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Patient Health Protection

## Assessment report Dexrazoxane-containing medicinal products

INN/active substance: dexrazoxane

Procedure number: EMEA/H/A-31/1275

Referral under Article 31 of Directive 2001/83/EC, as amended

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



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## 1. Background information on the procedure

### 1.1. Referral of the matter to the CHMP

On 8 July 2010, the United Kingdom triggered a referral under Article 31 of Directive 2001/83/EC, as amended for dexrazoxane-containing medicinal products, requesting the committee for Medicinal products for human use (CHMP) to evaluate the available data relating to evidence of an increased risk of second primary malignancies, myelosuppression and infection, particularly in paediatric patients, and on the use of dexrazoxane in the prevention of anthracycline-induced cardiotoxicity. The CHMP was requested to give its opinion on whether the marketing authorisations for dexrazoxane-containing medicinal products should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

## 2. Scientific discussion

### 2.1. Introduction

Dexrazoxane is authorised in Europe for the prevention of anthracycline (doxorubicin or epirubicin)-induced cardiotoxicity<sup>1</sup>. In April 2010, concerns were raised by the reference member state (RMS, France) for the products authorised through Mutual Recognition Procedure in the context of the assessment of data submitted within the periodic safety update report (PSUR) worksharing procedure. The review of the 3-yearly PSUR covering the period from 01 March 2006 to 28 February 2009 noted a signal emerging from the published literature (*Tebbi et al, 2007, Salzer et al, 2010*). Data from clinical trials raised concerns that exposure to dexrazoxane may increase the risk of second malignant neoplasms (SMN), in particular acute myelogenous leukaemia (AML)/myelodysplastic syndrome (MDS) and solid tumours in paediatric patients. An increased risk of myelosuppression and infection was also observed in paediatric patients.

A review of the benefit in terms of cardioprotection and the risk of secondary malignancies was undertaken by the RMS and discussed at the Pharmacovigilance working party (PhVWP) in June 2010. There were concerns regarding the potential carcinogenic/leukaemogenic risk of dexrazoxane, particularly as razoxane (a racemic mixture of S(+)dexrazoxane and R(-)levrazoxane), was shown to be mutagenic and carcinogenic in animals and that clinical trials for razoxane (a drug authorised in the 1970s in the UK for the treatment of malignant lymphomas and acute leukaemias) were suspended in 1983 due to safety concerns related to reports of AML in adults.

As a consequence, a referral procedure under Article 31 of Directive 2001/83/EC, as amended, for dexrazoxane-containing products was initiated on 22 July 2010. Available data on the increased risk of second primary malignancies, myelosuppression and infection, particularly in paediatric patients, and on the use of dexrazoxane in the prevention of anthracycline-induced cardiotoxicity was considered in the context of this procedure.

Dexrazoxane-containing medicinal products are authorised as prescription-only medicines in 20 EEA member states, including Austria, Czech Republic, Germany, Denmark, Finland, France, Greece, Hungary, Ireland, Italy, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain and the United Kingdom. These products are authorised through mutual recognition, decentralised or national procedures under the trade names Cardioxane, Cyrdanax, Dexrazoxane Cyathus, Enaxozar and Procard.

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<sup>1</sup> An additional dexrazoxane containing medicinal products is also centrally authorised in the EU as an orphan medicinal product, under the name Savene. It is indicated for the treatment of anthracycline extravasation, which occurs rarely. The concerns regarding an increased risk of second malignant neoplasms were not applicable and Savene was not included in the scope of this procedure.

## 2.2. Clinical efficacy

### 2.2.1. Non-clinical and clinical studies

#### 2.2.1.1. Non-clinical studies

A summary of the available mutagenicity studies with dexrazoxane and the racemic mixture, razoxane was considered in this review. The data showed that the mutagenic potency of razoxane in mouse lymphoma cells was highly dependent on the concentration and exposure time. In the Chinese hamster fibroblast cell line, razoxane was shown to be cytotoxic and mutagenic. In addition, inhibition of scheduled DNA synthesis and induction of unscheduled DNA synthesis was observed. In the Chinese hamster metaphase assay, razoxane up to 500 mg/kg orally induced abnormal chromosome condensation and an increase in structural chromosome aberrations (7-fold compared to control value) as well as an increase in the number of polyploidy cells (8-fold compared to control value). Effects were dose-dependent. At lower doses of 20 and 50 mg/kg, the types of damage (translocations and deletions) observed were different from the vehicle control and were considered to be of biological significance. In the mouse micronucleus test, a single oral dose of 1000 mg/kg of dexrazoxane was shown to be mutagenic. Razoxane at doses of 200 and 400 mg/kg intra-peritoneally was cytotoxic to bone marrow cells. A 5-fold increase in micronuclei in polychromatic erythrocytes was observed at the 200 mg/kg dose level.

#### 2.2.1.2. Clinical trials

The cardioprotective efficacy of dexrazoxane was evaluated in randomised controlled clinical trials. The majority of the studies evaluated the incidence of cardiac events using a subclinical endpoint (left ventricular ejection fraction, LVEF, a surrogate marker for risk of CHF) with or without a clinical endpoint (congestive heart failure, CHF). The majority of the trials were conducted in female patients with advanced breast cancer and most patients had not previously received anthracyclines. Clinical trial information is available from published literature. A summary of the most relevant trials is detailed below.

***Swain et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol 1997; 15: 1318-1332.***

In this study, breast cancer patients were randomised to two multi-centre, double-blind studies (088001 and 088006) and received fluorouracil, doxorubicin and cyclophosphamide (FAC) with either dexrazoxane or placebo. An increased death rate in the dexrazoxane group was observed in the first 9 months of these studies. The cause of this phenomenon was not found, but it led to a decision by the investigator to reduce the ratio of dexrazoxane to doxorubicin from 20:1 to 10:1. A total of 534 patients received the lower dose ratio. The risk of developing cardiac events (decrease in LVEF or CHF) in the latter patients was significantly reduced in the dexrazoxane arm compared to placebo in both studies. Combined analysis of both studies showed that the incidence of CHF was 8% (22 patients) in the placebo arm and 1% (2 patients) in the dexrazoxane arm. A lower incidence of CHF was reported in dexrazoxane recipients (0-3%) compared to control group patients (5-27%) which was statistically significant. The objective response rate for study 088001 was significantly lower on dexrazoxane (46.8%) than on placebo (60.5%) ( $p=0.019$ ); no difference in response rate was observed in study 088006). Grade 3/4 leucopenia recorded at nadir was significantly more common in dexrazoxane-treated patients than in the placebo recipients (78% versus 68%;  $p<0.01$ ). However, the incidence of grade 3/4 granulocytopenia and thrombocytopenia was similar between treatments. Patients in the dexrazoxane treatment group had lower overall platelet counts, but this was largely because of higher incidence of grade 1 toxicity compared with placebo (47% vs. 29%;  $P<0.01$ ). Other adverse events commonly associated with chemotherapy generally occurred at similar incidences in both arms. No major differences between dexrazoxane arms and placebo arms were reported regarding withdrawal due to non-cardiac adverse events or deaths during treatment. The combined total death rate from both studies was 20 out of 534 patients (3.7% in total, 3.2% on dexrazoxane and 4.2% on placebo).

