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Original article

Post Marketing Surveillance Study to evaluate the Efficacy and Safety for the Combination of Alpha Lipoic Acid, Gingko Biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate in the Patients of Tinnitus

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Abstract

Introduction: Tinnitus is the false perception of sound. Normally it is considered to be developed due to oxidative stress to the inner ear. This study was conducted to test the efficacy and safety for the combination of Alpha lipoic acid, Gingko biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate in the patients of tinnitus. ***Method:*** The study was conducted on 165 patients out of which 142 completed the study. Efficacy was evaluated by tinnitus symptom score (TSS). Patients were asked to rate the TSS ranging from 0 to 10 where 0 means no symptom and 10 means maximum tolerable symptoms. Safety assessment was made by analysing the adverse events reported by the patient. Efficacy and safety evaluation was done on day 0, 10 and 22. ***Results:*** Patients had TSS 6.26 on baseline visit which was reduced to 4.50 at day 10 and was further reduced to 2.47 at day 22. Also, in the clinical trial duration of 22 days, only 5 episodes of the adverse drug reactions were reported by the patient and all of them were of non-serious in nature and mild in intensity. ***Conclusion:*** The fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg was found to be efficacious and safe for the treatment of Tinnitus.

Keywords: ***Tinnitus, Alpha lipoic acid, Gingko biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate.***

Introduction

Tinnitus is the perception of sound in the absence of any external stimulus [1]. Tinnitus is one of the most common and distressing otologic issue which may cause variety of somatic or psychological disorders that may negatively impact one's quality of life [2]. Concentration problems, insomnia and reduced speech discrimination are the most common associated symptoms or particular discomforts those are related to the tinnitus [3]. The discomfort that most patients with severe tinnitus experiences, makes it difficult to fall asleep and it also makes it difficult to return to sleep during periods of wakefulness during the night [4,5]. The prevalence of tinnitus is approximately 10-15% of the adult population and severity of the disease varies from mild to severe disturbance in everyday life. Oxidative stress is considered to play the important role in the pathogenesis of tinnitus as oxidative stress can lead to changes in the hair cell apoptosis, cochlear degeneration, hair cells at cellular level, changes in nerve fibres of the acoustic nerve, changes in supporting structures and stria vascularis, dysfunction of the central cortex at the cellular level and irregular neural activity in the auditory pathway. Oxidative stress activates the mitogen-activated protein kinase/c-Jun N-terminal kinase (MAPK/JNK) pathway, which subsequently leads to the release of cytochrome c from mitochondria, which causes mitochondrial membrane damage and activates caspase pathway which promotes apoptosis [6].

Oxidative stress is considered to be one of the most common cause of tinnitus [7] and antioxidants can be used for the medical management of tinnitus [8,9,10]. This study was conducted to test the efficacy and safety for the combination of Alpha lipoic

acid, Gingko biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate in Indian patients of tinnitus.

Alpha lipoic acid is a compound commonly found in mitochondria which is required for a variety of enzymatic functions in the human body [11]. The pathogenesis of tinnitus is linked to oxidative stress, which has been linked to structural changes in hair cells, hair cell apoptosis, cochlear degeneration, changes in supporting structures and stria vascularis, changes in acoustic nerve fibres, abnormal neural activity in the auditory pathway and central cortex dysfunction [12,13]. Alpha lipoic acid acts as an antioxidant and not only strengthens but also restores the intrinsic antioxidant systems and facilitates their development or cell accessibility [14]. Alpha-lipoic acid is one of the most important antioxidant that helps to protect mitochondrial function by preventing reactive oxygen species accumulation, oxidative stress and apoptotic cell death [15].

Zinc is commonly found in the cochlea and especially in the stria vascularis in the form of Copper/Zinc superoxide dismutase which is the first line of defence against the free radicle and oxidative damage. Copper/Zinc superoxide dismutase activity and stability is considered to be impaired at low levels of plasma Zinc or plasma Copper [16,17]. Also the tinnitus can be caused due to increased spontaneous neural activity including increased neural firing which can be caused due to Zinc deficiency [18]. So according to the above mentioned information the Zinc supplementation can be used for the medical management of tinnitus.

