European Medicines Agency
Evaluation of Medicines for Human Use

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CONCEPT PAPER ON THE DEVELOPMENT OF A COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) GUIDELINE ON THE IN-VITRO INVESTIGATION OF MITOCHONDRIAL TOXICITY OF ANTI-HIV MEDICINAL PRODUCTS

Introduction

Mitochondrial toxicity of Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs/NtRTIs[1]) could pose a major threat to the long-term success of anti-HIV-therapy and is of great concern for children exposed *in utero* and/or postnatally to antiretroviral agents as part of vertical transmission prophylaxis.

Current national treatment guidelines recommend use of combinations of multiple antiretroviral agents in HIV-therapy, called HAART (Highly Activated Antiretroviral Therapy), which usually contain NRTIs. Such regimes may be critical for the development of additive or synergistic mitochondrial toxic effects or the development of new tissue targets.

The issue of NRTI-induced mitochondrial toxicity in patients treated with NRTI combinations and in children exposed *in utero* and/or postnatally to NRTIs has been discussed recently at the CHMP PhWP. It was concluded that there is a need for the investigation of mitochondrial toxicity of clinically relevant combinations of NRTIs *in vitro* and companies were requested to conduct further *in vitro* studies in cell cultures. These studies, which are based on different company-specific study protocols, are still ongoing.

Problem Statement

Until now no standardised and validated *in vitro* model exist for the investigation of mitochondrial toxicity. The study designs of the cell culture models currently used for the investigation of NRTI-induced mitochondrial toxicity vary greatly making it difficult to compare findings from different companies, i.e. to discriminate protocol-specific from compound-specific differences.

Discussion

There is a need for the development of a uniform and standardised strategy for *in vitro* testing of mitochondrial toxicity of single agents and clinically relevant combinations of NRTIs and of NRTIs with other classes of antiretroviral agents in order to improve comparability of the findings from different companies. This would facilitate the possibility of establishing a rank order of potencies of the compounds/combinations tested.

Recommendation

Based on an analysis of the methods/protocols and data available CHMP Safety Working Party (SWP) should develop a guideline with recommendations for a most suitable and uniform *in vitro* testing strategy for mitochondrial toxicity of NRTIs.

[1] For simplification nucleoside/nucleotide reverse transcriptase inhibitors are abbreviated as NRTIs

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Time table

The draft concept paper will be forwarded to the CHMP for adoption in January 2005.

Preparation of a draft Guideline will have to take into consideration the results of the *in vitro* studies currently conducted by the companies for which submission of study reports are anticipated by Q1, 2005.

Resource requirements for preparation

The preparation of this guideline will involve only the SWP.

Impact Assessment

The development of the proposed Guideline is consequence of recent scientific knowledge in this field and an update to state of the art is needed. It will result in a more consistent assessment for Marketing Authorisation of Anti-HIV medicinal products by regulators, set clear standards and expectations for industry, and therefore be helpful in a harmonised regulatory policy. The relatively small resource implications for the preparation of the Guideline are fully justified and are compensated by the fact that application of a Guideline will make assessment easier and will result in less resources being needed during assessment.

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