***Speyer et al. ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. J Clin Oncol 1992; 10: 117-27.***

In the Speyer study (NYU83-05-NCI), 150 patients were randomised to receive FAC with or without dexrazoxane at a ratio of dexrazoxane:doxorubicin of 20:1. The percentage of patients free of 'clinical or scan' toxicity (decrease in LVEF) was significantly higher in the dexrazoxane group. Two patients in

the dexrazoxane group developed CHF compared with 20 in the control group ( $p < 0.001$ ). One patient in the dexrazoxane group died of cardiac failure during treatment and one other patient in the dexrazoxane group developed CHF and died subsequently during the follow-up period. A statistically significant lower incidence of CHF was reported in dexrazoxane recipients (0-3%) compared to control group patients (5-27%). No statistically significant differences in the incidence of non-haematological and non-cardiac adverse events (alopecia, nausea and vomiting, stomatitis, fever and toxic-related deaths) were observed. Patients treated with a dexrazoxane had significantly lower platelet and leukocyte counts at nadir during chemotherapy cycles 1 and 2 respectively, than patients in the control group at the same time points ( $P < 0.05$  for both comparisons).

***Marty et al. Multicentre randomised phase III study of the cardioprotective effect of dexrazoxane (Cardioxane) in advanced/metastatic breast cancer treated with anthracycline-based chemotherapy. Ann Oncol 2006; 17: 614-622.***

This EU trial (CS-CX-002) was an open-label, randomised, controlled phase III study, in 164 relapsed breast cancer patients treated with either doxorubicin or epirubicin with or without dexrazoxane at a dose ratio of 20:1 and 10:1, respectively. The primary efficacy parameter was the incidence of cardiac events. All patients had received prior anthracycline therapy (either doxorubicin, epirubicin, or both) with a cumulative dose of approximately 240 mg/m<sup>2</sup> of doxorubicin and 400 mg/m<sup>2</sup> of epirubicin, and were treated with either epirubicin 90 mg/m<sup>2</sup> (n=63 [38%]) or doxorubicin 50 mg/m<sup>2</sup> (n=101 [62%]) during the study. Patients were randomised either to co-treatment with dexrazoxane+epirubicin (10:1 ratio) or dexrazoxane+doxorubicin (20:1 ratio) (treatment arm, n=85 [52%]) or chemotherapy alone (epirubicin or doxorubicin) without dexrazoxane (control arm, n=79 [48%]), and were followed for up to 5 years. The results showed that significantly ( $p = 0.001$ ) fewer overall cardiac events were reported in patients treated with dexrazoxane (10/78 [13%]) compared to controls (29/74 [39%]) based on LVEF results. The rate of cumulative clinical CHF events were consistent with overall cardiac events; there were significantly ( $p = 0.015$ ) fewer events in the dexrazoxane arms (n=1 [1%]), and with less severity (NYHA<sup>2</sup> class 2) than those in the control group (n=8 [11%]): NYHA class 2 (n=1), NYHA class 3 (n=3), and NYHA class 4 (n=4). At the doses used in clinical trials, dexrazoxane did not increase the incidence or severity of non-cardiac adverse events associated with anthracycline treatment with the exception of ECOG<sup>3</sup> grade 3/4 leucopenia which was higher in dexrazoxane-treated patients. Febrile neutropenia was also higher among dexrazoxane treated patients than in control patients (16% versus 11%).

***Venturini et al. Multicenter randomized controlled clinical trial to evaluate cardioprotection of dexrazoxane versus no cardioprotection in women receiving epirubicin chemotherapy for advanced breast cancer. J Clin Oncol 1996; 14: 3112-3120.***

This was a phase III, randomised, controlled open-label study (EC-CX-006) of the effect of dexrazoxane in 162 epirubicin-treated patients with advanced breast cancer. Patients were mostly anthracycline-naïve (n=135 [84%]), but some had received prior anthracycline therapy (epirubicin, doxorubicin, or both; n=25 [16%]). Patients received epirubicin during the study either as part of a regimen of fluorouracil (5FU), epirubicin and cyclophosphamide (FEC) (60 mg/m<sup>2</sup> epirubicin per cycle), or as high-dose epirubicin (120 mg/m<sup>2</sup> per cycle), and were randomised either to receive co-treatment with dexrazoxane 500 mg or 600 mg (10:1 ratio), or chemotherapy alone (FEC or epirubicin alone; control arm). Patients were followed for up to 5 years. The analysis of cardiotoxicity using the criteria for cardiac events in the original protocol (including LVEF fall  $\geq 20\%$ ), upon which the study was statistically powered, showed a statistically significant benefit for reducing the incidence of cardiac events in the treatment arm (epirubicin plus dexrazoxane) compared to the control arm (6/82 [7.3%] vs. 18/78 [23.1%]). The number of patients with a decrease of  $\geq 20\%$  from baseline in LVEF was 0 in the treatment arm, and 6 (9%) in the control arm. The cumulative probability of developing a cardiac event was significantly lower in the dexrazoxane plus chemotherapy arm than in the control arm (odds ratio (OR) 0.29, 95% CI: 0.09, 0.78;  $p = 0.006$ ). However, the cardiotoxicity analysis using amended criteria for cardiac events (i.e., fall in LVEF  $\geq 10\%$ ) did not show a significant difference in the incidence of cardiac events between the treatment arms: 24/63 (38%) for the dexrazoxane plus chemotherapy arm vs. 29/67 (43%) for the control arm ( $p = 0.55$ ). Two patients in the dexrazoxane group developed CHF compared with four in the control arm (non-significant). There were few differences in the incidence of severe non-cardiac toxicity except for a higher incidence of phlebitis (12.5%) for the dexrazoxane plus chemotherapy arm compared with controls (3.5%). Grade 1

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2 NYHA (New York Heart Association) is a functional classification of the extent of heart failure, placing patients in one of four categories based on the degree of limitation during physical activity.