Ginkgo biloba contains monoamine oxygenase inhibitors including ginkgolide and bilobalide as well as myricetin and quercetin flavonoids. Ginkgo biloba has antioxidant and protective effects on nerve cells in the brain, auditory cortex, and subcortical field because of which it can be used for the treatment of tinnitus [19].

Magnesium has been shown to minimise noise-induced vasoconstriction, caused by the formation of free radicals. Few epidemiologic studies have shown that magnesium consumption protects against hearing loss. Antioxidants work in tandem with Magnesium intake to help reduce hearing loss [20]. Also during the study conducted by Sinan Uluyol et al it was concluded that, Magnesium deficiency can have important role in the pathophysiology of tinnitus and Magnesium supplementation can be used for the medical management of tinnitus [21].

Vitamin E is an effective free radical scavenger and a potent fat-soluble antioxidant that protects the outer hair cells from oxidative stress and lipid peroxidation. Similar to vitamin E, vitamin C is also an important water soluble antioxidant and also have free radicle scavenging activity [22]. Also vitamin B6 is an antioxidant which reduces the oxidative stress, it is also a free radicle scavenger which scavenges free radicles and inhibits the lipid peroxidation. Also vitamin B6 serves as an coenzyme in the glutathione antioxidant defence system and indirectly plays a role as an antioxidant [23].

Methylcobalamin (vitamin B12) scavenges reactive oxygen species mostly superoxide, it has important role in the preservation of Glutathione because of which it also has indirect role in the scavenging of reactive oxygen species, it also modulates the cytokine and growth factor production to offer protection from body's immune response induced oxidative stress, reduction of oxidative stress due to homocysteine and reduction of oxidative stress caused by advanced glycation end products [24]. Chromium picolinate is an antioxidant [25] and due to its antioxidant properties it can be used for the medical management of tinnitus.

This study was conducted to test the efficacy and safety for the fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg in Indian patients of tinnitus.

Methodology

This post marketing surveillance (PMS) study was conducted at eleven clinical trial sites all across India for the duration of 22 days. For the study, total 165 patients were recruited by the investigators as per the inclusion and exclusion criteria mentioned below.

Inclusion and Exclusion Criteria:

Only patients of age between 18 to 75 years with no restrictions regarding gender, ethnicity or comorbidities with confirmed diagnosis of tinnitus were recruited for the study. Also, for the study only those patients were recruited who were ready to strictly adhere to the study procedures and who have stopped taking any medication or supplements containing ALA, lipoic acid, gingko biloba, folic acid, Magnesium, vitamin E and vitamin C for at least 3 month prior to initiation of the study.

Patients hypersensitive to the ingredients of investigational product, suffering from the middle ear pathologies such as otitis media and the perforation of the tympanic membrane, patient planning to go for any surgery in the study duration, patient suffering from any disease of the middle and external ear, patients with the history of clinically significant vestibular symptoms at the discretion of the investigator, patients who cannot adhere to the Protocol including mentally ill and Patients with psychological problem or condition or disease that, in the view of the investigator, might interfere with treatment compliance, study conduct or interpretation of the results such as psychiatric disease or suicidal tendencies were excluded from the study.

Investigational product:

Investigational product used for the PMS study was the fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule. The investigational product was provided to the investigator at no cost by the sponsor and to the patients recruited in the study the investigational product was dispensed at no cost by the investigator.

Study design:

The study design was of multicentric, non-randomized, open label, non-comparative, post marketing surveillance study. As it was a multicentric study, the study was conducted at 11 clinical trial sites all across India.

