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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 13 of Regulation (EC) No 1234/2008

Cardioxane

INN: dexrazoxane

Procedure number: EMEA/H/A-13/1453

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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1. Background Information

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/m² 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.

2. Scientific discussion

2.1. Introduction

Cardioxane is a dexrazoxane-containing medicinal product. Dexrazoxane (DRZ) is an analogue of ethylenediaminetetraacetic acid (EDTA) with an inhibitory activity on topoisomerase II. It prevents the chronic cumulative cardiotoxicity associated with the use of anthracyclines.

In 2011, in the frame of a referral under Article 31 of Directive 2001/83/EC¹, the Committee for medicinal products for human use (CHMP) (hereinafter ‘the Committee’) concluded that the benefit-risk balance of DRZ-containing medicinal products was positive in the following restricted indication ‘Prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin use in advanced and/or metastatic adult breast cancer patients who have received a prior cumulative dose of 300 mg/m² of doxorubicin or a prior cumulative dose of 540 mg/m² of epirubicin when further anthracycline treatment is required’. Moreover, the CHMP recommended the contraindication of DRZ-containing medicinal products in children and adolescents up to 18 years of age.

¹ Assessment report dexrazoxane-containing medicinal products (EMA/775079/2011).

The revision of the indication and the inclusion of the contraindication in the paediatric population were justified after the evaluation of the available data showing an increased risk of second primary malignancies (SPMs), risk of myelosuppression and therefore potential risk of serious infections, as well as a lack of evidence of cardioprotective effect in patients treated with DRZ containing medicinal products.

In particular, for the paediatric population, the Committee concluded that:

- The efficacy of DRZ in children had not been established
- There was an increased risk of SPMs, particularly acute myelogenous leukaemia (AML) and myelodysplastic syndrome (MDS) in children with Hodgkin disease treated with DRZ
- DRZ was associated with an increased risk of other toxicities including neutropenia, sepsis, thrombocytopenia, and pulmonary toxicity in paediatric patients with Hodgkin disease.
- A signal for an increased risk of solid tumours was also noted

In 2016, based on data generated since the last abovementioned CHMP review, the Marketing Authorisation Holder (MAH) of Cardioxane submitted a type II grouping of variations to the relevant Member States in order to request the removal of the contraindication in the paediatric population from the product information of Cardioxane, with consequential amendments to other aspects of the Product Information (PI) and Risk Management Plan (RMP).

In the view of the presented data, the Reference Member State (RMS) did not consider it acceptable to fully remove the contra-indication in children, as requested by the MAH. However, considering the high risk for long term occurrence of severe cardiomyopathy when using high cumulated dose of anthracycline (more than 300 mg/m² doxorubicin or 540 mg/m² epirubicin) and the medical need for pathology such as sarcoma in children or AML relapses in both children and adults, and based on updated safety data leading to reassurance as regard to efficacy of concomitant chemotherapy as well as occurrence of AML and MDS but not secondary long term tumours, the RMS considered acceptable to alleviate contra-indication in children. The proposed wording was the following: "Children and adolescents planned to receive cumulative dose of less than 300 mg/m² of doxorubicin or a cumulative dose of less than 540 mg/m² of epirubicin".

In the view of remaining uncertainties on the safety and efficacy of the product in the paediatric population, the UK did not concur with the RMS assessment. Therefore, a referral was made to the CMDh under Article 13 Regulation (EC) No 1234/2008. Following the CMDh discussion, in view of the remaining uncertainties and taking into account the previous outcome of the Article 31 referral, the UK was unable to agree with the RMS recommendation. The matter has therefore been referred to CHMP for arbitration to determine if the proposed lifting of the contraindication for a subset of anthracycline treated children is justified.

2.2. Assessment of the issues raised as a potential serious risk to public health

To support its claim to remove the contraindication in the paediatric population aged 0 to 18 years, the MAH submitted bibliographic data deriving from randomised control trials (RCTs) and non-Randomised Studies (NRSs).