3 ECOG (Eastern Cooperative Oncology Group) is a clinical cancer research organisation in the United States, which conducts clinical trials in all types of adult cancers.

thrombocytopenia was more common on dexrazoxane versus placebo (47% versus 29% respectively;  $p < 0.01$ ).

**Lopez et al, 1998: Randomized prospective clinical trial of high-dose epirubicin and dexrazoxane in patients with advanced breast cancer and soft tissue sarcomas.**

This trial included 129 patients treated with high-dose epirubicin (160 mg/m<sup>2</sup> every (q) 3 weeks) either with or without dexrazoxane (1000mg/m<sup>2</sup>). The study population included patients with advanced breast cancer (n=50 with epirubicin alone and n=45 with epirubicin+dexrazoxane) or soft tissue sarcoma (n=16 with epirubicin alone and n=18 with epirubicin+dexrazoxane), receiving epirubicin with or without dexrazoxane at a dose ratio of 6.25:1. The number of patients evaluable for cardiac toxicity in the epirubicin alone arm (control) was 62, and in the epirubicin plus dexrazoxane arm (treatment) was 59. Clinical signs of CHF were reported in 4 patients in the control arm, with none reported in patients in the dexrazoxane treatment arm. The incidence of cardiac toxicity (decrease in LVEF) was significantly higher in the control arm. There was, however, no significant difference in the incidence of CHF. In the control arm, the mean LVEF decreased from 65.00% at baseline to 56.76% at the last cardiac monitoring of the study. By contrast, the mean LVEF remained stable in dexrazoxane-treated patients, going from 64.39% at baseline to 63.62% at the last cardiac monitoring of the study ( $p < 0.0001$ ).

**Wexler et al. Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. J Clin Oncol 1996; 14: 362-372.**

In this randomised trial, 38 patients  $\leq 25$  years of age with sarcoma received doxorubicin with or without dexrazoxane. Patients in the dexrazoxane arm were significantly less likely to develop subclinical cardiotoxicity (22% vs. 67%,  $p < 0.01$ ) (decrease in LVEF). Elevation of hepatic enzymes occurred more frequently in the dexrazoxane group than in the control group. There was a statistically significantly higher incidence of grade 3 thrombocytopenia, lower platelet nadirs, higher incidence of grade 3 anaemia, and longer median time to recovery of absolute neutrophil count to  $>1,000$  u/l in the dexrazoxane group in various treatment cycles.

**Lipshultz et al. (2010): Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial.**

This was a long-term follow up the 2004 study by Lipshultz et al. (The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukaemia), in which 205 patients with high-risk acute lymphoblastic leukaemia (ALL) received doxorubicin with or without dexrazoxane (dexrazoxane:doxorubicin dose ratio of 10:1). Cardiac troponin T levels were significantly higher in the control arm ( $p < 0.001$ ) and the authors concluded that dexrazoxane prevents or reduces cardiac injury. Patients treated with doxorubicin alone were more likely than those treated with doxorubicin in combination with dexrazoxane to have elevated serial serum cardiac troponin T levels (50% versus 21%;  $p < 0.001$ ), extremely elevated troponin T levels (32% versus 10%;  $p < 0.001$ ), or multiple elevated troponin T levels (37% versus 12%;  $p < 0.001$ ). At 5 years, the difference in mean Z score for left ventricular fractional shortening between the doxorubicin plus dexrazoxane and doxorubicin alone groups was not significant (-0.41, 95% CI -1.07 to 0.26). Gender subgroup analyses showed dexrazoxane protection ( $p = 0.04$ ) for left ventricular fractional shortening at 5 years in girls (1.17, 0.24–2.11), but not in boys (-0.10, -0.87 to 0.68) and dexrazoxane protection ( $p = 0.046$ ) for the left ventricular thickness-to-dimension ratio at 5 years in girls (1.15, 0.44–1.85), but not in boys (0.19, -0.42 to 0.81). With a median follow-up for recurrence and death of 8.7 years (range 1.3–12.1), event-free survival was 77% (95% CI 67–84) for children in the doxorubicin-alone group, and 76% (67–84) for children in the doxorubicin plus dexrazoxane group ( $p = 0.99$ ). No child enrolled in the study developed symptomatic left ventricular dysfunction. The authors commented that whether the effects of dexrazoxane on left ventricular structure and function recorded in this study will translate into improved cardiac outcomes, such as a reduction in heart failure, is uncertain and needs longer follow-up.

## 2.2.2. Discussion on efficacy

### 2.2.2.1. Interference with anthracycline anti-tumour efficacy

Concerns were raised regarding the possibility of interference of dexrazoxane with anthracycline efficacy since both dexrazoxane and doxorubicin are topoisomerase inhibitors. A meta-analysis of six

randomised controlled trials (including the pivotal EU studies CS-CX-002 [Marty 2006] and EC-CX-006 [Venturini 1996] and the pivotal placebo-controlled US studies 088001 and 088006 [Swain 1997]), published by the Cochrane group found a non-significant trend toward lower response rates among those assigned to anthracycline plus dexrazoxane (46.1%; 193 of 418 patients) versus those assigned to anthracycline alone (52.8%; 232 of 439 patients; relative risk = 0.88; 95% CI, 0.77 to 1.01;  $p=0.06$ ). The largest study (088001) in the meta-analysis reported a statistically significant difference in response rates: the overall response rate was 47% in patients receiving dexrazoxane versus 61% in patients receiving placebo ( $p = 0.019$ ). Similar findings have been observed in children with advanced Hodgkin's disease. A lower rapid early response rate was reported in study POG 9425 in dexrazoxane-treated compared with control patients (69% versus 56%;  $p=0.07$ ).

The CHMP concluded that interference with the anti-tumour activity of anthracyclines is biologically plausible and that information on the possibility of interference with anthracycline efficacy should be included in the SPC.

