EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 April 2016
EMA/CHMP/427120/2016
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Pursuant to Article 30 of Directive 2001/83/EC

Novantrone and associated names

INN: mitoxantrone

Procedure no: EMEA/H/A-30/1399

Note

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

# Table of contents

# 1. Background information on the procedure

## 1.1. Background information on the basis of the grounds for referral

On 01 October 2014 the European Commission presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics (SmPC), labelling and package leaflet (PL) of the medicinal products:

Novantrone and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the October 2014 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Pieter de Graeff (NL) as rapporteur and Robert James Hemmings (UK) as co-rapporteur.

Novantrone medicinal products are registered in the following European Union (EU) Members States (MSs): Cyprus, Finland, France, Germany, Greece, Italy, Romania, Slovenia, Spain and Sweden as well as in Iceland and Norway. Marketing authorisations in Latvia were withdrawn for commercial reasons during the procedure.

# 2. Scientific discussion during the referral procedure

## 2.1. Introduction

Novantrone contains mitoxantrone, a synthetic anthracenedione antineoplastic agent that intercalates into deoxyribonucleic acid (DNA) through hydrogen bonding, thus causing crosslinks and strand breaks. Mitoxantrone also interferes with ribonucleic acid (RNA) and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA. It has a cytocidal effect on both proliferating and non-proliferating cultured human cells, suggesting lack of cell cycle phase specificity and activity against rapidly proliferating and slow-growing neoplasms. Novantrone is indicated in adults in a number of malignancies, including breast carcinoma, acute leukaemia and non-Hodgkin's lymphoma. It is also used to alleviate pain in prostate cancer in combination with corticosteroids and its immunosuppressant and immunomodulatory properties provide a rationale for use of mitoxantrone in highly active multiple sclerosis.

The first mitoxantrone-containing medicinal product was authorised in 1983 and Novantrone and associated names are currently authorised in 10 EU MS. Novantrone and associated names are approved for marketing as a 2mg/ml concentrate for solution for infusion for intravenous use in most EU MS. It is also authorised in a few EU MS as 2mg/ml concentrate for solution for injection or solution for intrapleural or intraperitoneal use and as concentrate for solution for injection/infusion.

Novantrone and associated names has been included in the list of products for summary of product characteristics (SmPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC.

Due to the divergent national decisions taken by MSs concerning the authorisation of the above-mentioned product (and its associated names), the European Commission notified the European Medicines Agency of an official referral under Article 30 of Directive 2001/83/EC in order to resolve

divergences amongst the nationally authorised Product Information (PI) and thus to harmonise the PI across the EU.

## 2.2. Critical Evaluation

### 2.2.1. Section 4.1 – Therapeutic indications

There are currently three main indications, approved in all member states where Novantrone has a marketing authorisation (MA), with however divergences in their exact wording: treatment of metastatic breast cancer, treatment of non-Hodgkin's lymphoma, treatment of acute myeloid leukaemia (acute non-lymphocytic leukaemia). In addition, indications in treatment of hepatoma/hepatocellular carcinoma, pain relief in patients with advanced, hormone-resistant prostate cancer (in combination with corticosteroids), reduction of neurologic disability and clinical relapses in secondary (chronic) progressive multiple sclerosis, treatment of blast crisis in (chronic) myeloid leukaemia and treatment of acute lymphocytic leukaemia are included in some of the MSs where Novantrone has a MA.

Treatment of metastatic breast cancer

This indication is approved in all MS where Novantrone has a MA with minor variations in the exact wording. The MAH submitted an overview of studies performed with mitoxantrone as single agent or in combination regimens for the treatment of patients with advanced or metastatic breast cancer.

**Table 1. Largest published clinical trials with mitoxantrone as a single agent or in treatment combinations in metastatic breast cancer**

| Source | Patients | Dose (mg/m²) | Study design | Results |
|---|---|---|---|---|
| Heidemann 2002 | 260 | M(12)[a] FEC[a] | RT | MBS: 1.69 vs. -1.79; p<0.001<br>CR: 7% vs. 12%; NS<br>ORR: 30% vs. 43%; NS<br>TTP: 4.4m vs. 6.2m; p=0.2<br>OS: 14.1m vs. 15.8m; p=0.7 |
| Henderson 1989 | 325 | M(14)[a] DXR[a] | RT | ORR: 20.6 vs. 29.3; p=0.07<br>RD: 151d vs. 126d; p=0.16<br>TTF: 70d vs. 104d; p=0.36<br>OS: 273d vs. 268d; p=0.40 |
| Ron 2001 | 145 | CNF CMF | RT | OS: 52.3m vs. 55.5m; p=0.6<br>DFS: 4.4y vs. 2.7y; p=0.04 |
| Bennett 1988 | 331 | CNF[a] CAF[a] | RT | ORR: 29% vs. 37%; p=0.16<br>DR: 171d vs. 254d; p=0.19<br>TTF: 125d vs. 147d; p=0.09<br>OS: 377d vs. 385d; p=0.78 |
| Namer 2001 | 281 | MV FAC/FEC | RT | ORR: 34.5 vs. 33.5; [90%CI of the difference: -8% to +11%, p=0.014]<br>PFS, prior adjuvant Tx: 8m vs. 5m; p=0.0007<br>PFS, untreated: 6m vs. 9m; p=0.014 |
| Venturino 2000 | 99 | MFF FF V | RT | ORR: 21% vs. 30% vs. 24%; p: NT<br>RD: 5.5m vs. 2.5m vs. 2m; p: NT |

