Dexrazoxane in children: European disagreements and arbitration

● **In 2017, *dexrazoxane* was re-approved in the European Union for use in children treated with high doses of anthracyclines. However, uncertainties remain.**

Dexrazoxane, an iron chelator with cytotoxic properties, is authorised for use as a cardioprotective agent in some patients treated with anthracyclines (1). Anthracyclines such as *doxorubicin* are cytotoxics that carry a risk of heart failure, sometimes several years after the end of treatment. The cardiotoxicity of anthracyclines increases with the cumulative dose received. *Dexrazoxane* seems to be particularly useful in patients at very high cardiac risk and/or for whom very high doses of anthracyclines appear to be justified (2).

In 2011, the use of *dexrazoxane* was contraindicated in children, due to an increased risk of so-called secondary cancers and unproven efficacy in children (3). In late 2015, the company submitted bibliographic data to the European authorities to justify the use of *dexrazoxane* in children. The lack of consensus between EU national agencies led to an arbitration procedure being carried out by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP). In 2017, this committee concluded that use of *dexrazoxane* was justified in children who receive cumulative doses of anthracyclines greater than 300 mg/m^2, for example for sarcomas or relapsed acute myeloid leukaemia. The CHMP justified its position on the basis of data showing prevention of heart failure with *dexrazoxane* in children exposed to high doses of anthracyclines (but with no details regarding the level of short-term protection). According to the CHMP, there did not appear to be any increased risk of secondary cancers in children followed for up to 12 years after exposure to *dexrazoxane* (4,5). Nevertheless, the low level of evidence provided by these data led to the following amendment to the European summary of product characteristics (SPC): *"The safety and efficacy (...) in children aged 0-18 years has not been established"*. This illustrates the uncertainty surrounding this decision (1,4).

In practice Since its introduction onto the European market in the 1990s, evaluation of *dexrazoxane* is insufficient to determine its harm-benefit balance. Nearly 20 years on, disagreement between agencies shows that substantial uncertainties remain.

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Selected references from Prescrire's literature search

1- ANSM "RCP-Cardioxane" 6 September 2017: 11 pages.
2- Prescrire Rédaction "Dexrazoxane: cardioprotection modérée et risques graves" *Rev Prescrire* 2014; **34** (365): 187.
3- Prescrire Rédaction "Dexrazoxane: restrictions d'utilisation bienvenues" *Rev Prescrire* 2012; **32** (342): 265.
4- European Commission "Annexes-Cardioxane" 19 July 2017: 10 pages.
5- EMA - CHMP "Assessment report. Referral under article 13 of Regulation (EC) No 1234/2008. Cardioxane-EMEA/H/A-13/1453" 18 May 2017: 10 pages.

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