#### 2.2.2.2. Efficacy of dexrazoxane in adults

Having considered the overall submitted data provided by the MAHs in writing, the CHMP concluded that the efficacy of dexrazoxane in the prevention of anthracycline-induced 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 in breast cancer patients treated with doxorubicin. Sub-analyses of these studies also showed a significant reduction of CHF events and a reduction in the severity of CHF events. In view of the infrequency of CHF events, data from the two US placebo-controlled studies were combined and a historical analysis was conducted comparing patients treated with FAC (fluorouracil, doxorubicin and cyclophosphamide) and placebo with patients treated with six courses of FAC and placebo followed by FAC and open-label dexrazoxane. The risk of CHF was substantially greater in patients who did not receive dexrazoxane from the seventh course of FAC (after a cumulative dose of more than 300 mg/m<sup>2</sup> of doxorubicin).

Only one adequately sized randomised study has evaluated the role of dexrazoxane in preventing epirubicin cardiotoxicity. A minority of patients received epirubicin in a second randomised study. The main study reported a significant reduction in the incidence of cardiac events in patients treated with dexrazoxane and epirubicin compared with epirubicin alone.

Regarding the use of dexrazoxane in patients with tumour types other than advanced breast cancer, only very limited data are available and the CHMP therefore considered that the indication for dexrazoxane should be limited to patients with advanced and/or metastatic breast cancer.

The CHMP noted that due to reports of a higher early death rate in the dexrazoxane arms of three US placebo-controlled studies, the dexrazoxane to doxorubicin dose ratio was reduced in these studies, from 20:1 to 10:1. The CHMP considered that there is no evidence that reducing the ratio to 10:1 will result in a loss of efficacy, with the best evidence of efficacy generated by the two US breast cancer studies employing a 10:1 ratio. The CHMP also noted that the available data confirmed efficacy of dexrazoxane in adult cancer patients after previous anthracycline containing treatment.

#### 2.2.2.3. Efficacy of dexrazoxane in paediatric patients

The CHMP noted that only two randomised trials have studied the efficacy of dexrazoxane in paediatric populations (*Wexler et al*, 1996 and *Lipshultz et al*, 2004) and considered the data on the efficacy of dexrazoxane in children to be limited. Although an effect on troponin T levels was observed in the Lipshultz study, the CHMP noted the limitations of the data. The only statistically significant difference between control and dexrazoxane-treated patients was a reduction in left ventricular wall thickness (females only) in a sub-group analysis; there was no evidence of clinical efficacy in an updated analysis after a median follow-up time of 5 years. The CHMP concluded that the efficacy of dexrazoxane in the paediatric patient population has not been adequately demonstrated.

## 2.3. Clinical safety

### 2.3.1. Data on safety

Safety information from spontaneous reports and published literature was considered in this review, including the PSUR covering the period 01 March 2006 to 28 February 2009, which identified new relevant safety findings. Concerns were raised that exposure to dexrazoxane may increase the risk of second malignant neoplasms (SMN), in particular acute myelogenous leukaemia (AML)/myelodysplastic syndrome (MDS) and solid tumours in paediatric patients. An increased risk of myelosuppression and infection was also observed in paediatric patients. In addition, concern was raised about spontaneous reports of AML in adults with breast cancer.

#### 2.3.1.1. Carcinogenic/leukaemogenic potential

The carcinogenic potential of razoxane (a racemic mixture of S(+)dexrazoxane and R(-) levrazoxane) was investigated by the US National Cancer Institute, which concluded that razoxane was carcinogenic for female rats, producing uterine adenocarcinomas. There have been reports of secondary malignancies (primarily AML) in patients treated chronically with oral razoxane. One case of T-cell lymphoma, a case of B-cell lymphoma and six to eight cases of cutaneous basal cell or squamous cell carcinoma have also been reported in patients treated with razoxane. In these patients, the total cumulative dose of razoxane ranged from 26 to 480 grams and the duration of treatment was from 42 to 319 weeks. Cases of AML have been associated with razoxane in patients with colorectal and pancreatic cancer. In a randomised controlled trial, 2.45% of patients on razoxane developed AML compared with no cases in control patients up to a median follow-up time of 5 years (*Gilbert et al*). The incidence of AML in the razoxane group was nearly 100 times that of the background incidence in a literature survey of patients with colorectal cancer (0.03%). Since dexrazoxane exhibits similar properties in vitro and in vivo as razoxane (both are cytotoxic, mutagenic and genotoxic and strongly inhibit topoisomerase II (the key enzyme controlling DNA topology and contributing to the replication and transcription processes, which has been associated with leukaemogenic properties), the CHMP discussed whether dexrazoxane is also leukaemogenic in humans.

There is no reason to believe that the carcinogenic effect in animals is limited to a single isomer. Repeat dose studies in rats and dogs showed that dexrazoxane induced macrocytic anaemia and leucopenia (but not leukaemia), and bone marrow toxicity in all species with severity depending on the dose level and scheme. While the design and duration of the pre-clinical safety studies are inappropriate for assessing the likelihood that dexrazoxane is also leukaemogenic in humans, cytogenic studies showed chromosomal aberrations including hyperdiploidy with a ring chromosome in one case and an abnormality of chromosome 7 in a second case. Monosomy 7 and trisomy 8 have been reported in AML cases associated with dexrazoxane. The well-defined 11q23 translocation associated with AML induced by etoposide has not been reported in razoxane or dexrazoxane-treated patients suggesting that the mechanism of leukaemogenesis differs between etoposide and the bis-dioxopiperazines, razoxane and dexrazoxane.

Cases of AML and MDS reported in the *Tebbi et al* publication raised concerns about the leukaemogenic potential of dexrazoxane in paediatric patients. The non significant excess of second malignancies in the group of patients receiving dexrazoxane strengthens the theoretical carcinogenic/leukaemogenic risk of dexrazoxane. It was also noted that the trend of an excess of SMN has been confirmed by the *Salzer et al* publication, who also reported a non-significant increase in SMN in children treated for ALL. In the absence of controls, it is not possible to assess the causal relationship of the spontaneous cases of AML reported in adult patients treated with dexrazoxane. However, the CHMP concluded that AML should be regarded as an identified risk in both children and adults.

