Betaserc 24 mg orodispersible tablet

23.9.2014, Version 2.1

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Betahistine is indicated for Ménière's Syndrome. Ménière's Syndrome is defined by the following main symptoms:

- vertigo (with nausea/vomiting)
- hearing loss (hardness of hearing)
- tinnitus

Betahistine is as well indicated for symptomatic treatment of vestibular vertigo.

Ménière's disease

A considerable disagreement in the literature exists with respect to the incidence and prevalence of Ménière's disease. The number of people suffering from Ménière's disease has been estimated as one per 1,000 of the general population, equally distributed by gender.

Risk factors include a family history of Ménière's disease, preexisting autoimmune disorders, allergies, trauma to the head or ear, and, rarely, syphilis (even several decades previously). Most people develop Ménière's disease between ages 20 and 50.

Vertigo

Vertigo is considered to be among the most frequent reason for medical consultation. It was estimated in a survey that 8.5 per 1,000 individuals per year were seeking consultation for vertigo.

Medications also taken in the target population

Betahistine is not limited to a specific patient population with respect to accompanying diseases and it has low probability of influencing or being influenced by other medications. Hence, there are no typical other medications used in the target population.

Other illnesses occurring frequently in the target population

The target population for betahistine consists almost exclusively of adults across a broad age

range. There are no identified specific illnesses occurring frequently in the population treated with betahistine.

VI.2.2 Summary of Treatment Benefits

The overall efficacy of betahistine for treatment of Ménière's disease and vertigo was reviewed separately using all clinical studies with betahistine in these indications that were performed and reported by Abbott Laboratories (formerly: Solvay Pharmaceuticals, Duphar) or identified in the international literature.

In total 77 studies were included, 23 sponsored by Abbott and 54 reported in the literature. Of the 54 studies published in the literature, 10 were with betahistine dimesylate and one with betahistine sustained release.

The total number of subjects exposed to betahistine in the 77 clinical studies was 12,134.

In the controlled studies, betahistine was prescribed for periods between two weeks and six months at daily doses between 16 and 72 mg.

In most of the studies, the method to measure the effect of treatment was to have the study participants fill in a diary with records number, severity and/or duration of vertigo attacks and/or the study physician analyzed the severity and impact of the attacks.

During the clinical development of betahistine in Ménière's disease, no specific pivotal studies were designed as such. It was therefore decided to include all studies in the approved indications with betahistine oral plain tablet (IR formulation) or liquid formulation in the review of efficacy. One additional study with an experimental sustained release (SR) formulation was included because this study got much attention in the Cochrane review on betahistine literature, and therefore reflects the interpretation of the authors.

VI.2.3 Unknowns Relating to Treatment Benefits

Various clinical trials, as well as experience gained since betahistine has been available on the market (1968), show that betahistine is well tolerated and acts as an highly effective treatment against Ménière's disease and vertigo.

There is currently no evidence that betahistine may be less effective in certain patient groups.

VI.2.4 Summary of Safety Concerns

Table 24. Important Identified Risks		
Risk	**What Is Known**	**Preventability**
Allergy like symptoms (Hypersensitivity, including anaphylaxis)	Mild cutaneous and subcutaneous reactions including rash, pruritus and rapid swelling of the dermis were found in clinical studies. Available data from Abbott do not allow for calculation of a frequency or confidence intervals. In post-marketing data most described allergy-like symptoms were skin reactions such as rash and urticaria. The patients recovered in most cases. No particular risk groups known. Dependent on severity of the allergic-like symptoms, impact on individual patients can vary from nearly no impact (e. g. mild skin rash) to significant impairment of patients quality of life (e.g. bronchospasm and anaphylactic shock). No public health impact is foreseen, as only individual patients are concerned of betahistine hypersensitivity.	The package information leaflet states that people with a known hypersensitivity to betahistine should not use the product. If signs of allergy occur, treatment should be immediately discontinued. Allergic symptoms can only be prevented by not using the product.

Table 25. Important Potential Risks	
Risk	**What is Known (Including Reason Why It Is Considered a Potential risk)**
Local tolerance (ODT)	Problems with local tolerance were not reported in an Abbott sponsored study in which healthy people received the ODT. However, there is still the possibility of local irritation when the product is used over a longer period of time, especially in dysphagic and nauseous people. In comparison, the immediate release tablets are instantly swallowed whole with water and therefore local tolerance of this formulation is not comparable to local tolerance of the ODT formulation. As the ODT is not on the market yet, the data from the Abbott database is not applicable. Therefore local tolerance is considered to be a potential risk for the new betahistine ODT.

Table 25. Important Potential Risks	
Risk	**What is Known (Including Reason Why It Is Considered a Potential risk)**
Use in patients with phenylketonuria (ODT)	Untreated phenylketonuria can lead to intellectual and body development retardation and neurological symptoms (e. g. seizures). Early diagnosis and strict diet with limited phenylalanine intake allow for a nearly normal development. ODT contains Aspartame (E951), a source of phenylalanine. This may be harmful for people with phenylketonuria, as these people are not able to metabolize phenylalanine. An excess of this amino acid may lead to brain development disorders such as intellectual disability and body development retardation as well as neurological symptoms.

Table 26. Missing Information	
Risk	**What Is Known**
Limited information on use in pregnant and lactating women	**Pregnancy** A search in the Abbott post-marketing safety database retrieved 29 - adverse event cases. In 20 cases normal pregnancies without problems for the mother and child were described. In the remaining nine cases no hint for a negative influence of betahistine on pregnancies could be detected, as most cases provided factors which may have contributed to the problems during pregnancies or were too limited to adequately assess these cases. Other products from the same medication group are under evaluation for this topic, but no concerns have been reported so far. **Lactation** A search in the Abbott post-marketing safety database retrieved three cases. All of them described betahistine use without any problems during lactation. There was also no indication for harmful effects of betahistine during lactation from the scientific literature. Nevertheless, betahistine should not be used in pregnant women and the importance of the drug to the mother should be weighed against the benefits of nursing and the potential risks for the child.

Table 26. Missing Information	
Risk	**What Is Known**
Limited information on use in children	Overall, Ménière's disease is rare in children, but incidence might be underestimated. Betahistine is not recommended for use in children below 18 years due to insufficient data on safety and efficacy. However, there are limited post-marketing reports available. There was no safety concern identified from an analysis of these reports.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

The Summary of Product Characteristics and the Package leaflet for betahistine can be found on betahistine's EPAR page.

This medicine has no additional risk minimization measures.

VI.2.6 Planned Post-Authorization Development Plan

Not applicable, as no post-authorization development plan exists.

VI.2.6.1. Studies which are a Condition of the Marketing Authorization

Not applicable, as no studies, which are a condition of the marketing authorization, exist.

VI.2.7 Summary of Changes to the Risk Management Plan over Time

The major changes to the Risk Management Plan over time is detailed in table below:

Table 27. List of Major Changes to the Risk Management Plan

Version	Date	Safety Concerns	Comment
1.0	11 March 2013	None	
2.0	07 April 2014	Hypersensitivity (including anaphylaxis) added as important identified risk. Local tolerance (ODT) and use in patients with phenylketonuria were added as important potential risk. Pediatric off-label use and use in pregnant and lactating women were added as missing information.	Safety concerns added due to assessment report to RMP 1.0 from Finish Medicines Agency
2.1	23 September 2014	Request to refer in the RMP to SmPC information (not CCDS information) for routine risk minimization activities for each safety concern.	Triggered by Draft Assessment Report of the Finnish Medicines Agency.