



The European Agency for the Evaluation of Medicinal  
Products  
*Human Medicines Evaluation Unit*

London, 17 December 1997  
CPMP/818/97

## **COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)**

### **POSITION PAPER ON THE GENOTOXIC AND CARCINOGENIC POTENTIAL OF PHENOLPHTHALEIN**

#### **INTRODUCTION AND BACKGROUND**

Phenolphthalein (3,3 -bis(*p*-hydroxyphenyl)phthalide) is used as a laxative in a number of over the counter (OTC) products. In the EU, phenolphthalein is currently authorised as a medicinal product in AT, BE, DE, ES, FR, IE, IT, LU, NL, PT, & UK. The recommended clinical dose is 50-200 mg given by the oral route as required and the anticipated human intake in normal users is 4 mg/kg/day (US Food & Drug Administration [FDA] estimate). Its toxicity, carcinogenic and mutagenic potential were evaluated by the US National Toxicology Program (NTP) in the early 1990s and their draft report was released in December 1995. Subsequently, further studies were undertaken and reported in April 1997.

- In May 1997, the FDA announced that the newly available NTP data had direct impact on the rulemaking for OTC laxative drug products. The FDA made the NTP data publicly available and allowed for a 30 day commenting period.
- The NTP data were discussed at the Safety Working Party (SWP) meeting on 4-5 June 1997.
- At the June 1997 meeting, the CPMP took note that the FDA was considering regulatory actions on phenolphthalein containing OTC laxatives based on new information from the NTP.
- On 29 August 1997, the FDA proposed to ban OTC sale of phenolphthalein. On 2 September, the US Federal Register published further information regarding this matter including the proposal to amend the tentative monograph for OTC laxative products (i.e. to reclassify phenolphthalein from category I to category II ('not generally recognised as safe and effective or misbranded'). Written comments were asked for by 2 October 1997.
- At the Pharmacovigilance Working Party (PhVWP) meeting on 8-9 September 1997, it was indicated that National Competent Authorities were either considering immediate suspension of phenolphthalein or were discussing with the relevant Marketing Authorisation Holders the withdrawal down to wholesale level on a voluntary basis. Some National Competent Authorities would be considering suspension action if voluntary action was not agreed by the Marketing Authorisation Holders. It was felt important for action to be taken in the EU over a relatively short period.
- On 23 September 1997, an Ad hoc Expert Group of the CPMP was convened to discuss the evaluation of the NTP data.
- On 23-24 September 1997, the report from the Ad Hoc Expert Group was subsequently discussed at the plenary meeting of the CPMP.
- On 16-17 December 1997, the report was adopted during the plenary meeting of the CPMP.

## COMMENTS ON THE NTP DATA

### Conventional rat carcinogenicity bioassay

This study was considered unreliable for the evaluation of carcinogenic hazard for the following reasons:

- The maximum tolerated dose (MTD) was markedly exceeded at all dose levels based on reduction in body weight gain in both sexes.
- The survival of male rats was below that normally expected for an adequate assessment of carcinogenic hazard.
- The extent of toxicity compromised the interpretation of the significance of the tumours types observed (renal and adrenal tumours).

### Conventional mouse carcinogenicity bioassay

This study was considered satisfactory in terms of dose selection and animal survival.

- There was evidence of carcinogenic effects with significant increases in histiocytic sarcoma and malignant lymphoma.
- Benign ovary tumours were significantly increased in all treatment groups.
- A No Effect Level (NOEL) for carcinogenicity was not identified in this study.

### Micronucleus studies in mice

One study indicated that phenolphthalein has *in vivo* clastogenic activity after long-term treatment (90 days). In a number of short term studies (3-7 days), where dose levels were above those normally recommended for this type of study, positive findings were also observed.

### Comments

Taken together, these studies have shown that phenolphthalein, at high dose levels, is carcinogenic in mice and has a weak genotoxic (clastogenic) activity *in vivo*.

With respect to the carcinogenicity studies, the FDA had stated '*the systemic exposures in rodents were approximately 40 to 70 fold and 60 to 100 fold the human exposure for rats and mice, respectively*'. However, it has not been possible to verify this statement from original data.

### Syrian hamster embryo (SHE) cells studies

Owing to a number of methodological and validation issues, data obtained in SHE cells were not considered relevant for the assessment of risk to human health.

### Transgenic p53 (+/-) female mouse study

- Based on a reduction in body weight gain, the MTD was markedly exceeded in all but one middle dose group.
- Phenolphthalein toxicity was markedly more severe in comparison to the strain used in the conventional bioassay.
- There was clear evidence of increased malignant thymic lymphomas in the top two dose groups. These thymic tumours demonstrated a loss of wild type p53 allele. No other tumour types were observed, i.e. the ovarian tumours seen in the conventional study were not seen in this model.

- A dose related genotoxic effect (increase in micronucleated erythrocytes) was observed with a positive effect seen at the lowest dose investigated.

### ***Comments***

The p53 (+/-) mouse model has been developed as a model system to detect mutagenic and carcinogenic events with greater sensitivity and timeliness than conventional models. However, the p53 (+/-) mouse model has not been evaluated for the identification of carcinogenic or mutagenic hazard. Therefore, the results obtained in this model have merely served to confirm the results observed in the previously reported mouse bioassay and the 90 days mouse micronucleus study in identifying a potential hazard. The p53 (+/-) mouse study cannot at present be used to provide information on the potency of carcinogenic and/or genotoxic risk of phenolphthalein to humans.

### **CONCLUSION**

Carcinogenicity and repeat dose genotoxicity studies of phenolphthalein in mice have identified a hazard with respect to carcinogenic and genotoxic activity that has been confirmed by data from a transgenic mouse model. The systemic exposures to active drug, both in the conventional rodent bioassays and p53 (+/-) mouse study, appeared to be well in excess of those likely to be encountered in normal human use. However, there are no adequate mechanistic data addressing whether a threshold exists for the carcinogenic effects in mice and the in vivo genotoxic effects. Without such data, it is not possible to establish whether the hazard identified in experimental animals is relevant for humans, and if so the extent of the risk.

The CPMP concluded that the content of this report can be used by National Competent Authorities in their considerations of any restriction of the availability of phenolphthalein containing medicinal products on national markets.