#### 2.3.1.2. Cases of second malignant neoplasms (SMN)

The data provided included details for five spontaneous reports of second primary malignancies in patients treated for breast cancer including three cases of acute myeloid leukaemia, one of cervix carcinoma and one of a stromal tumour in the pelvis. The case of cervix carcinoma was unlikely to have been associated with dexrazoxane therapy as exposure to the time to onset after exposure to the drug was only 18 days. Given the large size of the stromal tumour in the pelvis 164 days after first exposure to dexrazoxane, a causal relationship to dexrazoxane was also considered unlikely. However, a relationship between the drug and the cases of AML could not be ruled out, particularly since the racemic mixture, razoxane, is known to be associated with AML: 15 cases were reported in 1984, five



in patients with gastrointestinal malignancies and ten in patients with non-malignant disease (psoriasis). It is also relevant to note that two of the cases of AML associated with dexrazoxane use were probably receiving adjuvant chemotherapy for breast cancer which is associated with a comparatively low incidence of AML/MDS. An additional case of AML was also identified in the EMA Eudravigilance database: a 52 year old female treated with six cycles of an anthracenedione (not an anthracycline) antineoplastic agent and dexrazoxane. AML was diagnosed 17 months after treatment was discontinued and an association with dexrazoxane could not be ruled out. The MAHs also presented a sixth case of spontaneously reported SMN, which represents the fourth case of adult AML. The time between exposure to chemotherapeutic regime and the diagnosis of AML was 46 months, which is plausible for a causal relationship, although this time-to-onset is in the range more typical for alkylating agents than for topoisomerase inhibitors, and the administered cyclophosphamide is therefore considered a possible alternative cause. Epirubicin is also a confounding topoisomerase inhibitor. Using the guideline for quantifying adverse reactions from spontaneous reporting, the frequency of AML based on spontaneous reports post-marketing was categorised as "uncommon" (between 1/100 and 1/1000).

Regarding paediatric patients, the CHMP agreed that the cases of SMN reported in the *Tebbi et al* publication raise concern of this risk in children. The evidence for harm includes evidence from randomised controlled studies of a threefold increase in risk of second primary malignancies, and a significantly increased risk of other toxicities including myelosuppression, thrombosis, infection, sepsis and pulmonary toxicity which was reported by *Schwartz et al*. Even if non significant, the excess of second malignancies in patients receiving dexrazoxane strengthen the theoretical carcinogenic/leukaemogenic risk of dexrazoxane. The trend of an excess of SMN has been confirmed by the Salzer publication, who reported a non significant increased in SMN in children treated for ALL. Furthermore, the pre-clinical and clinical data concerning the racemic razoxane strengthen this signal. The CHMP also noted that the 8 spontaneous reports of paediatric SMN occurred in paediatric patients with Hodgkin's disease. Six out of the 8 patients developed AML (4) or MDS (2) and 2 patients developed solid tumours (bone sarcoma and papillary thyroid cancer). Four patients each received ABVE (doxorubicin hydrochloride (Adriamycin), bleomycin, vincristine and etoposide) or ABVE-PC regimen (ABVE together with prednisone and cyclophosphamide). Three patients received 2 cycles of ABVE and 2 patients received 4 cycles. The 3 patients who had been treated with ABVE-PC received 5 cycles of chemotherapy. Doxorubicin dosage ranged from 100 to 300 mg/m<sup>2</sup>, etoposide from 1.250 to 2.500 and cyclophosphamide dosage was 3.200 in the 3 patients receiving ABVE-PC regimen. Cytogenetic abnormalities were determined for 4 patients out of the 6 with haematological malignancies. Although several risk factors are probably involved in dexrazoxane-induced SMN such as the underlying malignancy and the associated chemotherapeutic agents, the CHMP considered that these data did not refute the risk of SMN.

#### 2.3.1.3. Other adverse events of special interest

The CHMP noted that there is evidence of an increase in mortality in some studies in dexrazoxane-treated patients. A meta-analysis of deaths in all randomised controlled studies showed that the rate of death on study was higher with the combination dexrazoxane plus chemotherapy (5.0%) compared to chemotherapy alone (3.4%), although the difference was not statistically significant.

Regarding myelosuppression, a cumulative search was made of one of the MAH's safety databases for relevant reports with a cut-off date of 01-Sep-2010, for cases reporting at least one of the following preferred terms (PTs): marrow depression and hypoplastic anaemia, thrombocytopenia, leucopenia, neutropenia. A total of 52 cases were retrieved. The CHMP considered that because dexrazoxane is indicated in combination with anthracycline chemotherapy, the risk of myelosuppressive effects may be additive to those of chemotherapy, which increases the risk of developing serious infections. This was reflected in an update of section 4.8 of the SPC.

Other adverse reactions reported more frequently on dexrazoxane combined with chemotherapy compared to chemotherapy alone included granulocytopenia, vomiting, febrile bone marrow aplasia, liver function abnormalities and phlebitis.

#### 2.3.1.4. Dosing ratio

Preclinical models showed efficacy when the dose ratio of dexrazoxane:anthracyclines was in the range of 5-20:1, with a clear dose-related effect for cardioprotection. Data from two small phase II studies conducted in 1992 (EC-CX-007 and EC-CX-014) comparing 20:1 and 10:1 dose ratios, respectively were provided. Although no significant differences were seen in either efficacy or safety outcomes, the

studies were not adequately powered to determine which ratio has the more favourable benefit-risk balance.. As discussed in the efficacy section, studies conducted with dexrazoxane in the EU selected a dexrazoxane to doxorubicin ratio of 20:1 However, in the US pivotal studies, the initial ratio of 20:1 was reduced to 10:1 following reports of a higher death rate in the dexrazoxane arms (Swain et al, 1997): during the first 9 months, six deaths occurred in the dexrazoxane arm of a study in advanced breast cancer and none on placebo; five deaths occurred in the dexrazoxane arm of a small cell lung cancer study compared to only one death on placebo. The CHMP concluded that the ratio of dexrazoxane:doxorubicin should be reduced to 10:1 since there is no evidence that this will result in a loss of efficacy and a reduction in dexrazoxane dose should have a favourable effect on dose-related safety issues such as myelosuppression,

Regarding the dose ratio of epirubicin, the CHMP noted the studies submitted by the MAHs to discuss the potential interaction between dexrazoxane and epirubicin as well as the clinical trial data obtained in two trials: EC-CX-006 (*Venturini et al* 1996), CS-CX-002 (*Marty et al* 2006). The CHMP considered the pharmacokinetic data on a potential interaction between epirubicin and dexrazoxane to be limited, however, based on the available data, there does not appear to be evidence that the co-administration of dexrazoxane and epirubicin results in alteration of the pharmacokinetic profiles of either drug that would compromise the anti-tumour effect of epirubicin. Animal studies, have indicated that the cardiac protective window is between 1:10 – 1:20 for doxorubicin. Since animal studies have shown that epirubicin is less cardiotoxic than doxorubicin at equimolar amounts, a dose ratio of 1:10 was adopted by clinicians to avoid the risk of increased incidence and severity of other tissue toxicities, primarily myelotoxicity. This ratio is supported by controlled clinical studies. Therefore, the CHMP concluded that the 10:1 dexrazoxane to epirubicin ratio should remain unchanged.

