

**Betahistine dihydrochloride or betahistine mesilate: two sides of the same coin or two different coins****Avijit Hazra\*, Niteeka Maroo**

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**ABSTRACT**

The antivertigo drug betahistine exerts a histamine modulatory action in the vestibular system and the brain. It is marketed both as the dihydrochloride and the mesilate salt in India. We conducted a published literature based systematic review to ascertain differences, in any, between the salt and ester forms of the drug. Search of the Medline database was supplemented by searching through references in full text papers and retrieving summary of product characteristic literature. Although the weight of published evidence is greater for betahistine dihydrochloride, in the absence of head-to-head studies comparing the efficacy of the two formulations in Ménière's disease and other vertigo disorders of vestibular origin, it is not possible to conclude that there are definite differences in this regard. However, potentially relevant differences exist to suggest that the two forms are not interchangeable for the treatment of vestibular dysfunction. Molecular weight comparison indicates that the pill burden would be higher for betahistine mesilate for delivering equivalent doses. There could be ethnically influenced differences in pharmacokinetic behavior. There are concerns of potential long-term DNA toxicity due to mesilate ester contaminants during production of betahistine mesilate, which is not there for the hydrochloride form. Detailed post-marketing surveillance data exists only for the dihydrochloride salt. Otorhinolaryngologists and other physicians seeking to optimize treatment with betahistine should be aware of these differences.

**Keywords:** Betahistine dihydrochloride, Betahistine mesilate, Ménière's disease, Vertigo, Vestibular dysfunction

**INTRODUCTION**

An active pharmaceutical ingredient may be used not only in different dosage forms but also in chemical variants such as different salts, esters, states of hydration, stereoisomers and so on. Selection of the salt or ester form is generally made in early development during the preformulation stage as it may impact on the physicochemical properties of the product, in particular crystal form, solubility, hygroscopicity, chemical stability and dissolution rate. There may also be differences in bioavailability with different salt or ester forms of a drug. Clarification of these seemingly minor differences may,

on occasions, be helpful for physicians seeking to optimize treatment and minimize risk and inconvenience to the patient.

Betahistine is a histamine modulatory drug used for the treatment of vertigo of Ménière's disease and other disorders of vestibular origin.<sup>1</sup> Two salt formulations of the drug are currently being marketed in India- betahistine dihydrochloride and betahistine mesilate. Prompted by queries from otorhinolaryngology colleagues, regarding differences between the two, we thought it worthwhile to conduct a comparative review of these two salt forms. To the best of our knowledge, this is

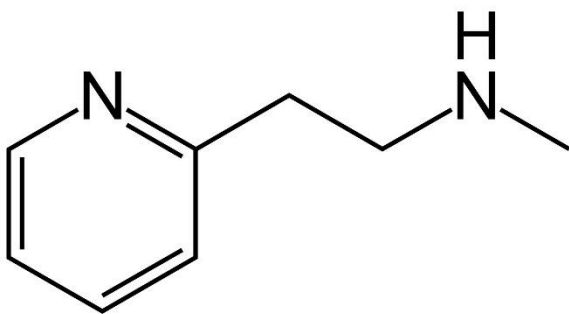
the first review looking at differences of potential clinical significance between these two betahistine forms.

## METHODS

We conducted a Medline search for peer-reviewed publications covering the period till May 2016 using the keywords 'betahistine dihydrochloride', 'betahistine mesilate', 'betahistine mesylate', 'betahistine', 'vertigo' and 'vestibular dysfunction'. Searches were refined with the search limits 'animals', 'humans', 'randomized controlled trial', 'clinical trial', 'meta-analysis' and 'practice guideline' in order to identify papers of relevance to us. Full texts were retrieved through the Science Direct gateway and by contacting colleagues with full text access to concerned journals. Further articles of relevance were found using the reference citations in full text papers. Summary of product characteristic (SPC) literature available online were verified by contacting the manufacturer of betahistine in India. Few Russian and Chinese language articles of relevance were located. Information from English language abstracts of these articles were used.

