NOVARTIS

DEAR HEALTHCARE PROFESSIONAL COMMUNICATION

Important Safety Information on Cardioxane® (dexrazoxane)

Dear Health Care Professional

Subject: Information on the association of Cardioxane® with an increased risk of secondarymalignancies in children.

Summary

Cardioxane® SmPC is being updated to reflect the increased risk of secondary malignancies. The SmPC is updated as follows:

- Section 4.4 Warnings and Precautions:
"*In clinical trials, secondary malignancies have been reported in paediatric patients with Hodgkin's disease and acute lymphoblastic leukaemia receiving chemotherapy regimes including several cytotoxics (e.g. etoposide, doxorubicin, cyclophosphamide).*
Since dexrazoxane is a cytotoxic agent, with topoisomerase II inhibition activity, combination of dexrazoxane with chemotherapy may lead to an increased risk of secondary malignancy".

- Section 4.8 Undesirable effects:
"*Secondary acute myeloid leukaemia (AML) / myelodysplastic syndrome (MDS) has been observed in paediatric patients with Hodgkin's disease or acute lymphoblastic leukaemia receiving dexrazoxane in combination with chemotherapy.*"

Further information on Cardioxane and the safety concern

Cardioxane (dexrazoxane) is an analogue of ethylene diamine-tetraacetic acid (EDTA) with a topoisomerase II inhibition activity. It is indicated for the prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin use in advanced and/or metastatic cancer patients after previous anthracycline containing treatment.

One publication (Tebbi, 2007) reported unexpected adverse outcomes from 2 clinical trials conducted in paediatric patients with Hodgkin lymphoma receiving dexrazoxane as cardiopulmonary protectant and treated with doxorubicin, bleomycin, vincristine, and etoposide (ABVE) or ABVE-PC (prednisone, cyclophosphamide)
A total of eight patients developed AML/MDS, of whom six were receiving treatment with dexrazoxane. There were two solid tumours (osteosarcoma and papillary thyroid carcinoma), and both occurred in recipients of dexrazoxane.
The 4-year cumulative incidence rate for any Second Malignant Neoplasms (SMN) was 3.43% +/- 1.2% in the dexrazoxane group vs. 0.85% +/- 0.6% in the non-dexrazoxane group (p=0.06).

The unusual pattern of the reported AML/MDS and solid tumours, suggests that occurrence of SMN could be attributable at least in part, to the effect of combining dexrazoxane with multiple topoisomerase II inhibitors (e.g. etoposide, doxorubicin).

NOVARTIS

More recently, Salzer et al, 2010, reporting long-term outcomes of paediatric trials in ALL, included one trial in which the 10-year cumulative incidence of second malignancies was 4.2±2.2% in patients who had received dexrazoxane versus 1.3±0.9% in patients who had not received dexrazoxane. In this study the patients had been exposed to only one topoisomerase II inhibitor, doxorubicin.

Although it is recognised that the underlying disease and the administration of chemotherapy can itself predispose to second malignancies, a potential risk of experiencing a second primary malignancy in children when Cardioxane is administered with several cytotoxic agents cannot be excluded.

Call for reporting:

Healthcare professionals should report any adverse event associated with the use of Cardioxane® to Novartis at (01) 2080612. Alternatively, this information may be reported to the Irish Medicines Board directly, in accordance with your local reporting requirements.

Communication information

Should you have any questions or require additional information regarding the use of Cardioxane please contact the Novartis Medical Advisor at (01) 2175853.

Literature references

[Salzer WL, Devidas M, Carroll WL, et al (2010)]. Long-term results of the pediatric oncology group studies for childhood acute lymphoblastic leukemia 1984-2001: a report from the children's oncology group. Leukemia 24:355-370

[Tebbi CK, London WB, Friedman D, et al (2007)]. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. J Clin Oncol; 25:493-500

Annexes

Revised SmPC and Patient Information Leaflet (with changes highlighted)

Karine Egan

Karine Egan, PhD
Medical Advisor

26 July 2010

Date