



Safety and Efficacy for the Combination of Alpha Lipoic Acid, Gingko Biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate for the Medical Management of Age Related Hearing Loss: Post Marketing Surveillance Study

Dr. Mayuresh Kiran ¹, Mr. Lalit Pawaskar ^{*2}, Ms. Shaheen Sheikh ³, Ms. Pramita Waghambare ³

¹Vice President, Medical Services and Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd.

²Executive, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd.

³Research Associate, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd.

*Corresponding author: Mr. Lalit Pawaskar; lalit@centaurlab.com

Received 26 June 2021;

Accepted 20 July 2021;

Published 23 July 2021

Abstract

Introduction: Age related hearing loss is defined as a bilateral, progressive, symmetrical age-related sensorineural hearing loss, which is most pronounced at the higher frequencies. It is considered that oxidative stress has a central role in the pathology of age-related hearing loss so, this study was conducted to test the efficacy and safety for the combination of antioxidants for the treatment of age-related hearing loss.

Methodology: This was a multi-centric study conducted at 11 clinical trial sites. Out of total 176 enrolled, 160 trial subjects completed the study. For efficacy assessment, 2 parameters were used including hearing related quality of life score and score obtained from hearing impairment questionnaire on day 0 (visit 1), 45 (visit 2) and 90 (visit 3). **Results:** At visit 1, the mean hearing related quality of life score was 4.437 increased to 5.725 at visit 2 and further increased to 6.906 at visit 3. At visit 2 and 3, the increase in hearing related quality of life score was 29.028% and 55.645% respectively as compared to baseline. The score obtained from hearing impairment questionnaire was 25.581 at visit 1 reduced to 16.200 and further reduced to 9.943 at visit 3. **Conclusion:** The combination of Alpha lipoic acid, Gingko biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methyl cobalamin, Vitamin E and Chromium Picolinate can be used for the medical management of age related hearing loss.

Keywords: Alpha lipoic acid, Gingko biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methyl cobalamin, Vitamin E and Chromium Picolinate, age related hearing loss

Introduction

Age-related hearing loss (ARHL) which is also called as presbycusis, is the most common condition in the geriatric population. It is defined as a bilateral, progressive, symmetrical age-related sensorineural hearing loss, which is most pronounced at the higher frequencies. Age related hearing loss is the third most common health condition, which affects geriatric population after heart disease and arthritis. It is not a deadly condition but it may cause depression, social isolation, cognitive decline and/ or psychological as well as medical morbidity. Previously conducted studies of post-mortem of human temporal bones on ARHL patients suggests that, it involves a number of auditory structures including degeneration of the auditory nerve, degeneration of the mechanotransducing cochlear inner and outer hair cells and

reduced function within the stria vascularis ^[1]. In many cases of ARHL, patients go for hearing aids which has low acceptance among the patients which can be due to social, psychological or financial issues ^[2].

Oxidative stress has a central role in the pathology of age-related hearing loss because of which antioxidants can be used for the medical management of age related hearing loss ^[3]. Antioxidants including Alpha lipoic acid, Gingko biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate can be used for the medical management of age-related hearing loss. As per the best knowledge of the author the combination of the above mentioned antioxidants is not clinically tested for the efficacy and safety for the medical management of age related hearing loss because of which 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 per capsule for the medical management of age related hearing loss in Indian patients.

Zinc is a structural component of the enzyme superoxide dismutase present in the cytoplasm of cells. Superoxide dismutase is an antioxidant enzyme which exerts its antioxidant action by conversion of two superoxide radicals into molecular oxygen and hydrogen peroxide and reduces the toxicity of reactive oxygen species. Another mechanism by which Zinc exerts its antioxidant action is by affecting the expression of glutamate-cysteine ligase, which is the rate-limiting enzyme of glutathione de novo synthesis [4]. Alpha-lipoic acid is a potent antioxidant which exerts its antioxidant mechanism by preventing accumulation of reactive oxygen species. Alpha-lipoic acid also prevents the apoptotic cell death [5]. Ginkgo biloba contains monoamine oxygenase inhibitors including ginkgolide and bilobalide as well as myricetin and quercetin flavonoids. Ginkgo biloba is also considered to have protective effect from the oxidative stress due to antioxidant action [6]. Vitamin E is an oil soluble antioxidant which exerts its antioxidant action due to its free radical scavenging activity. Due to antioxidant properties of Vitamin E, it protects hair cells from lipid peroxidation and oxidative stress [7]. 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 radical scavenging activity [7]. Vitamin C provides protection against oxidative stress-induced cellular damage by scavenging of reactive oxygen species [8]. It is believed that, in geriatric population, in inner ear, cochlea is the main region where hearing loss occurs. Low serum level of Vitamin B12 is considered to be associated with high homocysteine concentrations. Also, Low serum level of Vitamin B-12 can impair myelination of the neurons in the cochlear nerve. Also, vitamin B12 has antioxidant properties by directly scavenging the reactive oxygen species and indirectly by preservation of Glutathione [9]. Also Vitamin B6 has free radical scavenging activities because of which it has direct antioxidant activities and it also serves as a coenzyme in the glutathione antioxidant defence system and indirectly plays a role as an antioxidant [10]. Similarly Chromium Picolinate also has antioxidant activities can be used for the medical management of age related hearing loss [11]. As per the previously conducted animal studies, antioxidants act in synergy with Magnesium to prevent the hearing loss. Also Magnesium reduces the noise-induced vasoconstriction that occurs as a result of free radical formation [12].