## HISTORICAL PERSPECTIVE AND PHYSICO-CHEMICAL DIFFERENCES

Betahistine [N-methyl-2-(pyridin-2-yl) ethylamine; molecular formula  $C_8H_{12}N_2$ ; molecular mass 136.19 g/mol; ATC code N07CA01- belonging to class antivertigo preparations] is a structural analogue of histamine. It was first introduced for the symptomatic treatment of vascular and vasomotor disorders such as cluster headaches and vascular dementia.<sup>2</sup> Subsequently it was used in Ménière's disease and has been explored in other vertigo disorders of central and peripheral origin such as multiple sclerosis and motion sickness.<sup>3,4</sup> The structure of betahistine is depicted in Figure 1.



**Figure 1: Structure of betahistine.**

Betahistine dihydrochloride [N-Methyl-2-(2-pyridyl) ethylamine dihydrochloride; molecular formula  $C_8H_{12}N_2 \cdot 2HCl$ ; molecular mass 209.12g/mol] was the first betahistine salt to be developed and approved for clinical use- in Canada in 1968. It was subsequently registered in Europe in 1970 for the treatment of

Ménière's disease. It is currently registered in over 110 countries worldwide. Betahistine mesilate [N-methyl-2-(pyridin-2-yl) ethylamine dimethanesulfonate; molecular formula  $C_8H_{12}N_2 \cdot 2(CH_4O_3S)$ ; molecular mass 328.41g/mol) was first marketed in 1969 in Japan and is now marketed in several countries worldwide. The mesilate form of betahistine was introduced for treating dizziness and the feeling of dizziness resulting from Ménière's disease and vertigo.

Thus two formulations of betahistine are currently available for prescription use. Firstly, there is betahistine dihydrochloride (brand names of innovator company Abbott include BETASERC<sup>®</sup>, SERC<sup>®</sup>, VERTIN<sup>®</sup>) which is indicated (with slight variations depending on the country) for the treatment of vertigo, tinnitus and hearing loss associated with Ménière's syndrome and also vertigo of other causes, with a maximum recommended dose of 16 mg thrice daily.<sup>5</sup> Secondly, betahistine mesilate (brand name of innovator company Eisai Pharmaceuticals being MERISLON<sup>®</sup>) which is indicated for dizziness and feeling of dizziness resulting from Ménière's disease, Ménière's syndrome and vertigo, with a maximum recommended dose of 12 mg three times a day.<sup>6</sup>

## ACTIVITY OF BETAHISTINE

Betahistine's mechanism of action is only partly known. Various potential effects have been suggested based on preclinical as well as clinical studies. Through its histaminergic action, it may improve microcirculation of the inner ear labyrinth and cochlea and reduce endolymphatic pressure.<sup>1</sup> The parent drug as well as two metabolites, aminoethylpyridine and hydroxyethylpyridine (but not the major metabolite pyridylacetic acid), have been shown to increase cochlear blood flow in guinea pig model.<sup>7</sup> Betahistine is a partial histamine  $H_1$  receptor agonist and a potent  $H_3$  receptor antagonist.<sup>8,9</sup>  $H_3$  receptors exhibit constitutive activity, and recent data suggest that  $H_3$  receptor antagonists actually act as inverse agonists. The therapeutic effects of betahistine may result from enhancement of histaminergic neuronal activity through inverse agonism at presynaptic  $H_3$  autoreceptors.<sup>10</sup> An  $H_4$  receptor has been cloned recently and shown to be co-expressed with  $H_3$  receptors in vestibular neurons in the Scarpa's ganglion.<sup>11,12</sup> Its modulation may also influence vestibular system function and betahistine may work through combined  $H_3$  and  $H_4$  receptor effects.<sup>12</sup> Besides having a vascular action in the inner ear, betahistine also exerts modulatory effects in the central nervous system and may exert excitatory effects on neuronal activity in cortical and subcortical structures.<sup>12</sup> It interacts strongly with the histaminergic system to increase histamine synthesis and release in the tuberomammillary nuclei of the posterior hypothalamus. These latter effects are consistent with the concept of a neuromodulatory role that histamine plays in the regulation of vestibular function both centrally and peripherally.<sup>12</sup>