More than 4000 paediatric patients were exposed to DRZ in the data from the RCTs provided by the MAH, mainly affected by acute lymphoblastic leukaemia (ALL), Non-Hodgkin's lymphoma and Hodgkin's lymphoma. The majority of the randomised control trials considered was phase III studies conducted on the Children Oncology Group (COG) in the United States (US), where no paediatric contraindication is in place. Patients enrolled were mostly adolescents, treated with doxorubicin. The

cumulative doses of doxorubicin ranged from 100 to 600 mg/m². The dose of DRZ was given in a ratio of 10:1 (to the dose of doxorubicin) in the majority of the published studies^{2,3,4}, although it is noted that in one study⁵ the dose of DRZ used was higher (20:1). It should be noted that the dose currently recommended in adults is equal to 10 times the doxorubicin-equivalent dose (see section 4.2 of the Cardioxane Summary of Product Characteristics, SmPC). All RCTs used DRZ beginning with the first dose of doxorubicin. Only two RCTs have specifically reported their cardiotoxicity outcomes as full papers^{6,7}.

The paediatric NRSs submitted suffered from the usual limitations due to this type of design, mainly the selection biases commonly seen in the absence of random assignment. The most important bias commonly observed in these studies was time related selection bias. The follow-up time among patients on the DRZ arm was similar to that in patients on the control arm in only the minority of the studies. In view of these limitations, data deriving from the NRSs have to be interpreted with caution and were therefore considered non-supportive during this review.

2.2.1. Anthracycline-induced cardiotoxicity in children and adolescents

The cardiotoxic effects of anthracyclines in children aged 0 to 18 years are of particular concern as these cardiotoxic effects are often progressive and irreversible. However, the true incidence of cardiomyopathy in children after exposure to anthracyclines remains unknown. This can be due to several confounding factors, including variable definitions for the assessment of cardiotoxicity and differing cumulative doses of anthracyclines given. From the published data, the only independent risk factor identified for anthracycline cardiotoxicity was a cumulative dose of higher than 300 mg/m² of doxorubicin or equivalent anthracycline. No clear correlation between anthracycline cardiotoxicity and other risk factors has been identified.

Monitoring of cardiac toxicity is done through a variety of biochemical and echocardiographic cardiac surrogate markers (e.g. Cardiac troponin T, pro- Brain Naturetic Peptide as well shortening fraction, ventricular wall thickness and measurements of diastolic function), that have been used in various combinations to monitor acute effects of anthracycline cardiotoxicity and therefore to assess the acute cardioprotective effects of DRZ (as described in section 2.2.2.).

In children, high cumulative doses of anthracyclines are used in the treatment of rare solid and haematological malignancies (osteosarcoma, neuroblastoma, AML, Hodgkin's lymphoma). In such cases, the use of the best effective doses of anthracyclines is balanced by the risk of treatment failure (by using lower anthracycline doses) and the risk of acute and long-term treatment related cardiotoxicity.

² Asselin B., Devidas M., Zhou T., Camitta B., Lipshultz S. 'Cardioprotection and safety of dexrazoxane (DRZ) in children treated for newly diagnosed T-cell acute lymphoblastic leukaemia (T-ALL) or advanced stage lymphoblastic leukaemia (T-LL)', *Journal of Clinical Oncology*, Vol. 30:15 suppl, 2012, p. 9504

³ Lipshultz S.E., Miller T.L., Scully R.E., Lipsitz S.R., Rifai N. et al., 'Changes in cardiac biomarkers during doxorubicin treatment of paediatric patients with high-risk acute lymphoblastic leukaemia: associations with long-term echocardiographic outcomes', *Journal of Clinical Oncology*, Vol. 30(10), April 2012, p. 1042-1049

⁴ Schwartz C.L., Wexler L.H., Krailo M.D., Teot L.A., Devidas M. et al., 'Intensified Chemotherapy with Dexrazoxane Cardioprotection in Newly Diagnosed Non-metastatic Osteosarcoma: A Report from the Children's Oncology Group', *Pediatric Blood Cancer*, Vol. 63(1), January 2016, p. 54-61

⁵ Wexler L.H., Andrich M.P., Venzon D., et al. 'Randomized trial of the cardioprotective agent ICRF-187 in paediatric sarcoma patients treated with doxorubicin', *Journal of Clinical Oncology*, Vol. 14(2), 1996, p. 362-372.

