European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

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CHMP SWP Reflection Paper on PPARs (Peroxisome Proliferator Activated Receptors)

Introduction

Following a review of the data on rodent carcinogenicity studies on PPAR agonists, either marketed or in development in the EU, the CHMP SWP have prepared recommendations for the Regulatory acceptability of clinical trials of longer duration than 6 months with these agents.

Recommendations from CHMP SWP for clinical trial applications of longer than six month in duration

Based on review of the data the CHMP SWP considered that the most common tumour findings in animal carcinogenicity studies are epithelial cell carcinomas in the bladder of rats and hemangiosarcomas in mice. It is not possible to determine the relevance of this data to humans and therefore precautionary principles to determine the risk benefit profile should apply. The following recommendations are intended to provide some guidance for applicants and assessors with regards to the information that may be required by member states in order for acceptability of PPAR clinical trial applications longer than six months in duration. This in no way suggests that member states will approve trials provided the criteria below are satisfied. Every application will be assessed on its own merit.

1) Carcinogenicity data must be available. At the least, a draft final report should be provided detailing, amongst other salient features, pathology findings, histology findings and toxicokinetics.

2) For negative carcinogenicity studies, the appropriateness of the doses used in animals needs to be assessed. Drug exposure in animals should be reviewed and if there is a low exposure ratio between the high dose used in animals and the expected therapeutic dose in humans, it needs to be shown that animals were dosed up to the maximum tolerated dose.

3) For compounds that have positive or equivocal carcinogenicity findings (esp. with respect to haemangiosarcomas and transitional epithelial carcinomas), a general exposure safety margin between the clinical dose and the animal NOAEL of 10 fold would be acceptable. However, from the information assessed, this may be unlikely. Therefore, the company may be requested to analyse their pharmacological data and determine the ratio between the effective dose (based on AUC exposure) in animal pharmacology studies and the dose (based on AUC exposure) causing toxicological effects. Once the exposure multiple required to reach toxic effects from effective dose has been determined in animals, it should be estimated how many times the exposure multiple of the therapeutic dose in humans would need to be increased to reach toxic exposure levels.

4) If reversibility of effects (such as hyperplasia) was demonstrated in repeated dose toxicity studies that included a drug free period it may provide reassurance that the findings will not be irreversible.

5) If good mechanistic data for carcinogenic effects are available, it may help in the assessment of relevance to human safety.

6) The applicant should be encouraged to develop and identify relevant and valid biomarkers that may be clinically monitored.

7) Compounds that result in tumours in more than one species and at more than one site, without adequate safety margins, may contribute to an increased level of concern.

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