Taken together, these properties underlie the currently approved use of betahistine in Ménière's disease, a vestibular disorder characterized by the triad of vertigo, tinnitus and hearing loss, and in the symptomatic treatment of vestibular vertigo.<sup>13</sup> Clinical efficacy has been demonstrated in multiple double-blind, randomized, placebo or active controlled studies performed in diverse patient groups.<sup>14-17</sup>

In recent years, histamine has emerged as a key neurotransmitter in the regulation of feeding behavior and betahistine has been proposed as a treatment for obesity.<sup>18</sup> However, a recent randomized placebo-controlled trial of betahistine dihydrochloride in obese women failed to show change in either appetite or food intake.<sup>19</sup> Interestingly this appetite reducing role of betahistine is re-emerging lately with experimental and clinical evidence of successful use of betahistine in ameliorating weight gain associated with the widely used antipsychotic drug olanzapine.<sup>20,21</sup>

### MANUFACTURING ASPECTS

Mesilate salts are alternative to conventional hydrochloride salts because they help to obtain crystalline forms of amine containing drugs like betahistine, have higher solubility and may offer higher bioavailability.<sup>22</sup> Preclinical studies show that certain mesilate esters (e.g. methyl methanesulfonate, ethyl methanesulfonate or isopropyl methanesulfonate) are potentially toxic substances by virtue of DNA alkylation; they can form reactive, direct-acting intermediates that are potentially genotoxic and carcinogenic.<sup>22</sup> Concerns over the possible formation of such esters during the preparation of mesilate drug substances, by addition of methane sulfonic acid (MSA) to the free base dissolved in an alcoholic solvent, have led regulatory agencies to require that all applicants detail their synthetic method employed. Where necessary, the production method is to be validated to ensure that alkyl mesilates are not detectable in the final product.

Under optimal manufacturing conditions, mechanistic considerations relating mainly to the low nucleophilicity of the mesilate anion and experimental data indicate that alkyl mesilates should not form, except from MSA impurities, during mesilate synthesis.<sup>22</sup> Nevertheless, in 2008, the European Medicines Evaluation Agency (EMA) issued a directive to all marketing authorization holders for medicinal products containing mesilates (and also [di]isetonates, tosilates or besilates) to assess the risk of contamination with mesilate esters and related compounds in pharmaceuticals.<sup>23</sup> This directive on risk analysis also required disclosure of procedures related to the cleaning processes and the solvents used. It can be assumed that under this guidance mesilates can be taken without any risks. However, the status and findings of such risk assessment exercise by marketing authorization holders is currently unknown. No similar risks or concerns have emerged for the dihydrochloride salt.

### Comparison of the content of active substance and oral pharmacokinetic profile

The molecular weight of betahistine dihydrochloride is 209g/mol, while that of betahistine mesilate is 328g/mol; the molecular weight of betahistine is 136g/mol, the dihydrochloride group is 73g/mol and the mesilate group is 192g/mol. Therefore, each tablet of betahistine dihydrochloride 16 mg contains betahistine 10.4mg, equivalent to two tablets of betahistine mesilate 12mg, each containing 4.9mg betahistine. It may be noted that betahistine mesilate is currently not available in higher strength tablets, which may be a potential disadvantage with respect to the pill burden on the patient.

