Annex II

Scientific conclusions

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A type II grouping of variations application was submitted under the mutual recognition procedure for Cardioxane 500 mg powder for solution for infusion. The primary changes requested in the variation were:

- widening of the indication from “advanced and/or metastatic adult breast cancer patients” to “cancer patients”.
- removal of the contraindication in children and adolescents

The reference Member State (RMS) is: FR

The concerned Member States (CMS) are: CZ, DE, ES, IT, NL, PL and UK.

The mutual recognition procedure FR/H/0283/001/II/27G started on 28/11/2015.

The RMS considered that none of the data presented by the Marketing Authorisation Holder (MAH) were sufficiently supportive to widen the indication in adults; therefore, the first requested change on the widening of the indication to “cancer patients” was rejected.

Moreover, in the view of the presented data, the RMS considered not acceptable to fully remove the contra-indication in children, as requested by the MAH. However, the RMS considered acceptable to alleviate the contra-indication in children and proposed limiting it to children receiving low cumulative anthracycline doses (less than 300mg/m^2 of doxorubicin or equivalent).

UK did not concur with the RMS assessment related to the removal of the contra-indication for a certain subset of the paediatric population. In view of the potential serious risk to public health raised by UK, the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 13(1) of Regulation (EC) No 1234/2008 by France on 04/11/2016. The CMDh 60 day procedure was initiated on 02/12/2016.

Day 60 of the CMDh procedure was on 30/01/2017 and as no agreement could be reached, the procedure and the objections raised by the UK to the lifting of the contraindication for a subset of anthracycline treated paediatric population were referred to the CHMP on 31/01/2017 by the RMS.

Overall summary of the scientific evaluation by the CHMP

Anthracycline related cardiac damage can be acute, manifesting as acute heart failure, reduction in the shortening fraction or changes to the ventricular wall thickening. This usually occurs during treatment or within the first years post treatment. Delayed effects usually manifest as congestive heart failure which can occur up to 20 years post treatment. Although studies suggest there is no safe dose of anthracycline, it is known that the risk of anthracycline induced cardiotoxicity increases with higher cumulative dosing; guidelines imply that above 250 mg/m^2 there is sufficient cardiac risk to provide recommendations on lifelong surveillance[1]. High cumulative doses of anthracycline are rarely used in the paediatric population; however, they are requested for the treatment of some pathologies such as sarcomas and relapsed acute myeloid leukaemia. The affected paediatric patients consequently treated are at high risk of acute anthracycline cardiotoxicity, as a consequence of the high doses of chemotherapy received; therefore, a treatment with a cardioprotective agent is needed in this very small number of patients.

[1] Armenian S.H., Hudson M.M., Mulder R.L., Chen M.H., Constine L.S., et al. ‘Recommendations for Cardiomyopathy Surveillance for Survivors of Childhood Cancer: A Report from the International Late Effects of Childhood Cancer Guideline Harmonization Group’ Lancet Oncology, Vol. 16(3), March 2015, p. e123-e136

The data assessed during the Art.31 referral procedure in 2011 regarded the carcinogenic potential of dexrazoxane due its cytotoxic activity and on the occurrence of second malignant neoplasms in the paediatric population; such data justified the introduction of a contraindication of the product in children aged 0 to 18 years.

The evaluation of the data submitted as part of this procedure have allowed a better characterisation of the risk of the short term effects on SPM, myelosuppression and infections, following treatment with DRZ in children undergoing chemotherapy with anthracycline based regimens. However there are still remaining uncertainties with regard to long term effects for DRZ in children. DRZ efficacy as a cardioprotectant has not been demonstrated in children for cumulative anthracycline doses of less than 300 mg/m^2. This is due either to a low rate of clinical cardiac events in patients in the included RCTs or to the small numbers of patients who were treated with lower cumulative doses of anthracyclines and the relatively short duration of follow-up of these patients. With higher cumulative doses of anthracyclines, studies (including several RCTS and non-randomised studies) have showed that DRZ could improve the surrogate cardiac markers and therefore reduce subclinical acute cardiotoxicity. Although the cardiac markers used in the original studies may not be as robust as those used currently, they provide some evidence of DRZ acute cardioprotective effect. However, there is currently no established correlation between the used cardiac markers and the long term cardioprotective effects of DRZ as data are unavailable due to the length of follow-up needed. There is therefore no robust long term efficacy data that demonstrate that the use of DRZ prevents the chronic or long term cardiotoxic effects of anthracyclines in the paediatric population.