Methodology

This was a post marketing surveillance study which was of non-randomized, multicentric, open label and non-comparative in nature. This study was conducted at 11 clinical trial sites with ENT speciality investigators, total 176 patients were recruited for the study and out of which 160 completed the study and remaining were lost to follow-up.

Inclusion and Exclusion Criteria

As per the study inclusion criteria, patients of age 65 years and above were recruited for the study with the confirmed clinical diagnosis of age-related sensorineural hearing loss, of either gender, ethnicity or comorbidities, who can strictly adhere to the

study procedures, willing to sign the informed consent form and who have stopped taking any medication or supplements containing Alpha lipoic acid, Ginkgo biloba, Zinc, Magnesium, Chromium Picolinate, Vitamin C, E, B6 or B12 for at least 3 months prior to the start of the study were recruited for the study as trial subjects.

As per the study exclusion criteria, patients allergic to Alpha lipoic acid, Ginkgo biloba, Zinc, Magnesium, Chromium Picolinate, Vitamin C, E, B6 or B12 were excluded from the study. Patients suffering from any middle or external ear pathologies, patients planning to go for any ear surgery in the study duration, patients with history of clinically significant vestibular symptoms at the discretion of the investigator and also patients who cannot adhere to the protocol (mentally ill and patients with psychological problem) were excluded from the study. Also, patients with any known factor, condition or disease that, in the view of the investigator, might interfere with study conduct, interpretation or treatment compliance of the results such as psychiatric disease or suicidal tendencies were excluded from the study.

Study Intervention

The study intervention which is also referred as investigational product in this article was the fixed dose combination of Ginkgo biloba 120 mg, Alpha lipoic acid 200 mg, Zinc 12 mg, Vitamin C 30 mg, Vitamin B6 3 mg, Magnesium 10 mg, Methylcobalamin 1500 mcg, Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg and Vitamin E 10 IU per capsule. The interventional product was dispensed at no cost to the trial subjects by the investigator in the quantity of 46 and 44 capsules on day 0 and 45 respectively and were asked to take the same in the dose of 1 capsule a day for the study duration of 90 days.

Study design

Since this was a multicentric post marketing surveillance study, it was conducted at 11 clinical trial sites. As the study design was of non-comparative and open label nature, no control medication was applicable to this study.

Study Procedure

Since this was a multicentric study, it was conducted at 11 clinical trial sites. For the conduct of the study, ENT speciality investigators were selected all over the India. At each clinical trial site, trial subjects for the study were recruited as per the inclusion and exclusion criteria. Trial subjects were well informed about the study and the investigational product in their local or understandable language by the investigator and all doubts of the patients were resolved before recruiting them into the study as trial subject. The study was conducted for the duration of 90 days and during the study, trial subjects were asked to visit the clinical trial site for efficacy and safety assessment on day 45 (visit 2) and day 90 (visit 3) considering the baseline visit as day 0 (visit 1). Efficacy assessment on visit 1, 2 and 3 was done by 2 efficacy assessment parameters including score obtained from hearing impairment questionnaire and hearing related quality of life score. Efficacy assessment parameters are briefly described below in the section, "efficacy assessment". Safety assessment was done by the reported adverse events and their causality assessment. Brief description about the safety assessment is given in the section "safety assessment" below.

Concomitant therapy

In the study duration, trial subjects were not allowed to take any antioxidant concomitant therapy for the treatment of age related hearing loss.

Efficacy Assessment

Efficacy assessment was done by 2 parameters including “hearing related quality of life” and “hearing Impairment Questionnaire”. In hearing related quality of life, the patients were asked to rate the score about hearing related quality of life on a 10 point scale ranging from 1 (very poor) to 10 (very good). For efficacy assessment via hearing impairment questionnaire, patients were asked to answer 10 questions as mentioned below in table no 1. For answering the question, trial subjects were given 5 options whose score for the answer was ranging from 0 to 4 where, 0 means no difficulty at all to 4 means can’t hear at all and the total score obtained from all 10 questions was used for the efficacy assessment.