⁶ Lipshultz SE, Rifai N, Dalton VM, et al. 'The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia' *New English Journal of Medicine*, Vol. 351(2), 2004, p. 145-153.

⁷ Schiavetti A., Castello M.A., Versacci P., Varrasso G., Padula A., et al. 'Use of ICRF-187 for prevention of anthracycline cardiotoxicity in children: preliminary results' *Pediatric Hematology Oncology*, Vol. 14(3), May-Jun 1997, p. 213-222.

The vast majority of current paediatric protocols avoid high cumulative doses of anthracyclines. The exception is a small cohort of children who require treatment with high cumulative doses of anthracycline (>300mg/m² of doxorubicin or equivalent); these patients have poor survival outcomes, high risk disease, and these patients are at high risk of acute anthracycline cardiotoxicity which limits the intensity of the given chemotherapy. In such high risk patients, the aim of chemotherapy treatment remains curative, thus there is a need for an effective cardioprotective agent.

2.2.2. Efficacy of Cardioxane in the paediatric population

The efficacy of DRZ when used in children receiving low cumulative doses of anthracyclines (less than 300 mg/m² of doxorubicin) could not be reliably determined due to small numbers of patients given low cumulative doxorubicin doses, the low incidence of cardiotoxicity in both arms of the reported trials and the relatively short duration of follow-up of these patients⁸.

With higher cumulative anthracycline doses ≥ 300 mg/m², an acute cardioprotective effect, as assessed by the surrogate cardiac markers, was observed in patients who received DRZ with anthracyclines when compared to those who received only anthracycline treatment. Wexler et al describes the data among patients with anthracycline treated with cumulative doses ≥ 300 mg/m². Authors found that randomly assigned patients with sarcoma (n=38) who received DRZ had significantly smaller decrease in left ventricular ejection fraction during treatment than those who did not, which enabled the DRZ group to receive higher cumulative doxorubicin doses (410 mg/m²). Patients received the DRZ at a higher dosage (20:1) than the one currently recommended (10:1).

None of the presented studies were of sufficient duration to assess DRZ effect with regards to long term protection for anthracycline induced cardiotoxicity. Developments in the way biochemical assays are performed, as well as enhanced imaging techniques have improved the reliability and sensitivity of these markers when compared to those used in early paediatric studies. However, these cardiac surrogate markers are not yet known to correlate with long term cardiac dysfunction and thus cannot be safely used to predict the long term cardioprotective effect of DRZ. Therefore, there is no robust long term efficacy data showing a correlation between the used surrogate markers and the long term cardioprotective effects of DRZ.

An ongoing, long term, follow-up study in paediatric patients who were early recipients of DRZ may provide the evidence of such a correlation. Such study is the observational study ALTE11C2 on which preliminary data have been published in Chow et al 2016⁹. This study is currently enrolling patients from the previous US paediatric studies POG 9404, 9425 and 9426 which ran from 1996 to 2001. At the estimated completion date in January 2019, up to 23 years of follow-up post DRZ treatment will have been completed, with data available for evaluating DRZ long term cardioprotective benefit and secondary malignancy risk. The final clinical study report of this study will be helpful for the assessment of the long term cardioprotective effects and long-term safety of DRZ.

⁸ Shaikh F., Dupuis L.L., Alexander S., Gupta A., Mertens L., et al, 2015 'Cardioprotection and Second Malignant Neoplasms Associated with Dexrazoxane in Children Receiving Anthracycline Chemotherapy: A Systematic Review and Meta-Analysis', Journal of the National Cancer Institute, Vol. 108(4), November 2015

⁹ Chow E.J., Doody D.R., Armenian S.H., Aggarwal S., Baker K.S., 'Effect of Dexrazoxane on Heart Function among Long- Term Survivors of Childhood Leukemia and Lymphoma: A Report from the Children's Oncology Group (COG)', Blood, Vol. 128(22), 2016, p. 696