#### 2.3.1.5. Prior cumulative anthracycline exposure

The CHMP noted that no prospective randomised trials have been conducted which specifically address the cumulative dose of anthracyclines at which dexrazoxane treatment should be started. With the exception of the *Marty et al* study (CS-CX-002) which demonstrated that delaying the administration of dexrazoxane until patients have reached cumulative doxorubicin dose of 300 mg/m<sup>2</sup> provides effective cardioprotection, all trials of dexrazoxane have been conducted in anthracycline-naïve patients. The requirement for prior use of at least 300 mg/m<sup>2</sup> of doxorubicin in the US product information was based firstly on concerns about evidence that dexrazoxane interfered with the anti-tumour efficacy of the FAC (fluorouracil, doxorubicin and cyclophosphamide) regimen (*Swain et al*, 1997a) in anthracycline-naïve breast cancer patients and secondly on an indirect non-randomised comparison of patients who received only FAC plus placebo for at least seven cycles and patients who received FAC plus placebo for six cycles followed by FAC plus dexrazoxane for all subsequent cycles, which reported a significantly lower incidence of both cardiac events (25% vs 60%; P<0.001) and CHF (3% vs 22%; P<0.001) than patients given placebo throughout the whole study period. The incidence of CHF in a retrospective analysis (*Swain et al*, 2003) of 630 patients who were randomised to a doxorubicin plus placebo arm of two studies in patients with advanced breast cancer (the active treatment arms included dexrazoxane) increased from 5% at a cumulative doxorubicin dose of 400 mg/m<sup>2</sup> to 26% at 550 mg/m<sup>2</sup> and 48% at 700 mg/m<sup>2</sup>. The selection of 300 mg/m<sup>2</sup> of prior exposure would therefore appear to be reasonable for doxorubicin.

With regard to the cumulative dose of epirubicin, the CHMP accepted the proposal by one of the MAHs that based on data indicating that the dose ratio of doxorubicin to epirubicin for cardiac toxicity is 1:1.8, the minimum prior cumulative dose of epirubicin should be specified as 540 mg/m<sup>2</sup>.

#### 2.3.1.6. Published reports

A summary of the most relevant safety findings in published reports is presented below.

***Tebbi et al. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. J Clin Oncol 2007; 25: 493-500.***

*Tebbi et al* (2007) evaluated the incidence of AML/MDS and second primary malignancies in 478 patients below 21 years of age during treatment for Hodgkin's lymphoma in two studies: POG (Paediatric Oncology Group) 9425 and POG 9426. Patients were randomly assigned whether or not to receive dexrazoxane (300 mg/m<sup>2</sup>) together with doxorubicin (25-30 mg/m<sup>2</sup>) or bleomycin. With a median of 58 months' follow-up, ten patients developed second malignancies: four and six children in study POG 9425 and 9426, respectively. Six of eight patients who developed AML/MDS and both

patients who developed secondary solid tumours (osteosarcoma and papillary thyroid carcinoma) were treated with dexrazoxane. Using a Poisson regression model, a statistically significant increase in the incidence of AML/MDS was observed in the combined analysis of the two studies ( $p=0.0534$ ). The Standardised incidence ratio (SIR) for all second malignancies was significantly higher for dexrazoxane-treated patients ( $p=0.0231$ ). The significant difference between the dexrazoxane and no-dexrazoxane group was mainly attributable to trial POG 9426 in which five second malignancies occurred in dexrazoxane-treated patients and none in controls.

**Salzer 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**

This study reported long-term outcomes of 12 paediatric trials in ALL completed between 1984 and 2001. In one of these trials, POG 9404, 332 patients with T-cell ALL were randomised in a 2x2 factorial design to +/- high-dose methotrexate and +/- dexrazoxane (dose not specified). There was a non-significant 3 times higher risk of secondary malignancies in the 10-year cumulative incidence of second malignancies:  $4.2\pm 2.2\%$  on the dexrazoxane arm compared with  $1.3\pm 0.9\%$  on the no-dexrazoxane arm ( $p=0.15$ ). A total of eight second malignancies occurred (three AML, one MDS, 2 non-Hodgkin’s lymphoma, one right cranial tumour and one medulloblastoma) but the paper did not specify which occurred on which regimen.

**Schwartz 2009 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 2009; 114: 2051-2059.**

This was an update of the results on the 5-year event free survival and overall survival rates of the POG 9425 study (see Tebbi et al above). Hematopoietic/infectious toxicity was higher in the dexrazoxane group in comparison to the non-dexrazoxane group. Acute grade 3/4 pulmonary toxicity usually occurred early and in association with Grade 4 infection. It was unlikely to be attributable to bleomycin-induced pulmonary injury. Similarly, Grade 3/4 typhlitis occurred more frequently in patients with vs. those without dexrazoxane (9 vs. 3, NS). There were no additional cases of SMN than that reported in the Tebbi’s article. The authors concluded that *“Survivorship data note significant risk for cardiac dysfunction in the decades after anthracycline therapy with enhanced risk engendered by mantle radiation. Although we had hoped to abrogate cardiac risk with dexrazoxane, the unexpected hematopoietic/infectious toxicity in the dexrazoxane arm made its use inadvisable for this population.”*

**Barry et al. (2008): Absence of Secondary Malignant Neoplasms in Children With High-Risk Acute Lymphoblastic Leukemia Treated With Dexrazoxane**

This study evaluated the incidence of second malignancies in 205 paediatric patients randomly assigned to doxorubicin ( $30\text{ mg/m}^2$ ) alone ( $n=100$ ) or doxorubicin ( $30\text{ mg/m}^2$ ) plus dexrazoxane ( $300\text{ mg/m}^2$ ) ( $n=105$ ) during treatment for high-risk acute lymphoblastic leukaemia (ALL). Two malignant melanomas, outside the radiation field, occurred 3.1 and 9.4 years, respectively, after ALL diagnosis in patients assigned to doxorubicin alone. There were no cases of AML or MDS. With a median follow-up of 6.2 years, no differences in the incidence of SMNs were noted: 1 melanoma located outside of the cranial radiation field occurred in doxorubicin group and no SMNs were observed in patients randomly assigned to receive dexrazoxane. The authors concluded that dexrazoxane was not associated with an increased risk of SMNs in children treated for high-risk ALL.