Data are reassuring as regard to occurrence of SPMs in children after being exposed to DRZ, up to 12 years post treatment. However, data assessed are still insufficient to provide reassurance concerning the occurrence of long-term risk of SPM particularly solid SPMs. The assessment of this risk is confounded by concomitant chemotherapy treatments, small numbers of patients and the overall rarity of SPM events. The studies may not have been sufficiently powered to observe a statistically confirmed increase of SPM. Unravelling confounders for the cause of SPM would be difficult and overall the long term risk of SPM remains unknown at present.

The CHMP noted that the MAH will reflect the ongoing observational study (Effects of Dexrazoxane Hydrochloride on Biomarkers Associated with Cardiomyopathy and Heart Failure after Cancer Treatment, NCT01790152.) in their Risk Management Plan as appropriate.

The CHMP was informed that the MAH will conduct a prospective safety study in children using existing cancer disease registries to collect data on dexrazoxane use in the paediatric population, the incidence of adverse events (e.g. secondary malignancies, myelosuppression and infections) and the long-term (>12 years) cardiac effects (including cardiac failure, left ventricular failure).

It is acknowledged that DRZ may increase the risk of myelosuppression and infections; however these risks can be minimised by appropriate measures currently in place in standard paediatric treatment protocols. Moreover, there is evidence that there is no delay to chemotherapy treatment as a result of a potential DRZ myelosuppression effect. Furthermore, in the short (up to 5 years post treatment) to medium term (up to 12 years post treatment) anthracycline's anti-tumour efficacy was not compromised by DRZ use.

In this context and considering

- the high risk for long term occurrence of severe cardiomyopathy when using high cumulated dose of anthracycline in children and adolescents
- the medical need of high anthracycline dosing regimen for pathology such as sarcoma or AML relapses in children and adolescents

- updated safety data leading to reassurance as regard to the occurrence of SPMs, particularly AML and MDS,

The CHMP considers that the presented data support the removal of the contraindication for Cardioxane for the subset of paediatric population receiving high cumulative anthracycline doses (above 300mg/m^2 of doxorubicin or equivalent).

Grounds for the CHMP opinion

Whereas

- The Committee considered the referral under Article 13 of Regulation (EC) No 1234/2008.
- The Committee considered the data submitted by the MAH in relation to the objections raised on the lifting of the contraindication for Cardioxane in children and adolescents receiving high cumulative doses of anthracycline.
- The Committee noted the reassuring safety data on the occurrence of secondary primary malignancies in particular acute myelogenous leukaemia and myelodysplastic syndrome in children and adolescents aged 0 to 18 years, the high risk for long term occurrence of severe cardiomyopathy when using high cumulated dose of anthracycline in children and adolescents and the medical need of high anthracycline dosing regimen for pathology such as sarcoma or acute myelogenous leukaemia relapses in children and adolescents
- The Committee concluded that, in view of the above, it is justified to limit the contraindication for Cardioxane in children aged 0 to 18 years receiving low cumulative anthracycline doses (less than 300 mg/m^2 of doxorubicin or equivalent)
- The Committee was of the view that amendments to the product information are required, as well as the introduction of routine pharmacovigilance activities in the form of specific follow-up questionnaires to collect safety and efficacy on the use of the medicinal product in children.

The Committee, as a consequence, recommends the granting of the variation to the terms of the marketing authorisation for the medicinal products referred to in Annex I of the CHMP opinion subject to the amendments to the product information as set out in Annex III of the CHMP opinion and the amendments of the risk management plan as described above.