Table 1: Hearing Impairment Questionnaire

1	How much difficulty do you face while hearing in crowded places?
2	How much difficulty do you face while hearing in quiet places in one to one conversation?
3	How much difficulty do you face while hearing the sounds of the doorbell or the mobile phone ringing?
4	How much difficulty do you face while hearing the sound of the car honking?
5	How much difficulty do you face while hearing the sound of people whispering?
6	How much difficulty do you face while hearing the sound of a person in a telephonic conversation?
7	How much difficulty do you face while hearing the announcements made at the airport or at the Railway station or at any other public places?
8	Are there symptoms of dizziness or tinnitus in the ears when it is quiet?
9	Do you often ask people to repeat what they say?
10	Do you play the TV or the radio louder than your friends or relatives?

Safety Assessment

Trial subjects were asked by the investigator for any adverse events and the same, if present, were reported. These adverse events were categorized into serious and non-serious adverse events and also causality assessment was done for the same.

Regulatory Aspects

During this post marketing surveillance study, the informed consent form was read and signed freely by all trial subjects also all the doubts of the trial subjects or their guardians regarding the study or the investigational product were resolved by the investigator before signing the informed consent form.

Results

This post marketing surveillance study was conducted at 11 clinical trial sites all across India. At each clinical trial site, 16 trial subjects were recruited i.e. total 176 patients were recruited at 11 clinical trial sites. Out of 176 patients, 160 patients completed the study and others lost to follow-up. Mean age of the trial subjects completed the study was 73.5 years and out of 160 trial subjects completed the study, 101 were male and 59 were female.

Mean hearing related quality of life score at baseline visit was 4.437 which was increased to 5.725 at visit 2 which was increase of 29.028 % as compared to baseline and at visit 3, it was increased to 6.906 which was increase of 55.645 % as compared to baseline visit which is graphically presented below in figure 1.

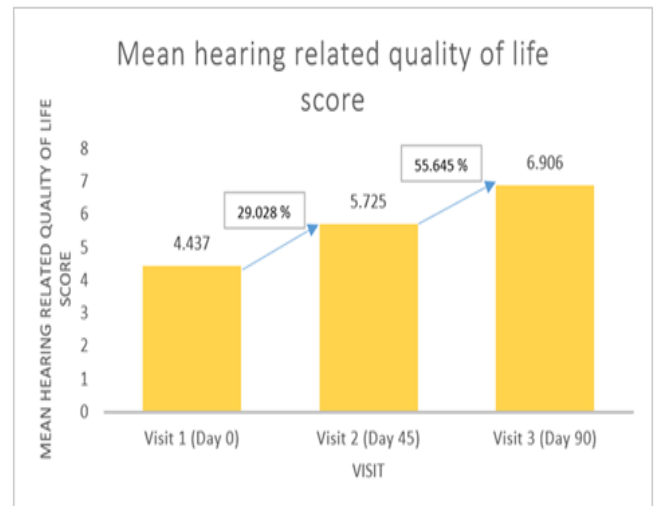


Figure 1: Mean hearing related quality of life score at visit 1, 2 and 3

Hearing impairment questionnaire was asked to all trial subjects recruited in the study and mean score was calculated. Mean score obtained from hearing impairment questionnaire was 25.581 at baseline visit which was reduced to 16.200 at visit 2 and was further reduced to 9.943 at visit 3 which is graphically presented below in figure 2. According to above mentioned results of efficacy assessment, it was observed that there was overall improvement in hearing function of trial subjects.

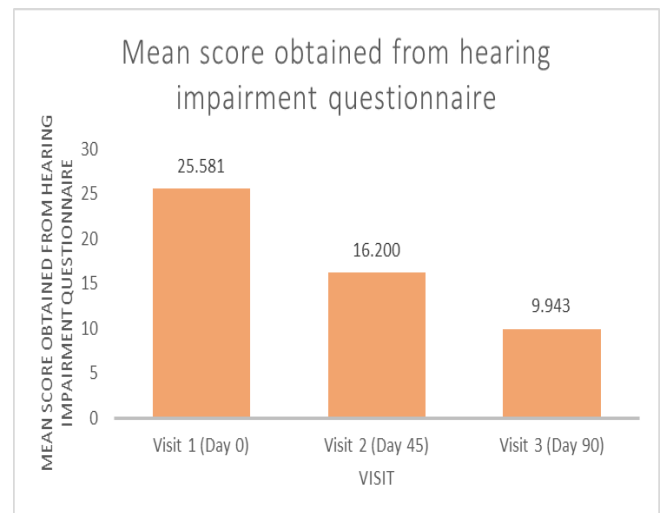


Figure 2: Mean score obtained from hearing impairment questionnaire at visit 1, 2 and 3

Safety assessment

In all the recruited patients total 5 episodes of adverse events were reported out of which 3 were of nausea and 2 were of diarrhoea. All the reported adverse events were of non-serious in nature and at the same time mild in intensity.