Study Procedure:

All eligible patients as per the inclusion and exclusion criteria were shortlisted for the study by the investigator. All shortlisted patients were well informed about the study objective and study procedures and only patients who were ready to get recruited in the study, the signed consent was collected on informed consent form. To all the recruited patients, 22 capsules of the investigational product was provided and were advised to take it in the dose of 1 capsule a day with food. Also in the study duration, patients were strictly instructed not to take any pharmacological intervention for the

treatment of tinnitus. All the recruited patients were asked to visit the clinical trial site on day 10 (visit 2) and day 22 (visit 3) for efficacy and safety evaluation considering baseline visit (visit 1) as day 0. Investigators were asked to discontinue the Investigational product in the event of a significant adverse event and discrepancy. Patients were advised to keep a register of everyday symptoms. In the case of any safety-related complications, adverse events or severe adverse events, the investigators were authorized to remove the patient from the study and could be treated according to the severity of the symptoms.

Efficacy Assessment:

Efficacy assessment was done by tinnitus symptom score (TSS). Patients were asked to rate all their tinnitus related symptoms as tinnitus symptom score (TSS) on tinnitus symptom score scale such as ringing in the ears, screaming, humming, hissing, whistling, nausea or headache on day 0, 10 and 22. Tinnitus symptom score scale was ranging from 0 to 10 where 0 was considered as no symptom and 10 was considered as maximum symptoms. The efficacy evaluation was done on day 0, day 10 and 22. Tinnitus symptom score was further extrapolated to tinnitus symptom severity scale which was a 4-point scale including no symptom for 0 tinnitus symptom score, mild for tinnitus symptom score ranging from 1 to 3, moderate for tinnitus symptom score 4 to 6 and severe for tinnitus symptom score 7 to 10.

Safety assessment:

All the recruited patients were asked to report the adverse events and reported adverse events were analysed for safety assessment of the investigational products.

Regulatory Matters:

The investigational product was approved for manufacturing and marketing in India. The informed consent form was read and signed freely by all the patients recruited in this study.

Results

The study was conducted at 11 clinical trial sites on total 165 patients out of which 142 patients completed the study. The mean tinnitus symptom score at baseline was 6.26 which was reduced to 4.5 on day 10 (visit 2) and was further reduced to 2.47 on day 22 (visit 3). Graphical presentation of the mean tinnitus symptom score at visit 1, 2 and 3 is presented below in Figure 1.

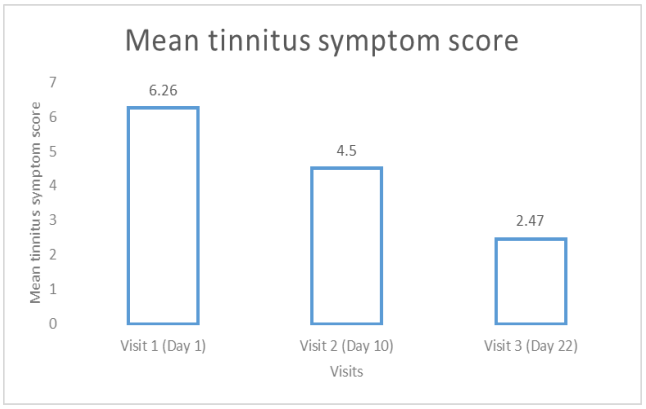

Fig.1 Mean tinnitus symptom score at visit 1, 2 and 3

At day 10 and day 22, the percentage reduction in the mean tinnitus symptom score was 28.11 % and 60.54 % respectively as compared to baseline which is graphically presented below in figure 2.

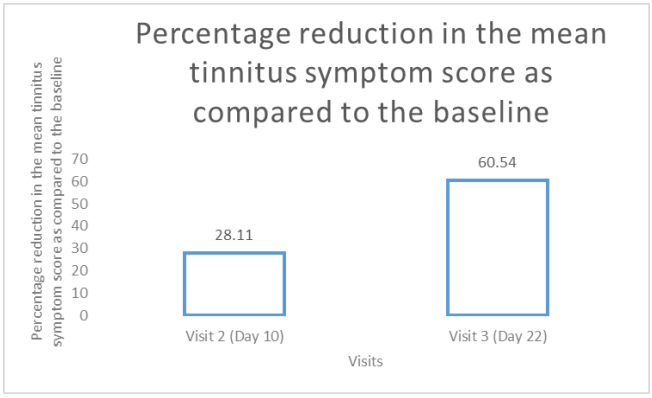

Fig. 2 Percentage Reduction in the mean tinnitus symptom score at visit 2 and 3 as compared to the baseline.

