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CORRESPONDENCE

Artesunate- and Amodiaquine-Associated Extrapyramidal Reactions

Information Gained from an African-Based Risk Management Plan

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In an article recently published in *Drug Safety* [1], McEwen mentions that "… the Summary of Product Characteristics (SPC) for Artesunate Amodiaquine Winthrop® refers to somnolence, paraesthesias, headache, dizziness, convulsion and rare neuromyopathy. There is no mention of movement disorders, extrapyramidal disorders or their common pathognomonic symptoms, which is curious as the SPC purports to include additional types of events that have been attributed to amodiaquine in the published literature". I think it may be helpful to provide further information on this.

As Marketing Authorization Holder and supplier of Artesunate-Amodiaquine Winthrop®, the Access to Medicines Department of Sanofi, in 2008, took the initiative of setting up a Risk Management Plan (RMP) together with our partner DNDi (Drugs for Neglected Diseases initiative). The aim of this RMP was to assess this drug's safety and efficacy profile in a large variety of settings because we knew that pharmacovigilance in malaria-endemic countries, especially those in Africa, is not operational enough to provide reliable data, and that no data could be expected from industrialized countries where the product is not marketed.

This RMP was built following the European Medicine Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) template. As Artesunate-Amodiaquine Winthrop® was pre-qualified by the WHO, the RMP was presented to the relevant WHO teams in February 2009 and July 2011. At present, this RMP includes a total of 20 clinical studies set up in 23 malaria-endemic countries and is expected to gather data from nearly 30,000 malaria episodes. This is, to our knowledge, the first RMP set up almost entirely in Africa (out of 23 countries involved, 2 are in Asia and 2 in Latin America).

Since its inception, and in line with EMA terminology for RMPs, extrapyramidal symptoms (EPS) were among the 'important potential risks', to be documented through this RMP.

In October to December 2011, following some notifications of EPS collected during this extensive RMP programme, Sanofi's pharmacovigilance department carried out an assessment of extrapyramidal reactions for several antimalarials, including Artesunate-Amodiaquine Winthrop®. This work, including bibliographic review, led to the recommendation of adding acute extrapyramidal disorders (such as dystonia, dyskinesia, tongue protrusion, torticollis) to the labelling and package insert of Artesunate-Amodiaquine Winthrop®. These changes were made to our SPC documents and sent to the WHO in April 2012. We received comments from the WHO on the final wording in September 2012. We are in the process of implementing these changes in our SPC and product leaflets. This requires approval by the regulatory authorities that have approved Artesunate-Amodiaquine Winthrop®. In fact, in order to save time, work was initiated to speed up approval of this new wording before we received feedback from the WHO.

We fully agree with Dr McEwen's statement that says "Extrapyramidal reactions are unpleasant and frightening and the association warrants being more clearly recorded in official treatment guidelines and Summary of Product

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Characteristics documents", and we have undertaken the necessary actions.

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Reference

1. McEwen J. Artesunate- and amodiaquine-associated extrapyramidal reactions: a series of 49 cases in VigiBase™. Drug Saf. 2012;35(8):667–75.