CPMP/578/95

FINAL OPINION OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS IN ACCORDANCE WITH ARTICLE 12 OF DIRECTIVE 75/319/EEC AS AMENDED

Name of products	*see attached list*
International non-proprietary name (INN)	Naftidrofuryl
Strength	*see attached list*
Pharmaceutical form	solution for infusion
Route of administration	parenteral

Summary of Facts

By letter of 22 February 1995, the Grand-Duchy of Luxembourg initiated the procedure under Article 12 of Council Directive 75/319/EEC, as amended (letter appended to this Opinion).

The Committee for Proprietary Medicinal Products considered the matter at its meeting of 15 March 1995 and appointed a British Rapporteur and an Austrian Co-Rapporteur. At this meeting the Committee considered a list of questions to be asked to marketing authorisation holders. This list was circulated by the Rapporteur on 22 March 1995 and approved by the CPMP on 27 March 1995 by written procedure (questions appended to this opinion).

The Rapporteur submitted these questions on 28 March 1995 to those marketing authorisation holders identified by Member States in response to the Rapporteur's request of 15 March 1995. On 10 April 1995, the Rapporteur requested marketing authorisation holders to respond to the questions by 28 April 1995.

In accordance with the timetable agreed by the Committee for Proprietary Medicinal Products at its meeting of 26-27 April 1995, the draft assessment report was circulated on 22 May 1995 by the Rapporteur to other Members of the Committee for Proprietary Medicinal Products and the companies involved. At its meeting of 1 June 1995, the Pharmacovigilance Working Party examined the matter (CPMP/207/95 appended).

The Committee for Proprietary Medicinal Products adopted its Opinion at its meeting of 7-8 June 1995, saying that marketing authorisations for Naftidrofuryl should be withdrawn (Opinion and assessment report CPMP/345/95 appended to this Opinion).

Intentions to appeal were notified by marketing authorisation holders on 23, 26, 28 and 29 June and 4 July 1995. The grounds for appeal were jointly lodged by the marketing authorisation holders on 11 August 1995.

No new data was submitted by the marketing authorisation holders during the appeal procedure.

A draft assessment report was prepared the German Rapporteur further to his appointment as Rapporteur at the Committee for Proprietary Medicinal Products meeting of 11-13 July 1995. This was circulated to other Committee Members on 7 September 1995 proposing that the conclusions of the Opinion of 8 June 1995 be maintained. The assessment report (CPMP/624/95) is appended to this Opinion.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel: (+44-171) 418 84 00 Fax: (+44-171) 418 84 16
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

Grounds for appeal

The grounds for appeal lodged by marketing authorisation holders can be summarised as follows:

1. that the decision to revoke marketing authorisations is based on Article 11 which is different from Article 5 of Council Directive 65/65/EEC which sets out grounds for rejection of applications for marketing authorisations. Therefore the applicant does not have the burden of proof to show efficacy in the revocation of a marketing authorisation;
2. that there has been either insufficient or no justification of alleged harmful effects of Naftidrofuryl;
3. that modern biometric techniques cannot be used to prove the efficacy of Naftidrofuryl.

Final Opinion

Regarding the grounds for appeal lodged by the marketing authorisation holders, the CPMP considers that:

1. the burden of proof to show efficacy lies with the holder of the marketing authorisation and not, as claimed in the grounds of appeal, with the national competent authorities (see assessment report CPMP/624/95 III 3.3);
2. There is sufficient evidence to substantiate potentially harmful adverse reactions due to Naftidrofuryl (see assessment report CPMP/624/95 III 3.2);
3. no new data was submitted in the appeal procedure and no methodologically acceptable study is available which demonstrates efficacy (see assessment report CPMP/624/95 III 3.1)

The CPMP is also of the opinion that the inclusion of further precautions and contra-indications in the SPC would not be sufficient to reduce the risk.

The Committee for Proprietary Medicinal Products, having regard to its Opinion of 8 June 1995 and the grounds for appeal submitted on 11 August 1995, is of the Opinion that marketing authorisations for all medicinal products referred to in the Annexe to this final opinion should be withdrawn.

The present Opinion is forwarded to the Commission of the European Communities, the Member States and the above mentioned marketing authorisation holders, together with a report describing the assessment of the medicinal product and stating the reasons for its conclusions together with its annexes and appendices.

London, 19 October 1995

Prof. J M Alexandre
Chairman, on behalf of the CPMP

ANNEX

Scientific conclusions presented by the European Agency for the Evaluation of Medicinal Products following an opinion of the Committee for Proprietary Medicinal Products formulated under Article 12 of Council Directive[1] 75/319/EEC of 20 May 1975

SAFETY

There is significant concern about the safety of the parenteral infusion of Naftidrofuryl (200mg/10ml), especially with regard to serious cardiovascular and neurological reactions. The margin of safety for this product is considered to be low and has not been defined in patients with severe peripheral arterial occlusive disease. Although marketing authorisation holders had introduced further precautions and contra-indications to encompass the identified risk factors and so reduce the likelihood of toxicity, there is doubt that these will be adhered to under normal conditions of use.

EFFICACY

The efficacy of parenteral infusion of Naftidrofuryl (200mg/10ml) in the treatment of rest pain in patients with severe peripheral arterial occlusive disease had not been proven. At best, there is some improved relief of pain compared to placebo. In the patients who would benefit from surgery or angioplasty, conventional analgesia provides adequate pain relief and the marketing authorisation holders have not provided evidence to show that reduction in the use of conventional analgesia in the short term is clinically beneficial. Therefore it was considered to have no place in the management of this condition.

In addition, given the need for pharmacotherapy in about 10 % of patients with critical limb ischaemia who have unreconstruturable disease and given that many of these patients have multiple problems, the number of contra-indications required to improve the safety of parenteral infusion Naftidrofuryl (200mg/10ml) would limit its therapeutic indications.

CONCLUSION

The studies failed to demonstrate efficacy in the proposed indication at the dosage (200mg/10ml) mentioned in the summary of product characteristics as defined in Article 4a of Council Directive[2] 65/65/EEC of 26 January 1965 and there is significant concern about the safety of parenteral infusions under normal clinical conditions of use at the dosage proposed. As a result, due to the unfavourable balance of risks and benefits, the European Agency for the Evaluation of Medicinal Products recommends the withdrawal from the market of parenteral infusion of Naftidrofuryl (200mg/10ml).

---

1 OJ No L 147 of 09.06.1975 p 13 as last amended by Council Directive 93/39/EEC of 14.06.93; OJ No L 214 of 24.08.1993 p 22

2 OJ No 22 of 09.02.1965 p 369 as last amended by Council Directive 93/39/EEC of 14.06.93; OJ No L 214 of 24.08.1993 p 22