comparator medication (betahistine, dimenhydrinate, Ginkgo biloba extract). Primary endpoints across all studies were improvements in the number, intensity, and duration of daily vertigo/dizziness 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 number of daily attacks. The individual reductions were adjusted to the mean age and baseline values of the study by a covariance analysis. The studies were considered as comparable.

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, see figure 9).

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

Figure 9. Meta-analysis of all four studies with the key parameters number, intensity, and duration of episodes (mean reduction of intensity and duration on a scale 0-4)



Key Fact

A meta-analysis confirmed results of individual studies showing positive results for Vertigoheel®

1.6 Quality of life in patients with 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.⁴⁶

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 functioning
- Role-physical
- Bodily pain
- General health
- Vitality
- Social functioning
- Role-emotional
- Mental health

Patients completed the SF-36 Health Survey and a vertigo-specific patient questionnaire with 4 categories capturing vertigo symptoms, intensity of vertigo during specific activities, vertigo associated symptoms (such as tinnitus, headache, tachycardia, nausea) and vertigo-related limitations of daily activities on the first and last days of treatment.

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 all 4 categories in both treatment groups which corresponds to positive change in quality of life.

Key Fact

Vertigoheel® demonstrates efficacy, good tolerability and quality of life benefits

1.7 Observational studies involving a large patient population demonstrated effectiveness and safety of Vertigoheel®

Two observational studies have been performed in large patient population:

Study 1.

In an observational study 3386 patients suffering from vertigo originating from various causes were documented by 487 physicians from different specialist areas. The documentation of the vertigo symptom complex was in accordance with the data acquisition form published as the Neurootological Case-History Questionnaire (Neurootological Data Evaluation-Claussen, NODEC).

Therapeutic success with the assessment very good, good, or satisfactory was achieved for 91.9% of the cases.

The tolerability of the preparation was judged as very good. Many patients had concomitant diseases and concomitant medications respectively (51.7 %).⁴⁷

Study 2.

In a study over 9 months 493 hypertensive patients older than 50 years (mean 76 years) with vertigo were observed in 106 general practices in Germany. Effectiveness was evaluated by physician and patient assessment of overall symptomatic improvement (Likert scale) as well as number, duration and intensity of vertigo attacks.

Clinically relevant symptomatic improvements were reported for 82% of the subjects. 80% vertigo attacks lasting >2 minutes at baseline were reduced to 26% at last observation. The majority of physicians (87%) as well as patients (90%) judged the overall effectiveness as 'very good' or 'good'. The treatment was well tolerated.⁴⁸

In patients with concomitant diseases especially hypertension, Vertigoheel® demonstrated effectiveness and good tolerability.

1.8 Vertigoheel® in the guidelines

The Vertigoheel® clinical studies have been under review for medical guidelines in Germany and Spain.

The German Society for General Medicine and Family Medicine ("Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin, DEGAM") has issued Guideline S3 for acute vertigo in General Practice.

This guideline refers to the meta-analysis by Schneider et al., 2005 (level Ia evidence).⁴⁵ It states that Vertigoheel® has the same efficacy as betahistine in an equivalence study in patients with unspecific vertigo.⁴⁹

The Spanish Society of Primary Care Physicians (Sociedad Española de Médicos de Atención Primaria, SEMERGEN) has recommended Vertigoheel® as a bioregulatory medicine for vertigo.⁵⁰