Tinnitus symptom score was further extrapolated to tinnitus symptom severity scale. At baseline visit, 71 patients had severe intensity, 55 patients were of moderate intensity and 16 patients were of mild intensity symptoms of tinnitus. On day 10, 1 patient had no symptom of tinnitus, 24 patients had mild intensity symptoms, 110 patients had moderate intensity symptoms and only 7 patients had severe intensity of tinnitus. On day 22, 25 patients had no symptom of tinnitus, 83 patients had mild intensity symptoms, 29 patients had moderate intensity symptoms and only 5 patients had severe intensity symptoms of tinnitus.

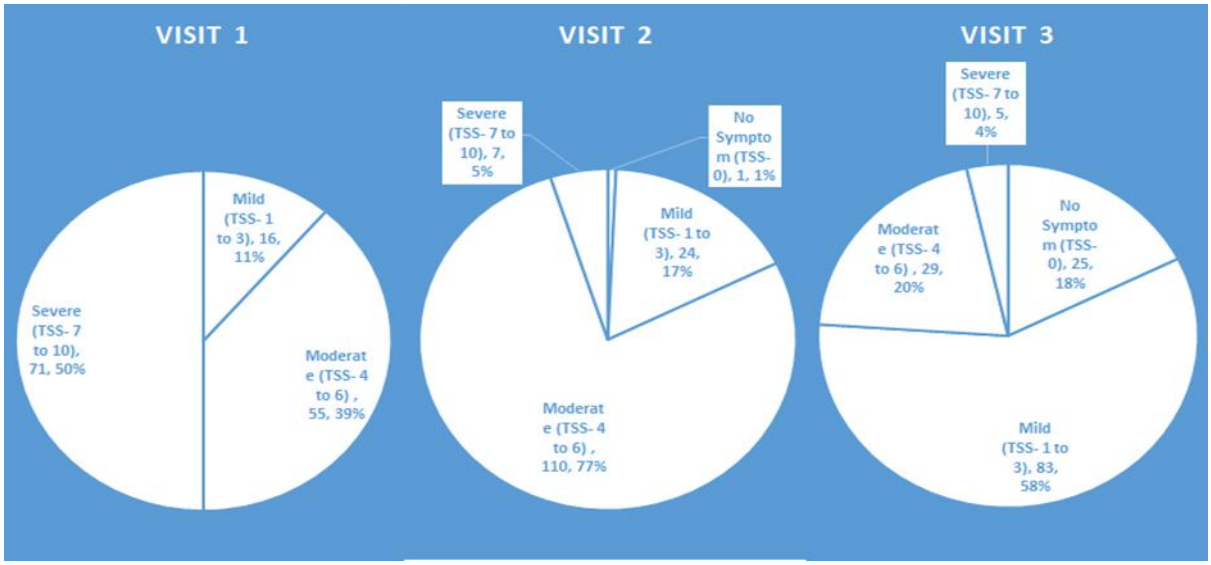

Fig.3: No. of patients with no symptom of tinnitus, mild, moderate and severe intensity symptoms of tinnitus at visit 1, 2 and 3

Safety Assessment:

In the study duration, 3 patients reported 5 episodes of adverse drug reactions which is presented in the tabular form below in the table 1.

Table 1: Adverse drug reactions along with the no. of episodes reported and the no. of patients

Adverse Event	Number of patients	Number of episodes
Skin rashes (mild intensity)	1	2
Nausea	1	1
Diarrhea	1	2

All the reported adverse drug reactions were of mild intensity and of non-serious nature.

