WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

DRS/MtH/IEA.49 4 May 1995

DRS Information Exchange Service

ALERT No. 49

Cyproterone acetate - indications restricted because of hepatotoxicity and possible carcinogenicity

(European Commission, Germany)

European Commission. The Committee for Proprietary Medicinal Products has (CPMP) of the European Commission has evaluated toxicology data on cyproterone acetate after concern was expressed by the German health authorities about genotoxicity and carcinogenicity in man - particularly liver cancer - associated with this product.

Cyproterone acetate is a synthetic anti-androgen and progestin with a gestagenic and a strong anti-androgenic effect. It is authorized in all European Union Member States for a range of indications including prostate cancer, precocious puberty, inhibition of sexual drive in male sexual deviations, and (in combination with ethinylestradiol) for the treatment of acne.

On 17 August, the German Federal Institute for Drugs and Medical Devices (BfArM) circulated a rapid alert citing recent research that had given rise to concern about the suspected genotoxicity of cyproterone acetate.

After reviewing available data, the Committee concluded that, despite considerable exposure to cyproterone acetate, cases of primary hepatic cancer are uncommon. However, there was evidence of significant hepatotoxicity, seen mainly in patients being treated for prostatic cancer, which appeared to be related to dose and duration of treatment.

Therefore it was agreed that an additional warning statement on hepatotoxicity should be included in the summary of product characteristics for medicinal products containing cyproterone acetate (50 mg or more). A statement would also be included describing the preclinical findings and their relevance to the clinical situation.

Indications and dosage for products containing cyproterone acetate were agreed as follows:

- cyproterone acetate 2 mg in combination is prescribed in all EU Member States for treatment of acne in women. In some countries this is qualified as, for example, severe acne, oral contraception in women with severe acne, androgen-related acne, hirsutism.
- cyproterone acetate 50 mg and higher doses may be recommended for use in the management of patients with prostatic cancer: (1) to suppress "flare" with initial LHRH analogue therapy (recommended dosage: 300 mg/day which may be reduced to 200 mg/day); (2) in long-term palliative treatment where LHRH analogues or surgery are ineffective, not tolerated or contraindicated, or where oral therapy is preferred (recommended dosage: 200-300 mg/day); (3) to treat hot flushes in patients treated with LHRH analogues or who have had an orchidectomy (recommended dosage: a lower initial dose with upward titration if necessary).

1211 GENEVA 27-SWITZERLAND Telegr.: UNISANTE-GENEVA Telex: 415416 OMS Fax: 791.07.46 1211 GENÈVE 27-SUISSE Télégr.: UNISANTE-GENÈVE

- cyproterone acetate may also continue to be used to treat sexual deviation in adult males at an initial dosage of 50 mg daily.
- the indication of precocious puberty is no longer appropriate.
- cyproterone acetate 1 mg + estradiol valerate is approved in France, Luxembourg, the Netherlands and Belgium as hormone replacement therapy and in the treatment of osteoporosis.
- cyproterone acetate 2 mg in combination is *not* authorized in any Member State *solely* as an oral contraceptive, and should not be used solely for this purpose.[1]

Germany. Subsequently, the BfArM has restricted the indications for medicinal products containing cyproterone acetate (Diane® 35 coated tablets, Androcur®-10 tablets, Androcur® tablets and Androcur® depot solution for injections), with effect from 1 July 1995.[2]

- Oral contraception is no longer listed as an indication of cyproterone acetate-containing products in combination with estrogen (Diane® 35).

- This product is now only indicated for women suffering from severe androgenization, such as intense acne accompanied by pronounced scarring, in cases where both local treatment and oral antibiotic therapy have failed or where neither was tolerated.

- Diane® 35 is also indicated for certain forms and stages of loss of scalp hair in women.

- High-dose cyproterone acetate products (50 mg) have been restricted to use by women for whom all other therapies have failed (e.g. local treatment, antibiotic therapy, low-dose cyproterone acetate, other androgenic steroids).

The BfArM acknowledges that the currently available findings are neither qualitatively nor quantitatively sufficient for a final assessment of the carcinogenic potential of cyproterone acetate in man. Only one well-documented clinical case of liver cancer has been reported so far in Germany which could have been induced by Diane® 35 [3]. The patient had been taking Diane®/Diane® 35 for contraception for over 14 years and developed a fatal liver carcinoma. No other risk factors had been found. Pharmaceutical companies have been requested to conduct extensive studies to help clarify the risk potential of cyproterone acetate. In the meantime, the measures taken to limit use are considered to be necessary in the interest of patient health protection. The product remains available for therapeutic purposes in medicinal products with newly specified indications.

References:

1) *Committee for Proprietary Medicinal Products, European Commission. Pharmacovigilance Opinion No. 19 - Cyproterone acetate. Meeting of 13-14 December 1994.*
2) *BfArM Press release No. 3/95 dated 30 March 1995, Federal Institute for Drugs and Medical Devices, Berlin.*
3) *Lancet 1995, 345: 452.*

★ ★ ★