**Table 1: Oral pharmacokinetic profiles of betahistine dihydrochloride and betahistine mesilate.**

Parameter	Betahistine dihydrochloride <sup>24</sup>	Betahistine mesilate <sup>25</sup>
Study subjects	Indian (n = 12)	Chinese (n = 20)
Dose administered (Single dose)	24mg oral in fasting state	24mg oral in fasting state
Peak plasma concentration (C <sub>max</sub> )*	786.7ng/mL	339.4ng/mL
Time to peak plasma concentration (T <sub>max</sub> )*	≈ 0.7 hour	≈ 1 hour
Area under plasma concentration time curve (AUC <sub>0-∞</sub> )*	3524ng.h/mL	1154 ng.h/mL
Elimination half-life (t <sub>1/2</sub> )*	3.5 hours	Range: 2-11.4 hours Mean: 5.2 hours

\* This is of the principal metabolite 2-pyridylacetic acid. Betahistine itself undergoes almost complete first-pass metabolism in man so that plasma concentration of the parent drug is very low. The principal metabolite, 2-pyridylacetic acid, is pharmacologically inactive and is primarily excreted by renal route.

Following an open label trial in patients with Ménière's disease, it has been suggested that a higher dose of betahistine (as dihydrochloride) and longer-term treatment would be more effective than low dose and short-term treatment.<sup>15</sup> The maximum dose recommended for betahistine dihydrochloride according to product literature is 48 mg per day (divided in 2-3 doses). Given the possibility that higher doses of betahistine are more effective, it may be worthwhile attempting to reach the maximum recommended daily dose as optimal treatment for an individual patient. Ménière's disease and other forms of vestibular vertigo are usually chronic conditions and therefore good patient compliance is needed to re-establish the patient's functioning and quality of life. A

reduced pill burden through higher strength tablets should contribute to improved compliance.

Table 1 summarizes the pharmacokinetic differences of the two formulations. Given that both genetic and environmental factors can influence drug metabolism, it is possible that these pharmacokinetic differences in Indian and Chinese subjects relate to ethnicity.<sup>24,25</sup> Alternatively, differences may be attributable to the different chemical forms used in these two studies. Comparative studies in similar volunteer groups are needed to answer this question convincingly.

### **Comparison of clinical efficacy**

There are potentially relevant differences in the number and quality of clinical studies on the efficacy of betahistine dihydrochloride and mesilate for their licensed indications. Around 34 published studies on use of betahistine dihydrochloride in Ménière's disease were identified, along with over 20 studies in treating recurrent vertigo, in comparison to 10 studies with betahistine mesilate. No head-to-head comparison studies were located.

A meta-analysis of randomized, double-blind, parallel-group or cross-over studies on the efficacy of betahistine dihydrochloride and betahistine mesilate versus placebo in vertiginous syndromes, such as paroxysmal positional vertigo and vertigo secondary to arterial deficiency of the vertebrobasilar area (i.e., symptoms not related to Ménière's disease) has been conducted.<sup>26</sup> Of 104 publications obtained through search of Medline, EMBASE and CINAHL databases, 7 studies involving a total of 367 patients were extracted and analyzed. This meta-analysis also looked at the sub-groups identified by the experimental design (parallel or crossover design), range of dosages (32-48mg/day) and treatment duration (3 weeks to 4 months). Results confirm the therapeutic benefit of betahistine, both as dihydrochloride and mesilate, versus placebo. Clinical improvement in the pooled sample showed odds ratio of 3.52 (95% confidence interval 2.40-5.18) in favor of betahistine, while analysis of sub-groups suggests maximum efficacy with doses of 32-36mg and treatment periods of 3-8 weeks.

A more recent meta-analysis of 12 double blind, randomized, placebo controlled trials with betahistine in Ménière's disease or vestibular vertigo reached a similar conclusion.<sup>27</sup> The author used a new effect parameter, the odds of a favorable treatment outcome. For each study a separate odds ratio was estimated. All but one of the study-specific odds ratios were >1.0, implying a favorable effect of betahistine on vertigo symptoms in rest 11 studies. The pooled meta-analytical odds ratio was 2.58 (95% confidence interval 1.67-3.99). When analyzed separately, for Ménière's disease, the meta-analytical odds ratio was 3.37 (95% CI 2.14-5.29) and for vestibular vertigo, the odds ratio was 2.23 (95% CI 1.20-4.14).