Discussion

Tinnitus is a perception of sound in the absence of any external stimulus [1]. Tinnitus is one of the most common and distressing otologic issue which may cause variety of somatic or psychological disorders that may negatively impact one's quality of life [2]. Oxidative stress is considered to be one of the most common cause of tinnitus [7] and antioxidants can be used for the medical management of tinnitus [8,9,10]. This study was conducted to test the efficacy and safety for the combination of Alpha lipoic acid, Gingko biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate in Indian patients of tinnitus. Efficacy assessment for the study was done by tinnitus symptom score which was done by the use of 11 grade tinnitus symptom score scale ranging from 0 (no symptom) to 10 (maximum tolerable symptoms), where patients were asked to rate the tinnitus related symptoms. The mean tinnitus symptom score at day 0 was 6.26 which was reduced to 4.5 at day 10 which was a reduction of 28.11 % as compared to baseline and was further reduced to 2.47 at day 22 which was a reduction of 60.54 % as compared to baseline. Tinnitus symptom score was further extrapolated to 4-point tinnitus symptom severity scale as no symptom, mild intensity symptoms, moderate intensity symptoms and severe intensity symptoms. At baseline visit, 71 patients had severe intensity, 55 patients were of moderate intensity and 16 patients were of mild intensity symptoms of tinnitus. On day 10, 1 patient had no symptom of tinnitus, 24 patients had mild intensity symptoms, 110 patients had moderate intensity symptoms and only 7 patients had severe intensity of tinnitus. On day 22, 25 patients had no symptom of tinnitus, 83 patients had mild intensity symptoms, 29 patients had moderate intensity symptoms and only 5 patients had severe intensity symptoms of tinnitus. So according to the results we have got the, the investigational product was found be beneficial for the treatment of tinnitus to reduce the symptoms of tinnitus. Also, during the study, only 5 episodes of adverse events were reported and all of them were of non-serious in nature and mild in intensity. Below we have discussed some of the published clinical trials which supports the results of this post marketing surveillance study.

Anna I. Petridou et al. conducted a randomized, double-blind, placebo controlled clinical trial to determine the effect of antioxidant supplementation on patients of tinnitus for the clinical trial duration of 3 months. For a clinical trial, 70 patients were recruited out of which, 35 were randomized to the combination of antioxidants out of which 34 patients completed the clinical trial and 35 were randomized to placebo out of which 29 completed the clinical trial. The combination of antioxidants used in the study was the combination of Vitamin A (acetate) 781 µg (2600 iu), Magnesium (as oxide) 50 mg, Vitamin D3 10 µg (400 iu), Zinc (gluconate) 15 mg, Vitamin E (dl-alphatocopherol acetate) 100 mg (150 iu), Copper (gluconate) 1.2 mg, Vitamin C (Ascorbic acid) 150 mg, Manganese (gluconate) 4 mg, Thiamine (Vitamin B1) (mononitrate) 25 mg, Selenium (as L-Selenomethionine and sodium selenite) 100 µg, Riboflavin (Vitamin B2) 25 mg, Chromium (picolinate) 200 µg 500, Niacin (Vitamin B3) 25 mg, Molybdenum (as molybdate) 500 µg 1000, Pyridoxine (Vitamin B6) (Pyridoxine Hydrochloride) 10 mg, 714 Iodine (potassium iodide) 150 µg 100, Folic acid 200 µg 100, Choline (Bitartrate) 25 mg, Vitamin B12 10 µg 400 Inositol 25 mg, Biotin 150 µg 300 PABA 25 mg, Pantothenic acid (Vitamin B5) (calcium pantothenate) 25 mg, Grapeseed extract (GSE)(Provided by 1mg of a 500:1 extract) 500 mg, Calcium (as phosphate) 62 mg and Iron (ferrous fumarate) 14 mg. The efficacy evaluation was done by serum total antioxidant capacity, superoxide dismutase and oxidized LDL, tinnitus minimum masking level, loudness and frequency as well as scores in tinnitus handicap inventory questionnaire and visual analogue scale and tinnitus functional index (TFI) at baseline and follow-up visits. Tinnitus minimal masking level and loudness was found to be reduced from baseline to post measure ($p < 0.001$) only in the group of patients treated with the combination of antioxidants and not in the group of patients treated with placebo. Also, the improvement or the reduction was found in tinnitus handicap inventory questionnaire scare and visual analogue score only in the group of patients treated with the combination of antioxidants. Also, the significant improvement was found in superoxide dismutase, serum total antioxidant capacity and oxidized LDL in the group of patients treated with the combination which was statistically significant as compared to the group of patients treated with the placebo. It was concluded that the study combination was favourably effective for the treatment of tinnitus by reducing the tinnitus intensity and subjective discomfort [25].