*CAF* cyclophosphamide (500 mg/m²; d1) + doxorubicin (50 mg/m²; d1) + 5-fluorouracil (500 mg/m²; d1); CI confidence interval; *CNFa* cyclophosphamide (500 mg/m²; d1) + mitoxantrone (10 mg/m²; d1) + 5-fluorouracil (500 mg/m²; d1); *CNF* cyclophosphamide (600 mg/m²; d1) + mitoxantrone (12 mg/m²; d1) + 5-fluorouracil (600 mg/m²; d1); *CMF* cyclophosphamide (600 mg/m²; d1) + methotrexate (40 mg/m²; d1) +5-fluorouracil (600 mg/m²; d1); d day; DR duration of response; DXR

doxorubicin (75 mg/m²); *FAC* 5-fluorouracil (500 mg/m²; d1) + doxorubicin (50 mg/m²; d1) + cyclophosphamide (500 mg/m2; d1); *FEC* 5-fluorouracil (500 mg/m²; d1) + epirubicin (50 mg/m²; d1) + cyclophosphamide (500 mg/m²; d1); *FF* 5-fluorouracil (370 mg/m² d1-d5 Q 4w) + folinic acid (100 mg/m²; d1-d5 Q 4w); M mitoxantrone; MBS modified Brunner's score; *MFF* mitoxantrone (12 mg/m²; d1 q 4w)+5-fluorouracil (370 mg/m² d1-d3 Q 4w) + folinic acid (100 mg/m²; d1-d3 Q 4w); *MV* mitoxantrone (12 mg/m²; d1) + vinorelbine (25 mg/m²; d1, d8); NT not tested; OS overall survival; PFS progression-free survival; ORR overall response rate; Q every; RD response duration; RT randomized trial; TTF time to treatment failure; Tx treatment; V vinorelbine (30 mg/m² weekly); w week.

[a] Q 3w

The CHMP considered that the efficacy of mitoxantrone in treatment of breast cancer has been demonstrated in these studies and this, with comparable results to other standard anthracycline containing regimens. The use of mitoxantrone for the treatment of breast cancer is included in current hospital guidelines. The studies presented included in majority patients with metastatic breast cancer, this patient population was therefore considered acceptable for the harmonised indication.

Treatment of non-Hodgkin's lymphoma (NHL)

This indication is approved in all MS where Novantrone has a marketing authorisation. As NHL is a heterogeneous group of diseases, the standard of care differs e.g. by type, stage and prognostic factors. The MAH presented an overview of studies performed with mitoxantrone as single agent or in combination regimens for the treatment of patients with specific subgroups of NHL, pre-treated or treatment naïve.

A small study with thirty-five patients with non-Hodgkin's lymphoma, who had relapsed from or failed prior cytotoxic regimens including doxorubicin, received mitoxantrone at a dose of 14 mg/m$^2$ every 3 weeks (Foss-Abrahamsen, Lenner et al. 1987). The overall objective response rate was 43% (95% CI, 25%-61%) for all patients. The response durations ranged from 7 to >11 months. Time to treatment failure was 4.5 months. Results were confirmed by a larger study where mitoxantrone was evaluated in the treatment of 206 patients with relapsed non-Hodgkin's lymphoma (NHL, n=178) or Hodgkin's disease (HD, n=28) previously treated with other agents (Silver, Case et al. 1991). The patients received 14 mg/m$^2$ of mitoxantrone every 3 weeks. The combined complete responses (CR) and partial response (PR) rates were 37% (60 of 163) for NHL patients, of which 12% with CR; the median duration of response and the median survival times were respectively 323 days and 337 days for NHL patients.