Discussion

Age related hearing loss is defined as a bilateral, progressive, symmetrical age-related sensorineural hearing loss, which is most pronounced at the higher frequencies. Oxidative injury triggered by free radical disruption is the most fundamental cause of age-related hearing loss pathology. Oxidative damage is one of the factors that plays an important role in the pathogenesis of age related hearing loss. Free radicals have been implicated as a mediator of oxidative stress and damage. Because of the role of oxidative damage in the

pathogenesis of age-related hearing loss, antioxidants can be used for the medical management of age related hearing loss. This study was conducted to test the efficacy and safety for the combination of antioxidants in the Indian patients of age related hearing loss. This was a post marketing surveillance study conducted to analyze the efficacy and safety for the fixed-dose combination of the Alpha lipoic acid 200 mg, Ginkgo biloba 120 mg, Vitamin C 30 mg, Zinc 12 mg, Magnesium 10 mg, Vitamin B6 3mg, Methylcobalamin 1500 mcg, Vitamin E 10 IU and Chromium Picolinate 1.66 mg equivalent to elemental chromium 200 mcg per capsule in the Indian patients of age related hearing loss. For this study total 176 patients were enrolled at 11 clinical trial sites out of which 160 patients completed the study. Efficacy assessment for the study was done by the hearing related quality of life score and the score obtained from the hearing impairment questionnaire. At baseline visit, the mean hearing related quality of life score was 4.437 which was increased to 5.725 at visit 2 and was further increased to 6.906 at visit 3. Mean score obtained from hearing impairment questionnaire was 25.581 at the baseline which was decreased to 16.200 on visit 2 and further decreased to 9.943 at visit 3. So, from the efficacy assessment it was observed that, there was overall improvement in the hearing of patients suffering from age related hearing loss which could be due to antioxidant actions of investigational product. Also in the study duration, no serious or unexpected adverse event was observed. Through only 5 episodes of adverse events were reported out of which 3 were of nausea and 2 of diarrhoea. So even after the benefit risk assessment, the investigational product was found to be beneficial as compared to the risks offered based on the efficacy and safety data which we have gathered from this study.

Taye Jemilat Lasisi et al conducted a clinical trial to study the serum Zinc and Retinol levels in the patients of age-related hearing loss and of normal hearing threshold of age ≥ 60 years. The median values of serum Retinol and Zinc levels in the elderly participants with normal hearing threshold at high frequencies were 70.3 and 99.9 Ig/L respectively, while among those with hearing loss at high frequencies were 46.9 and 83.2 Ig/L, respectively ($p = 0.000$ and 0.005 , respectively). So, it was concluded by the author that, Serum Retinol and Zinc levels were significantly lower among elderly with hearing loss at high frequencies. It was also said that the further study is required to study the effect of antioxidant supplementation for the control of age related hearing loss^[13].

As per the best knowledge of the author, there was no study conducted to test the efficacy and safety for combination of Alpha lipoic acid, Ginkgo biloba, Vitamin C, Zinc, Magnesium, Vitamin B6, Methylcobalamin, Vitamin E and Chromium Picolinate in Indian patients of age related hearing loss so this was the first study conducted to test the safety and efficacy in Indian patients.

Conclusion

The fixed dose combination of Alpha lipoic acid 200 mg, Ginkgo 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 can be used in the medical management of age related hearing loss.

Acknowledgement

We would like to acknowledge Dr. Kusum Patidar (Madhya Pradesh), Dr. Manojkumar Patodi (Madhya Pradesh), Dr. Dilip

Kolekar (Madhya Pradesh), Dr. Nilam Sathe (Maharashtra), Dr. Vitthal Kale (Maharashtra), Dr. Sumeer Verma (Madhya Pradesh), Dr. Devika Shere (Maharashtra), Dr. Rohan Shetty (Maharashtra), Dr. Sakoyuba Imchen (Nagaland), Dr. Vikramjit Singha (Assam) and Dr. S N Mukherji (Assam) who were investigators in this study.

Disclosure

This study was conducted as a part of Pharmacovigilance activity for investigational product whose brand name is Otopac Capsule which is a fixed dose combination of Alpha lipoic acid 200 mg, Ginkgo 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. Otopac capsules is the product of Centaur Pharmaceuticals Pvt. Ltd which is available in India.

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