N. Quaranta et al conducted a study to determine efficacy of Alpha lipoic acid for the treatment of noise induced hearing loss. The study conducted on 30 volunteers having age between 20-30 years. Volunteers recruited for the study were randomized to 3 groups as group A, B and C were exposed to noise, without administration of Alpha lipoic acid, one hour after taking 600 mg of ALA and 10 days after taking 600 mg of Alpha lipoic acid orally every day respectively. The aim of this study was to see whether alpha-lipoic acid affects the temporary threshold shift (TTS2) caused by a 3 kHz tone in young normally hearing subjects 2 minutes after the end of the exposure. Individuals were allocated to one of three classes at random. For 10 minutes, Group A (10 subjects) was exposed to a 90 dB HL 3 kHz pure sound. One hour after oral ingestion of 600 mg of ALA, Group B (10 subjects) was exposed to a 90 dB HL 3 kHz pure sound. After 10 days of oral ingestion of 600 mg of ALA, Group C (10 subjects) was exposed to a 90 dB HL 3 kHz pure sound. Leading up to the exposure, data analysis showed that the hearing levels of the three groups did not vary significantly. TTS2 of group C was slightly lower at 6 kHz (p 0.03) than TTS2 of groups A and B, and TEOAEs amplitude shift after noise exposure was lower in group C ($p = 0.089$) than in groups A and B ($p = 0.03$). In clinical practise, Alpha lipoic acid is an effective lipophilic antioxidant and free radical scavenger. A single dose of 600 mg Alpha lipoic acid did not protect the TTS2 from a 90 dB HL 3 kHz sound, but 10 days of therapeutic dosage expectation of ALA was correlated with substantial safety at 6 kHz. The findings of this study indicated that a short course of ALA protects humans from TTS2, indicated that further research

was required to better define the role of ALA in noise-induced hearing loss prevention [26].

Cevette et al. conducted phase 2, single-arm, open-label clinical trial to test the efficacy of oral Magnesium (525 mg/ day) in lessening the severity of tinnitus. The study was conducted for the duration of 3 months in 26 patients out of which 19 patients completed the study. Severity of the symptoms of the tinnitus was evaluated by using tinnitus distress rating scale ranging from 0 means no tinnitus symptoms to 10 means worst possible tinnitus symptoms. The Tinnitus Handicap Inventory (THI) was also used for the efficacy assessment was further extrapolated to 5 grade tinnitus severity scale. It was found that patient had significant improvement in the tinnitus symptoms which could be because of Magnesium supplementation [27].

As per the best knowledge of the author, this is the first study that was conducted for the fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule to test the efficacy and safety on Indian population suffering from tinnitus.

Conclusion

The fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chronium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule was found to be efficacious as well as safe for the treatment of tinnitus in Indian patients.

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Disclosure

This study was conducted as a part of Pharmacovigilance activity for investigational product whose brand name is Otocap capsules which is a fixed dose combination of Alpha lipoic acid 200 mg, Gingko biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3 mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chronium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule which is a product of Centaur Pharmaceuticals Pvt. Ltd.

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