### **Betahistine dihydrochloride**

The clinical efficacy of betahistine dihydrochloride in Ménière's disease in particular and vertiginous disorders in general has been documented through multiple randomized, double blind, controlled studies.

Results from a non-blinded trial in which Ménière's disease patients received either a low dose of betahistine dihydrochloride (16 or 24mg thrice daily) or a higher dose (48mg thrice daily) demonstrate the utility of the higher dose.<sup>15</sup> After 12 months of treatment the mean (median) number of attacks dropped from 7.6 (4.5) to 4.4 (2.0) ( $p < 0.001$ ) in the low dosage group, and from 8.8 (5.5) to 1.0 (0.0) ( $p < 0.001$ ) in the high dosage group. The number of attacks showed significantly greater reduction in the high dosage group. The treatment was well tolerated in both groups. Although the highest approved dose of betahistine dihydrochloride is currently 48mg/day in 2-3 divided doses, results from this study, with the caveat of its open-label design, suggest that a higher dose may provide still greater therapeutic benefit.<sup>6</sup>

A recently conducted randomized, double-blind, placebo controlled study investigated the extent to which betahistine dihydrochloride 24 mg thrice daily improved vestibular compensation in 16 Ménière's disease patients undergoing curative unilateral vestibular neurectomy (UVN).<sup>17</sup> There was statistically significant improvement with active treatment over placebo, with regards to static posturography, motion analysis and perception of verticality, at one week and at one month. These findings were corroborated by subjective vertigo scale assessment-patients on betahistine dihydrochloride became effectively normal one month after UVN compared to 3 months with placebo. Improvement in torsional eye movement was not significant.

Studies also document the benefits of betahistine dihydrochloride in vestibular dysfunction not associated with Ménière's disease. In a trial in benign paroxysmal positional vertigo, addition of betahistine to liberatory maneuvers and gradual otolith dispersal technique of Brandt and Daroff produced faster recovery compared to maneuvering alone.<sup>28</sup> Small studies also document beneficial effects in vertebrobasilar insufficiency, balance disorders following head trauma and attenuation of postoperative nausea, vomiting and dizziness after middle ear surgery.<sup>29-31</sup>

Comparative studies between betahistine and other drugs used in the management of vertigo of vestibular origin are few in number but have shown the benefits of betahistine. Albera et al, compared the effect of betahistine dihydrochloride and flunarizine on dizziness handicap in patients with recurrent vestibular vertigo, through a double-blind, randomized, multicenter study, and observed greater benefit with the former at 8 weeks.<sup>32</sup> Bodla et al, compared the efficacy and tolerability of cinnarizine 25mg with betahistine

dihydrochloride 16mg in the treatment of otogenic vertigo.<sup>33</sup> Both drugs were given thrice daily for 4 weeks. Betahistine treatment led to significantly greater improvements in mean vertigo scores compared to cinnarizine. This was evident as early as 1 week after starting treatment, and at the end of 4 weeks, betahistine decreased the intensity of vertigo symptoms about 2-fold compared with cinnarizine. Both drugs were well tolerated.

Monzani et al, reported their 10 year experience of combination treatment with betahistine and the calcium channel blocker nimodipine versus betahistine alone in the long-term treatment of Ménière's disease.<sup>34</sup> A total of 113 medical records were analyzed; 53 patients received betahistine dihydrochloride (32mg daily) for six months, and 60 patients were treated with the same regimen plus nimodipine (40mg daily) as added therapy during the same period. A moderate reduction of the impact of vertigo on quality of life was obtained in patients on betahistine, but a more pronounced effect was achieved in patients treated by combination therapy. In the latter group, better control of vertigo was seen with a greater reduction of frequency of attacks. Both protocols resulted in a significant improvement of static postural control, although a larger effect on body sway in all tests was obtained by the combination of drugs. Only the combination achieved beneficial effect with regards to tinnitus annoyance and hearing loss. The authors concluded that nimodipine represents a potential valid add-on therapy to betahistine for Ménière's disease.

