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Committee for Medicinal Products for Human Use (CHMP)

Lysodren

Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation

International non-proprietary name: mitotane

Procedure No.: EMEA/H/C/000521/PSUV/0016

Period covered by the PSUR: 29 April 2011-28 April 2014

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for Lysodren, the scientific conclusions of PRAC are as follows:

Four literature reports concerning CYP3A4 induction by mitotane treatment have been provided. This interaction is clinically relevant leading to: 1) drug-drug interaction between mitotane and other drugs also metabolized through CYP3A4, for instance, decreased sunitinib and midazolam exposure which can result in inadvertent therapeutic failure of the co-administered drugs; and 2) higher dose of glucocorticoid substitution therapy in mitotane-treated patients since the increase clearance rate of endogenous and exogenous glucocorticoids. The MAH should include this interaction in sections 4.4 and 4.5 of the SmPC. The package leaflet should be updated accordingly.

Isolated hepatic enzyme increase has been very commonly reported in mitotane- treated patients, especially isolated increase of Gamma-glutamyltransferase (GGT). Liver damages (hepatocellular, cholestatic and mixed) and autoimmune hepatitis have been reported. Patients with adrenal cortical carcinoma may have hepatic metastasis and hepatic dysfunction resulting from this. They may receive concomitant therapy with ketoconazole, a hepatotoxic drug, for the treatment of hypercortisolism and this may result in an increase in liver enzymes levels or a pre-existing hepatotoxicity. The SmPC should be updated to include a warning to recommend monitoring of liver function test. The package leaflet should be updated accordingly.

The MAH stated that a free service for testing plasma levels of mitotane in order to help prescribers to safely reach the therapeutic window (14-20 mg/L) is provided. Sections 4.2 and 4.4 of the SmPC highlight the relevance of monitoring mitotane plasma levels to adjust the mitotane dose. However, the information on the free testing service is not included in the SmPC of mitotane. The MAH should include this relevant information in the SmPC.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for Lysodren, the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing the active substance mitotane is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation should be varied.