ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET PRESENTED BY THE EMA

Scientific conclusions

Overall summary of the scientific evaluation of dexrazoxane-containing medicinal products (see Annex I)

Dexrazoxane is authorised in Europe through mutual recognition (MR), decentralised and national procedures for the prevention of anthracycline (doxorubicin or epirubicin)-induced cardiotoxicity. During the evaluation of a periodic safety update report (PSUR), concerns were raised regarding an increase risk of second malignancies neoplasms (SMN), in particular acute myelogenous leukaemia (AML)/myelodyspastic syndrome (MDS) and solid tumours in paediatric patients observed in studies reported in the literature. An increased risk of myelosuppression and infection was also observed in paediatric patients. In addition there were concerns regarding the potential carcinogenic/leukaemogenic risk of dexrazoxane, which is a known cytotoxic agent with topoisomerase II inhibition activity. The fact that clinical trials of razoxane (a racemic mixture of S(+)dexrazoxane and R(-) levrazoxane) were suspended due to safety concerns related to AML added to the concerns.

Dexrazoxane efficacy in the prevention of anthracycline cardiotoxicity is supported by available clinical trial data. The majority of studies in adults have been conducted in breast cancer patients. In particular, three open randomised studies conducted in the EU and the US and two placebo controlled studies conducted in the US showed that dexrazoxane significantly reduced the incidence of cardiac events (primarily a fall in left ventricular ejection fraction – LVEF) in breast cancer patients treated with doxorubicin. Sub-analysis of these studies also showed a significant reduction of congestive heart failure (CHF) events and a reduction in the severity of CHF events. The role of dexrazoxane in preventing epirubicin cardiotoxicity was also investigated in clinical studies which reported a reduction in the incidence of cardiac events (primarily a fall in LVEF) in patients treated with dexrazoxane and epirubicin compared with epirubicin alone.

Dexrazoxane is indicated in combination with anthracycline chemotherapy, and the risk of myelosuppressive effects may be additive to those of chemotherapy, which increases the risk of developing serious infections. In addition to serious infections, other important potential safety risks include a higher incidence of death observed in some studies in groups treated with dexrazoxane plus chemotherapy compared to those treated with chemotherapy alone, and evidence of possible interference with anthracycline efficacy. AML was also identified as an uncommonly reported adverse reaction.

Following the consultation of the Scientific Advisory Group (SAG) on oncology, the CHMP agreed that the therapeutic indication should be restricted to adult breast cancer patients who had received a prior cumulative dose of 300 mg/m^2 of doxorubicin or a prior cumulative dose of 540 mg/m^2 of epirubicin when further anthracycline treatment is required. The CHMP further advised that dexrazoxane should not be used in combination with adjuvant breast cancer therapy or chemotherapy intended as curative. In addition, considering the observed risks, including myelosuppression and excess early mortality reported in placebo-controlled US studies employing a dexrazoxane:doxorubicin dose ratio of 20:1, the CHMP considered that a reduction in the dexrazoxane dose is expected to have a favourable effect on dose-related safety issues. This was also the view of the SAG Oncology and the CHMP therefore recommended that the ratio of dexrazoxane to doxorubicin should be reduced from 20:1 to 10:1. The dose ratio of dexrazoxane to epirubicin remained unchanged at 10:1.

Regarding use of dexrazoxane in paediatric patients, available data on the efficacy of dexrazoxane was considered very limited by the CHMP, as only one adequately sized randomised study which used troponin T as a surrogate endpoint is available. Although a significant effect on troponin T levels was observed in an early report there was no evidence for clinical benefit in an updated analysis after a medium follow-up time of 5 years. Two large randomised open studies in childhood Hodgkin's disease and acute lymphoblastic leukaemia (ALL) reported a three-fold increase in the incidence of second primary malignancies (particularly AML and MDS) in dexrazoxane treated patients compared with controls. A significantly increased risk of other toxicities compared to controls were also reported

in the study in paediatric patients with Hodgkin's disease and included grade 4 neutropenia, grade 3/4 thrombocytopenia, grade 3/4 sepsis and grade 3/4 pulmonary toxicity. In addition, a signal of increased risk of solid tumours was noted. Based on the limited data on efficacy in this patient population, and the observed safety concerns, the Committee recommended that the use in children and adolescents up to 18 years of age should be contraindicated.

The CHMP considered that a direct healthcare professional communication should be sent in order to inform adequately on the changes recommended. As additional risk minimisation measures, the PSUR submission cycle will be shortened to an annual submission and the monitoring of the effectiveness of the risk minimisation measures will be conducted through a drug utilisation study.

Grounds for amendment of the summary of product characteristics and package leaflet

Whereas

- The Committee considered the referral under Article 31 of Directive 2001/83/EC, as amended, for dexrazoxane-containing medicinal products;
- The Committee took into account all available data, including the responses from the MAHs and the conclusion of the SAG Oncology;
- The Committee considered that the benefit-risk balance of dexrazoxane for the prevention of anthracycline (doxorubicin and epirubicin)-induced cardiotoxicity remains favourable in adult patients with advanced and/or metastatic breast cancer who have received a minimum prior cumulative dose of anthracyclines; therefore the CHMP recommended a restriction of the indication accordingly.
- The Committee also recommended that the ratio of dexrazoxane to doxorubicin should be reduced to take due account of the safety risks observed, including myelosuppression;
- The Committee considered that use of dexrazoxane in children and adolescents up to 18 years of age is associated with second primary malignancies and should therefore be contraindicated;
- The Committee recommended conditions to the marketing authorisation, including a direct healthcare professional communication, the shortening of the PSUR submission cycle to an annual submission and the monitoring of the effectiveness of the risk minimisation measures by means of a drug utilisation study.

the CHMP recommends the variation to the terms of the marketing authorisation of dexrazoxane-containing medicinal products (see Annex I), for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III. The CHMP also recommends conditions to the marketing authorisations, as set out in Annex IV.