Some dose comparison studies are also reported in literature. Gananca et al, conducted an open label comparison of betahistine at doses of 16 mg thrice daily and 24mg twice daily, with 60 subjects in each group, and found that efficacy and tolerability were similar in the treatment of vertigo in Ménière's disease. The treatment duration was 24 weeks.<sup>35</sup>

### ***Betahistine mesilate***

Pialoux et al, studied betahistine mesilate in patients with Ménière's disease or isolated tinnitus for efficacy/tolerance ratio.<sup>36</sup> The study was conducted in two stages - a conventional open trial, followed by a comparative crossover trial. The drug was clearly effective in relieving vertigo and associated symptoms without tolerability problems.

In a study of oral multidrug treatment for subjective tinnitus, patients were given betahistine mesilate, vitamin B complex and diazepam in combination.<sup>37</sup> After 5 weeks, 54% of patients felt treatment had been effective. Thus betahistine mesilate, as part of a multidrug treatment combination, may provide relief for some patients with tinnitus. In another study with 60 adult patients of subjective tinnitus, 30 were given betahistine mesilate and flunarizine while another 30 received Vitamin B<sub>6</sub> and flunarizine.<sup>38</sup> Tinnitus loudness matching

assessment after 1 week showed that the betahistine group fared better - the responder proportion was 65.5% compared with 39.3% among controls - a statistically significant difference. There were no serious adverse reactions. Vestibular paroxysmia is a rare episodic peripheral vestibular disorder that can cause acute short attacks of vertigo. It is generally treated by carbamazepine. Yi et al, compared carbamazepine, carbamazepine plus betahistine mesilate and oxcarbazepine plus betahistine mesilate in treating vestibular paroxysmia in a retrospective review.<sup>39</sup> After 12 weeks' treatment, the carbamazepine plus betahistine mesilate group had a greater reduction in the frequency of vertigo, vertigo duration and vertigo score than the other two groups. The oxcarbazepine plus betahistine group also did better than betahistine alone group. The authors concluded that betahistine provides useful augmentation of the effect of either carbamazepine or oxcarbazepine in the treatment of vestibular paroxysmia.

Despite the above examples, evidence of efficacy for the mesilate formulation appears to be limited compared to that available for the dihydrochloride salt. Only 6 publications over the last 10 years, on the effects of betahistine mesilate in vertigo, were identified during database searches and these are mostly Chinese language papers. On balance therefore, at the moment the weight of scientific evidence lies with betahistine dihydrochloride rather than with betahistine mesilate.

### **COMPARISON OF SAFETY**

In general, both forms of betahistine are safe. Manufacturers' product literature, heeding betahistine's role in increasing histamine levels throughout the body, warn of the possibility of hypersensitivity reactions. For both formulations, pheochromocytoma, peptic ulceration and bronchial asthma are listed as contraindications or situations requiring special precaution.

There is extensive clinical experience with betahistine dihydrochloride. Over 130 million patients in 82 countries are estimated to have used this drug since its registration in 1968.<sup>40</sup> Worldwide post-marketing surveillance data of over 35 years reveal a satisfactory safety profile.<sup>40</sup> There are no concerns of treatment-emergent carcinogenicity or genotoxicity among a total of 554 suspected adverse drug reaction (ADR) reports, spanning 994 individual signs and symptoms, reviewed by the marketing authorization holder. The principal findings are summarized in Table 2. In a more recent 3-month multicentre, open-label post-marketing surveillance study of betahistine (24mg twice daily or 16mg thrice daily) in patients with vertigo of peripheral vestibular origin, Benecke et al, reported that patients with recurrent peripheral vestibular vertigo experience improvements in objective measures of health-related quality of life with satisfactory tolerability at this dose level.<sup>41</sup> A total of 76 ADRs were recorded from 49 patients (2.4%), of which 75 were classified as mild or



