ORPHAN EUROPE

THE ORPHAN PHARMACEUTICAL COMPANY

25 May 2007

CYSTAGON_DHPC n°2

IMPORTANT SAFETY INFORMATION

Direct Healthcare Professional Communication on the association of cysteamine (Cystagon®) and Ehlers-Danlos like syndrome

Dear Doctor,

Summary

Orphan Europe in agreement with the European Medicines Agency (EMEA) and the Irish Medicines Board (IMB), is writing to inform you about additional safety information on the Ehlers-Danlos like syndrome that occurred in patients treated with Cystagon® above the recommended dose. Recently, 3 new cases of Ehlers-Danlos like syndrome have been reported. The characteristics of these cases are similar to the cases initially reported. Moreover, new information on the biopsy results has been received. These biopsies revealed abnormalities of collagen as well as angioendotheliomatosis. Based on this information, the EU-Summary of Product Characteristics has recently updated in sections 4.2, 4.4 and 4.8.

Further information on the safety concern

On 22 December 2004, we informed current prescribing physicians and dispensing pharmacists about 3 reports describing the occurrence of similar ecchymotic skin lesions located on the elbows of 3 children in the EU of 5, 8 and 10 years of age treated with Cystagon®; one of whom died in November 2004 (with MRI features of acute cerebral ischemia and vasculopathy).

Since then, we were informed of 3 similar reports, confirmed by health care professionals, occurring in other EU member states . In the few patients who underwent skin biopsy, histologic examinations showed abnormalities of collagen and elastin fibers as well as angioendotheliomatosis.

The features of these cases are similar to some of the abnormalities observed in connective tissue disorders such as Ehlers-Danlos syndrome. Cysteamine has a chemical structure close to D-penicillamine, known to potentially interfere with cross-linking of collagen fibers. These modifications have been associated with skin disorders resembling Ehlers-Danlos syndrome. Therefore, the suspicion of a similar type of mechanism of action on collagen has been raised for cysteamine.

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The affected patients were treated with a dose of Cystagon® above the recommended dose (expressed in mg/kg/day) for children up to age 12 years. A dose reduction, in two of the above-mentioned patients, was associated with resolution of skin lesions on elbows. Further concerns about potential bone or vascular lesions have been raised because advanced bone lesions might not be expected to resolve. For this reason, it is recommended to regularly monitor patient's skin and to consider X-ray examinations of the bone as necessary.

Further information on recommendations to healthcare professionals

Consequently, considering the seriousness of this safety information and its consequences for the dose and duration of CYSTAGON® , the following recommendations have been included in the in the EU Summary of Product Characteristics:

- "For children up to age 12 years: CYSTAGON® dosing should be on the basis of body surface area (g/m^2/day). The recommended dose is 1.30 g/m^2/day of the free base divided four times daily."
- "The use of doses higher than 1.95 g/m^2/day is not recommended."
- "A few cases of Ehlers-Danlos like syndrome on the elbows have been reported in children chronically treated with high doses of cysteamine preparations (cysteamine chlorhydrate or cystamine or cysteamine bitartrate) mostly above the maximum dose of 1.95 g/m^2/day). In some cases, these skin lesions were associated with skin striae and bone lesions first seen during an X-ray examination. Therefore, it is therefore recommended to regularly monitor patient's skin and to consider X-ray examinations of the bone as necessary. Self-examination of the skin by the patient or the parents should also be advised. If any similar skin or bone abnormalities appear, it is recommended to decrease the dose of CYSTAGON®."

In addition to these changes in Product Information, Orphan Europe has agreed to monitor Ehlers-Danlos like syndrome and to provide annual safety update reports on this matter to European Authorities. . Furthermore, any subsequent information related to this topic will be communicated to you in due course.

Despite detection of this new safety signal, the benefit/risk ratio for CYSTAGON® is considered favorable for the treatment of proven nephropathic cystinosis.

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Call for reporting

We would like to remind you that any adverse reactions should be reported according to your national spontaneous reporting system. Should you have any further questions or suspect adverse reactions to report, please contact:

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The full text of the new Product Information, approved by the European Authorities is enclosed with this information.

Sincerely yours,

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