### 2.3.2. Discussion on safety

The CHMP noted the nonclinical and clinical data for razoxane and the carcinogenic/leukaemogenic potential of dexrazoxane due to its cytotoxic activity and the excess of SMN, in particular AML and MDS, in the paediatric population with Hodgkin’s disease and acute lymphoblastic leukaemia receiving chemotherapy and treated with dexrazoxane reported in several studies published in the literature. The CHMP concluded that dexrazoxane should be considered as potentially carcinogenic/leukaemogenic in humans. The frequency of AML was categorised as “uncommon” (between 1/100 and 1/1000) and a warning was added to section 4.4 of the SPC to alert prescribers to this risk. This particular issue will be closely monitored as part of the RMP.

The CHMP noted that, since both dexrazoxane and doxorubicin are topoisomerase inhibitors, it is possible that dexrazoxane may interfere with the anti-tumour efficacy of doxorubicin. Use of dexrazoxane in combination with adjuvant breast cancer therapy or chemotherapy intended as curative is therefore not recommended. This was reflected in section 4.4 of the SPC.

The CHMP also noted the evidence of an increase in early mortality in adult dexrazoxane-treated patients, with a higher rate of death on study for the combination dexrazoxane plus chemotherapy (5.0%) compared to chemotherapy alone (3.4%), although the difference was not statistically significant. The CHMP considered that it was plausible that dexrazoxane contributed to this higher incidence of death. This risk was reflected in section 4.4 of the SPC, in addition to section 5.1.

The risk of myelosuppressive effects that may be additive to those of chemotherapy was already reflected in the SPC; the risk was further strengthened by adding a statement that "cell counts at nadir may be lower in patients treated with dexrazoxane" in section 4.4 of the SPC.

With regards to other side effects of chemotherapy associated with concomitant administration of dexrazoxane, the CHMP noted that most of the studies, irrespective of the population treated, showed myelotoxicity which is well documented in the dexrazoxane SPC. In combination with anthracyclines and at the doses recommended for cardioprotection, dexrazoxane did not increase the incidence or severity of clinical signs of toxicity of anthracycline based regimens, with the exception of haematological effects that are reported more frequently. These were mostly neutropenia that can be severe, sometimes serious and very rarely, associated with thrombocytopenia and/or anaemia, or even bone marrow aplasia. Other adverse reactions reported more frequently on dexrazoxane combined with chemotherapy compared to chemotherapy alone included granulocytopenia, vomiting, febrile bone marrow aplasia, liver function abnormalities and phlebitis.

The product information was updated according to these conclusions and important identified and potential risks were included in the risk management plan (RMP, see section 2.4).

## 2.4. Risk management plan

### 2.4.1. Risk management plan

The MAHs submitted a risk management plan (RMP), which included a risk minimisation plan. A tabular summary of the RMP, adapted from version 1 dated 26 May 2011 provided for this review is presented below.

Safety concern	Proposed pharmacovigilance activities (routine and additional).	Proposed risk minimization activities (routine and additional)
<b>Important identified risks</b>		
SPM in children	Routine pharmacovigilance including cumulative analysis in PSUR.	<p><b>Routine:</b>  <u>Proposed changes in SPC</u>            In SPC section 4.1, the indication for the use of dexrazoxane in the SPC will be modified to specify (new text in bold):  <b>"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/m<sup>2</sup> of doxorubicin or a prior cumulative dose of 540 mg/m<sup>2</sup> of epirubicin when further anthracycline treatment is required."</b></p> <p><u>Additional proposed changes to the SPC:</u>            In SPC section 4.3 a contraindication was added to state that dexrazoxane "is contraindicated in children and adolescents up to 18 years"</p> <p>Further reference to this risk are appropriately communicated through changes to SPC section 4.4, SPC section 4.8 and SPC section 5.3.</p> <p><u>Additional</u></p>

<b>Safety concern</b>	<b>Proposed pharmacovigilance activities (routine and additional).</b>	<b>Proposed risk minimization activities (routine and additional)</b>
		A DHPC letter will be sent to dexrazoxane prescribers. A drug utilisation study will be conducted as a means of monitoring the effectiveness of the risk minimization communication, and the results will be summarised in a report after each follow-up survey.
Myelosuppression	Routine pharmacovigilance including cumulative analysis in PSUR.	This risk is appropriately communicated in SPC section 4.4 and in SPC section 4.8 by including the reporting of the relevant preferred terms as AES. Additional details were added in SPC section 4.4: "Cell counts at nadir may be lower in patients treated with dexrazoxane."
AML in adults	Routine pharmacovigilance including cumulative analysis in PSUR.	This risk is communicated in SPC section 5.3 In SPC section 4.4, the following sentence regarding increased risk of second malignancy was moved up to make this a general statement to include adults: "Since dexrazoxane is a cytotoxic agent, with topoisomerase II inhibition activity, combination of dexrazoxane with chemotherapy may lead to an increased risk of second primary malignancy." Additional sentence in the SPC section 4.4 Special warnings and precautions for use, and in section 4.8 Undesirable effects: "AML has been reported uncommonly in adult breast cancer patients post-marketing."
<b>Important potential risks</b>		
Serious infections	Routine pharmacovigilance including cumulative analysis in PSUR.	This risk is appropriately communicated in SPC section 4.8 by including the reporting of the relevant preferred terms as AES.
Early death	Routine pharmacovigilance including cumulative analysis in PSUR.	This risk is appropriately communicated in SPC section 5.1 and in SPC section 4.4: "In some studies, a higher incidence of death has been observed in the groups treated with dexrazoxane plus chemotherapy compared to those treated with chemotherapy alone. The possibility that dexrazoxane was a contributing factor to the imbalance cannot be ruled out."

### 2.4.2. Periodic safety update reports (PSURs)

A specific analysis of reported cases of AEs associated with the use of dexrazoxane will be submitted within the PSURs. It was agreed that the current PSUR cycle of 3-yearly submission needed to be shortened to guarantee an adequate close monitoring of the important identified risks, such as SPM in children, myelosuppression and AML in adults and other important potential risks, as detailed in the table summarising the risk management plan shown above. The PSUR cycle was shortened to an annual submission which should also allow close monitoring of the measures implemented.

