

URIACH CONSUMER HEALTHCARE OPINION ON THE RISK OF INSULIN AUTOIMMUNE SYNDROME DUE TO THE USE OF TIOBEC AND SINOPOL

INTRODUCTION

Recently, a safety concern has been raised about the possible association of insulin autoimmune syndrome (IAS) with the use of alpha-lipoic acid in medicines and food supplements (DTU memo dated June 7th, 2016; Pharmacovigilance Risk Assessment Committee recommendations on signals, EMA/PRAC/590240/2015)

In this context, and following a request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) has published a draft opinion on the relationship between the intake of alpha-lipoic acid (ALA, or thiotic acid) and the risk of IAS (EFSA, 2021) and an open consultation of this document has been launched by EFSA, where interested parties are invited to submit written comments by 25 February 2021.

Uriach Consumer Healthcare S.L. Spain (Uriach CHC Spain) is currently marketing in Spain two different families of products containing ALA in their composition: Tiobec and Sinopol. The aim of this document is to evaluate the safety data collected by the Corporate Vigilance System (CVS) of Uriach to aid in the characterization of the possible association between ALA and IAS, as well as to outline the opinion of Uriach Consumer Healthcare S.L. in this issue.

BACKGROUND

First reported in 1970 by Hirata et al (Hirata, 1970), insulin autoimmune syndrome (IAS) is a rare autoimmune disorder characterized by hyperinsulinaemic hypoglycemic episodes associated with the presence of autoantibodies to insulin in patients that have not been exposed to exogenous insulin previously.

Even though the exact cause that triggers IAS has not been elucidated, two factors have been associated with its development (EFSA, 2021). First, there seems to be a strong association between IAS incidence and the HLA-DR4 haplotype of the Human Leukocyte Antigen, mainly with alleles HLA-DRB1*0406 (in Asian cases) and HLA-DRB1*0403 (in Caucasian cases, where IAS is much less frequent). Second, IAS has been associated with the intake of products that contain a sulfhydryl group.

The more accepted hypothesis is that the sulfhydryl group of these substances reduces the disulphide bridges between chains A and B of the insulin, causing the rupture of the molecule and increasing the immunogenicity of endogenous insulin, an effect that would be more pronounced in those patients with the HLA-DR4 haplotype.

However, even though these associations have been widely described in the literature, other studies have also described the presence of insulin autoantibodies in patients exposed to products that contain a sulfhydryl group without developing symptoms of IAS (Cooper, 1999).

In this scenario, an increasing number of cases of IAS have been associated with other substances with sulfhydryl groups, such as the alpha-lipoic acid (ALA). The ALA is found naturally in the human body, mainly acting as an acyltransferase cofactor of several enzymes involved in key steps of the metabolism. Additionally, exogenous ALA is also widely used as nutritional supplement with different potential objectives (antioxidant, etc.). For instance, *in vitro* (Konrad, 2001) and clinical studies (Scaramuzza, 2015) have shown that ALA may improve glucose homeostasis, protecting the body against the damage caused by oxidation and protein glycation.

This use it is also supported by the fact that several studies have demonstrated a very good safety profile of ALA administered in the elderly (Sarezky, 2016), pregnant women (Parente, 2017) or adults at doses as high as 2400 mg/day for periods up to 6 months (Costantino, 2014).

DISCUSSION

Based on the potential benefits and the good safety profile described, Uriach CHC Spain has been marketing in Spain since 2017 two different families of food supplements containing ALA in different presentations and concentrations: Tiobec and Sinopol. In these 4 years, Uriach CHC has sold to pharmacies a total of 142.433 packs of these products.

Following the internal SOPs, at Uriach CHC Spain all the adverse events of the different types of products (drugs, medical devices, cosmetics or food supplements) are processed in the same way and all their safety information is centralized in a Corporate Vigilance System (CVS) that receives, analyzes and performs the follow-up of all these events. Regarding the post-marketing experience since the Uriach CHC Spain products containing ALA (Tiobec and Sinopol) were first commercialized, and up to 15 February 2021, only one adverse event has been received. The case, summarized in Table 1 below, corresponds to an adverse reaction to Tiobec that bears not apparent relation with IAS.

In addition to Uriach CHC, several other companies commercialize ALA in Spain, and more than 1 million units were sold to consumer in pharmacies in the past 4 years (HMR, 2001, sell-out data, Spain, pharmacy channel). No cases of IAS associated to ALA consumption were found in Spain in a dedicated search of the scientific literature in that period, and only one previous case in 2015, already cited in the NDA draft opinion, has been reported (Michalopoulou, 2015).

Taken together, our internal sales data and the supportive data coming from global ALA market sales to consumer in Spain, as well as reported cases in the literature, did not permit to identify any signal or concern regarding a major incidence of IAS by ALA in Spain.

| Product | Dose | Cummulative dose | Country | Sex | Age | Undesirable effects (Verbatim/MedDRA LT/ MedDRA PT) |
|------------|--------------------------------|--------------------|---------|-----|-----|--|
| Tiobec 400 | 2 tablets/day (800 mg ALA/Day) | 3.2 gr (8 tablets) | Spain | F | Unk | Itchy right hand and feet/Localized Itching/Pruritus |

TABLE 1. Cummulative Adverse Events with Tiobec and Sinopol

CONCLUSIONS

1. Alpha-lipoic acid has been widely used as food supplement, showing a good safety profile.
2. Uriach CHC has been marketing two different families of products including alpha-lipoic acid as one of the components in their formulation since 2017: Tiobec and Sinopol.
3. In the post marketing surveillance activities of these products, only one case including one adverse reaction without relation to IAS has been reported.
4. To date, both products, Tiobec and Sinopol, have shown a positive safety profile and no case of IAS has been received at Uriach CHC Spain with these products.

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