moderate and 54 were possibly related to betahistine. Detailed post-marketing safety data for betahistine mesilate is not available in published form. Tolerability

issues that have been investigated are summarized in Table 2.<sup>42,43</sup>

**Table 2: Safety profiles of betahistine hydrochloride and betahistine mesilate.**

Betahistine dihydrochloride	Betahistine mesilate
<ul style="list-style-type: none"> <li>From global postmarketing safety data, skin reactions are the most frequently reported complaints.<sup>40</sup> They are usually self-limiting maculopapular rash with pruritus or urticaria, and reversible on drug withdrawal.</li> <li>One report of anaphylactoid reaction and one of Stevens-Johnson syndrome, without fatal outcome.</li> <li>Gastrointestinal complaints mostly concern nausea and vomiting or nonspecific mild abdominal pain.</li> <li>Hepatobiliary involvement includes rise in hepatic enzyme levels, without death or liver failure.</li> <li>Nervous system related ADRs are heterogeneous and do not suggest any specific profile.</li> <li>Asthma or bronchospasm has been reported 8 times.</li> <li>Four deaths are included in the postmarketing surveillance data - the causal relationship to betahistine dihydrochloride in two reports has been assessed as unrelated, in one as unlikely and in the other as not assessable.</li> </ul>	<ul style="list-style-type: none"> <li>Detailed post-marketing safety data for betahistine mesilate is not available in published form.</li> <li>Investigated for drowsiness and impact on the ability to drive machines. Effect of repeated dosing (72mg thrice daily) on low speed driving performance tests was investigated in healthy volunteers - there was no difference from placebo in any of the tests performed.<sup>42</sup></li> <li>Influence on vigilance investigated. Spontaneous brain electrical activity on the electroencephalogram, acoustic late evoked potentials, and reaction time were measured before and 90 and 180 minutes after drug intake. The drug (12mg) did not impair capacity.<sup>43</sup></li> <li>In the study of betahistine mesilate pharmacokinetics in Chinese men, all 20 subjects receiving 24mg of the drug completed the evaluation without significant vital sign changes or other treatment emergent adverse effects.<sup>25</sup></li> </ul>

Betahistine is devoid of mutagenic, carcinogenicity and teratogenic potential.

## CONCLUSION

Review of the published evidence suggests that potentially relevant differences exist between the two available forms of betahistine, the dihydrochloride and the mesilate. Therefore, it cannot be stated that the two are readily interchangeable for the treatment of vestibular dysfunction. Patient convenience and consequent adherence to treatment is a vital aspect of drug therapy, particularly in chronic diseases, and this is facilitated by reduced pill burden. Chemical structure and molecular weight comparison suggest that for delivery of equivalent dose, a patient would need to take fewer tablets of betahistine dihydrochloride than of betahistine mesilate, taking currently available formulations and maximum recommended doses into account. Although there are no reports of clinical toxicity linked to betahistine mesilate, concerns over the potential long-term DNA damage risk of contaminated mesilates remain. There is no such concern with the dihydrochloride salt. There are no notable short-term safety concerns with either form. The quantum of published clinical trials is greater for betahistine dihydrochloride. This could be due to the wider availability of this salt form. It could also be due to greater visibility of the concerned manufacturer or greater support for studies with the dihydrochloride salt. A dose effect relationship has been clearly documented only for the dihydrochloride form. However, in the absence of

head-to-head comparisons between the two, it is not possible to conclude whether there is any difference in efficacy. Nevertheless, recent trials seem to have been conducted only with the dihydrochloride salt and postmarketing surveillance activity is also greater for this form, suggesting that clinical development of betahistine dihydrochloride has progressed continuously, unlike that of the mesilate form. Otorhinolaryngologists and other physicians seeking to optimize treatment with betahistine should be aware of these differences.

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