### 2.4.3. Drug utilisation study

The CHMP requested the MAHs to conduct a drug utilisation study (DUS) which will be included in the RMP. The DUS will be implemented as a means of monitoring the effectiveness of the risk minimisation measures and will be conducted in several EU member states, surveying a randomly selected representative population of prescribers (oncologists, paediatric oncologists) to obtain data on their prescribing history for dexrazoxane over the last two years. This will include indications for treatment and numbers of patients, to establish a baseline. These prescribers will be surveyed again every year

for the next two years, to obtain data on their prescribing history during the intervening year. The results will be summarised in a report after each year's follow-up. The protocol and the timelines of this study will be provided to the RMS and other member states within one month of the commission decision concluding this referral procedure.

## **2.5. Overall benefit-risk assessment**

### **2.5.1. SAG**

The CHMP requested the advice of the SAG oncology; a meeting was held on 04 March 2011. The SAG considered that anthracycline-induced cardiotoxicity did not pose an important clinical concern in adults with advanced or metastatic cancer because for most patients the long-term prognosis is too short for the development of CHF. In addition, adequate monitoring and consideration of risk factors are in place to prevent the risk of significant cardiotoxicity associated with anthracyclines. However, specific patient groups can be defined in which cumulative dose restriction is limiting optimal treatment, e.g. patients who have received optimal treatment for early disease containing an anthracycline and who, after long term, develop relapse and who then cannot be adequately treated anymore with an anthracycline, or in patients who develop a second primary tumour for which an anthracycline may be effective treatment but cannot be given because of anthracycline treatment of the first breast tumour.

Regarding the selection of the doxorubicin dosage, the SAG expressed concerns about the higher dose recommended in the EU in view of the potentially adverse pharmacodynamic interactions with anthracyclines and the risk of lack of efficacy, as well as the safety risks. The lack of rationale and data to justify the different dose regimens was considered unacceptable. The SAG considered that from a pharmacological point of view, dexrazoxane interference with the anti-tumour efficacy of anthracyclines is a possibility and a cause of concern as the mechanism of action of the drug is not fully understood.

The SAG was of the opinion that the safety and efficacy of dexrazoxane in children have not been established and that dexrazoxane should therefore not be used in children due to the risk of second malignancies and potentially negative pharmacodynamic interaction with anthracyclines.

### **2.5.2. Conclusions on benefit-risk**

Regarding the benefit-risk of dexrazoxane in adult patients, the CHMP considered that the available data confirms the cardioprotective efficacy of dexrazoxane in breast cancer patients pre-treated with anthracyclines. However, since it was possible that dexrazoxane could impair the anti-tumour efficacy of doxorubicin, the CHMP advised that dexrazoxane should not be used in combination with adjuvant breast cancer therapy or chemotherapy intended as curative. The assessment of the safety of dexrazoxane raised some concerns including the risk of AML and of increased myelosuppression, but the CHMP considered that the proposed risk minimisation measures addressed these satisfactorily. Regarding the use of dexrazoxane in patients with tumour types other than advanced breast cancer, the CHMP considered that only very limited data are available. Regarding paediatric patients, the CHMP considered that the available data on efficacy and long term safety in this population is insufficient to support the use of dexrazoxane while the use is associated with an increased risk of second primary malignancies.

In conclusion, the CHMP was of the opinion that the benefit-risk of dexrazoxane-containing medicinal products is positive in the following revised 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/m<sup>2</sup> of doxorubicin or a prior cumulative dose of 540 mg/m<sup>2</sup> of epirubicin when further anthracycline treatment is required*".

Five CHMP members expressed divergent positions, considering that there is only modest evidence of clinically important benefits in relation to reduction of anthracycline-related cardiotoxicity and that the optimal dosing regimen has not been fully investigated. Concerns regarding a decrease in tumour response rate due to dexrazoxane interference with the anti-tumour efficacy of doxorubicin were also raised. Taking into account the risk of AML seen in adult patients, the evidence of increased myelosuppression in patients treated with dexrazoxane and an increase in early mortality in dexrazoxane-treated patients, the divergent members were of the opinion that the benefit-risk balance of dexrazoxane in adults with advanced breast cancer is unfavourable.

## 2.6. Communication plan

As part of this referral procedure, the CHMP agreed on the wording of a Dear healthcare professional communication designed to inform prescribers about the new restrictions to the dexrazoxane indication, as well as the paediatric contraindication. In addition, information on increased early mortality and interference with anthracycline efficacy was included. The following action plan for the distribution of the DHPC was agreed upon:

23 June 2011:	CHMP opinion on the draft DHPC
7 July 2011:	Translations of DHPC from MAHs to National Competent Authorities (NCAs)
14 July 2011:	Final DHPC translations agreed by NCAs
18 July 2011:	MAHs to distribute the DHPC together with the harmonised Product Information to adult and paediatric oncologists and haematologists

## 2.7. Changes to the product information

Regarding the SPC, section 4.1 was revised to reflect the restriction of the indication of use in advanced and/or metastatic adult breast cancer patients who have received a minimum prior cumulative of anthracyclines. Section 4.2 was revised to reflect the reduction in dexrazoxane to doxorubicin ratio, from 20:1 to 10:1. The dose ratio of dexrazoxane to epirubicin remained unchanged at 10:1. In section 4.3, a contraindication in children and adolescents up to 18 years of age was added. In section 4.4, the identified risk of acute myeloid leukaemia (AML) in adult breast cancer patients post-marketing was added, with a cross-reference to section 4.8. Statements on the additive effect of myelosuppression, the observed higher incidence of death and the significant decrease in tumour response rate were also added. Section 4.8 was revised to align the wording with that of section 4.4. AML was added to the table of adverse reactions. The package leaflet (PL) was updated accordingly. In addition, the SPC and PL were revised in accordance with the current QRD template.

## 3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing, the CHMP concluded that the efficacy of dexrazoxane in the prevention of anthracycline-induced 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 in breast cancer patients treated with doxorubicin. Sub-analyses of these studies also showed a significant reduction of 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. 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 the 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<sup>2</sup> of doxorubicin or a prior cumulative dose of 540 mg/m<sup>2</sup> 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 CHMP recommended that the use in children and adolescents up to 18 years of age should be contraindicated.

The CHMP also agreed conditions to the marketing authorisation, including a direct healthcare professional communication to be sent in order to inform adequately on the changes recommended, 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.

In conclusion, the CHMP recommended the variation of the terms of the marketing authorisation of dexrazoxane-containing medicinal products set out in Annex I of the opinion. The relevant amended sections of the SPC and PL are set out in Annex III of the opinion. The conditions affecting the marketing authorisations are set out in Annex IV of the opinion.