2.2.3. Safety of Cardioxane in the paediatric population

2.2.3.1. Risk of Secondary Primary Malignancies

The data provided by the MAH on the RCT suggest that, among paediatric patients with Secondary Primary Malignancies (SPMs, particularly AML and MDS), after a follow-up of more than 5 years, DRZ use did not seem to compromise long term survival¹⁰. These data lead to reassure as regard to potential AML/MDS induction after DRZ exposure. It is noted that the rarity of paediatric cancers limits the robustness of the data provided by these studies (including the Asselin 2016 study¹¹). With regards to the non-randomised studies, any association between the use of DRZ and the occurrence of second malignancies is difficult to evaluate as the results are confounded by the concomitant use of other chemotherapy agents which are known to increase by themselves the risk of SPM.

2.2.3.2. Risk of myelosuppression and infection

Myelosuppression and infections are known adverse drug reactions of DRZ and are documented in sections 4.4 and 4.8 of the DRZ's SmPC. However, three of the presented studies^{5,11,12}, also report that the additive myelosuppressive effects of DRZ did not delay chemotherapy treatment nor led to significant dose modifications of the chemotherapy regimens used. Although further assessment is needed to establish any potential influence of DRZ on chemotherapy regimens, these data provide reassurance that DRZ treatment do not significantly alter short (5 years post treatment) to medium term (up to 12 years post treatment) related outcomes for treated patients.

3. Benefit-risk balance

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/m² there is sufficient cardiac risk to provide recommendations on lifelong surveillance¹³. 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.

The data assessed during the Article 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

¹⁰ Chow E.J., Asselin B.L., Schwartz C.L., Doody D.R., Leisenring W.M., Aggarwal S., et al. 'Late mortality after dexrazoxane treatment: A report from the Children's Oncology Group', *Journal of Clinical Oncology*, Vol. 33(24), August 2015, p. 2639–2645

¹¹ Asselin B.L., Devidas M., Chen L., Franco V.I., Pullen J., et al. 'Cardioprotection and Safety of Dexrazoxane in Patients Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic Non-Hodgkin Lymphoma: A Report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404', *Journal of Clinical Oncology*, Vol. 34(8), March 2016, p. 854-862

¹² Schwartz C.L., Constine L.S., Villaluna D., Wendy B. L., Hutchison R.E., et al. 'A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of POG 9425', *Blood*, Vol. 114(10), September 2009, p. 2051-2059

¹³ 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

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/m². 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/m² of doxorubicin or equivalent).

4. Risk management

The CHMP considered that the risk management plan (RMP) should be amended to reflect the updated safety specifications, the risk minimisation measures and pharmacovigilance activities as described below.

A revised risk management plan should be submitted within 1 month from the EC Decision on this procedure.

- Part II (**Safety Specification**) of the RMP should be amended to include “Lack of long-term (>12 years) cardioprotective effects (leading to adverse effects such as cardiac failure, left ventricular failure) in children” as an important potential risk.
- The MAH shall develop a specific **follow-up questionnaire** to collect further information for adverse events reported with use of Cardioxane in children. The information should notably relate to:
 - Cardioxane use (dose, date and duration, etc.), concomitant medication received (cumulative anthracycline dose, any other chemotherapy and radiotherapy received),
 - any acute adverse events (e.g. cardiac, haematological, severe infection),
 - any information available on the follow-up of patients (such as outcomes, post medical history, treatment given for adverse events etc.).

The proposed follow-up questionnaire should be described in the pharmacovigilance activities section of the RMP.

- **Updates to the Product Information:** the CHMP considered that amendments to sections 4.2 and 4.3 of the SmPC were necessary to reflect the outcome of this review, as described in the attachment 1 of this Assessment Report. The Package Leaflet should be updated accordingly. The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation measures are required beyond the routine ones included in the product information.

Periodic Safety Update Reports submission

The CHMP is of the opinion that the already existing entry in the EURD list for dexrazoxane needs to be amended as follows: the PSUR cycle should follow a yearly cycle. The next data lock point will be 28/02/2018. This will allow an adequate close monitoring of the safety concerns for this medicinal product.

5. Grounds for 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/m² 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.