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Flumioxazin:
Classification for Developmental Toxicity

Introduction:

Flumioxazin is a protoporphyrinogen oxidase (PPO) inhibitor, currently classified as Repr. Cat 1B (under the CLP Regulation) on the basis of the developmental toxicity seen in rats. In rats a reduced number of live pups per litter, lower foetal bodyweight despite smaller litter size, and an increase in developmental defects (of which the primary lesion of concern is a ventricular septal defect of the heart) are seen at a dose of 30 mg/kg bw/day without evident maternal toxicity. In contrast, in rabbits no evidence of an effect on the foetus is seen at doses up to 3000 mg/kg bw/day; there is a strong species difference.

Species-specific developmental toxicity in the rat is seen by the oral and dermal routes, and also in the multigeneration study.

Since the last consideration of classification in which Repr. Cat1B was concluded, new evidence is provided to demonstrate that humans are probably less sensitive to PPO inhibition than the rat. The new data are:

A pharmacokinetic study in rats (**Takada, 2012**) including bile duct cannulation, demonstrating absorption of a single high dose (1000 mg/kg bw) of flumioxazin to be limited (ca. 12%);

A comparative pharmacokinetic study in rats and rabbits (**Shirai, 2009**) at 30 mg/kg bw (the teratogenic dose in rats) showing concentrations of radiolabel in tissues to be generally higher in rats than rabbits. Radiolabel was, once again, poorly distributed to the foetus.

A study of normal blood development in the foetus during GD 11-14 (**Ihara, 2011**).

An in-vitro study of relative PPO inhibition (**Abe, 2011a**) by flumioxazin and four of its metabolites, of which flumioxazin was much the more potent inhibitor.

An in-vitro study of flumioxazin on the differentiation of a human erythroid cell line (**Kawamura, 2012a**). PPIX was seen to accumulate in a dose-related manner. In a separate study flumioxazin metabolites were ineffective (**Kawamura, 2012b**).

An in-vitro study of PPIX accumulation in rat, rabbit, monkey and human hepatocytes (**Abe, 2011b**). The study appears confirmatory that humans are intermediate in sensitivity between rat and rabbit.

PBPK modelling of human foetal exposure (**Takaku, 2012b**). The model was constructed using physiological data for humans drawn from literature, supplemented by the studies above, and appeared to predict accurately concentrations known to be achieved in rat tissues in-vivo. The model concludes that the human foetus would not be vulnerable to a maternal dose as high as 1000 mg/kg bw.

Comment on Classification (Developmental toxicity)

This author does not claim expertise to assess the validity of the PBPK model or its conclusions. However, the developmental toxicity of flumioxazin is strongly species-specific. The data provided give insight into the species specificity, and appear to show humans would not be sensitive to any exposure that could be actually achieved. The mechanistic data clearly fulfil the criterion of "*raises doubt about the relevance of the effect for humans*".

On this basis, this author is strongly of the opinion that flumioxazin should not be regarded as a "presumed human reproductive toxicant", and Repr Cat 1B is not appropriate.

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18 October 2013