**Table 2. Largest published clinical trials with mitoxantrone in treatment combination in NHL**

| Source | Patients | MTZ Dose (mg/m²) | Study design | Results |
|---|---|---|---|---|
| Mainwaring 2001 | 516 | PMitCEBO[1] PAdriaCEBO | RT | OS (4y): 50% vs. 28%; p=0.0067 ORR:78% vs. 69%; p=0.05 CR: 60% vs. 52%; p=0.12 |
| Burton 2006 | 784 | PMitCEBO[2,a] CHOP[a] | RT | FFS (3y): 42% vs. 44%; p=0.64 ORR: 83% vs. 84%; p=0.69 |
| Osby 2003 | 455 | CNOP[a] CHOP[a] | RT | CR: 43% vs. 60%; p<0.01 |
| Nickenig 2006 | 415 | MCP CHOP | RT | CR: 14% vs. 21%; p=0.064 ORR: 82% vs. 91%; p=0.026 RD: 51m vs. 29m; p=0.16 OS (5y): 61% vs. 68%; p=0.14 |
| Federico 2013 | 534 | R-FM R-CVP R-CHOP | RT | TTF (3y): 59% vs. 46% vs. 62% (R-CHOP vs. R-CVP p=.003; R-FM vs. R-CVP p=0.006; R-FM vs. R-CHOP p=0.763) ORR: 91% vs. 88% vs. 93%; overall p=0.247 PFS: 63% vs. 52% vs. 68%; overall p=0.11 |

CHOP: cyclophosphamide (750 mg/m²; d1) + vincristine (1.4 mg/m²; d1) + doxorubicin (50 mg/m²; d1) + prednisone (100 mg/m² d1-d5) Q 3 w; CNOP: cyclophosphamide (750 mg/m²; d1) + vincristine (1.4 mg/m²; d1) + mitoxantrone (10 mg/m²; d1) + prednisone (100 mg/m² d1-d5) Q 3 w; CR complete response; m month(s); FFS failure-free survival; G-CSF granulocyte colony-stimulating factor; MCP: mitoxantrone (8 mg/m²; d1, d2) + chlorambucil (9 mg/m²; d1-d5) + prednisone (25 mg/m²; d1-d5) Q 4w; OS overall survival; ORR objective response rate; PAdriaCEBO (weekly, for ≥8w): cyclophosphamide (300 mg/m²; d1) + adriamycin (35 mg/m²; d1) + etoposide (150mg/m²; d1) + prednisolone (50 mg 50 mg daily w1 –w4, then alternate d) + vincristine (1.4 mg/m²; d 8) + bleomycin (10 mg/m²; d8); PMitCEBO1 (weekly, for 16w): cyclophosphamide (300 mg/m²; d1) + mitoxantrone (7 mg/m²; d1) +etoposide (150mg/m²; d1) + prednisolone (50 mg 50 mg daily w1 –w4, then alternate d) + vincristine (1.4 mg/m²; d 8) + bleomycin (10 mg/m²; d8); PMitCEBO2 (weekly, for 16w): cyclophosphamide (300 mg/m²; d1) + mitoxantrone (7 mg/m²; d1) + etoposide (150mg/m²; d1) + prednisolone (100 mg d1 – d5, 50 mg daily w1 –w4, then alternate d) + vincristine (1.4 mg/m²; d 8) + bleomycin (10 mg/m²; d8); R-CHOP: rituximab (375 mg/m²; d1) + cyclophosphamide (750 mg/m²; d1) + vincristine (1.4 mg/m²; d1) + doxorubicin (50 mg/m²; d1) + prednisone (100 mg/m² d1-d5) Q 3 w; R-CVP: rituximab (375 mg/m²; d1) + cyclophosphamide (750 mg/m²; d1) + vincristine (1.4 mg/m²; d1) + prednisone (40 mg/m² d1-d5) Q 3 w; RD response duration; R-FM: rituximab (375 mg/m²; d1) + fludarabine (25 mg/m²; d1-d3) + mitoxantrone (10 mg/m²; d1) Q 3 w; RT randomized trial; Q every; TTF time to treatment failure; w week; y year.

a with or without G-CSF.

These studies demonstrate the efficacy of mitoxantrone, in combination therapy, in the treatment of NHL and support the use of mitoxantrone regimens as an alternative when regimens such as R-CHOP may not be possible. Studies showing efficacy of mitoxantrone as monotherapy or in combination regimens in the salvage treatment of relapsed NHL have also been presented. Although mitoxantrone is not one of the most frequently used chemotherapy regimens in NHL, the CHMP acknowledged that it could represent an alternative treatment option and considered the proposed harmonised wording acceptable.

Treatment of acute myeloid leukaemia

The indication acute myeloid leukaemia (AML) is approved, as such or as acute non-lymphocytic leukaemia, in all MS where Novantrone has a marketing authorisation. The MAH has submitted an overview of studies performed in this indication including single agent studies and large randomised comparative studies using mitoxantrone in combination with other agents and comparing with other regimens, in support of the proposed following wording "*Mitoxantrone, in combination with other approved drug(s), is indicated in the initial therapy of acute non-lymphocytic leukaemia (ANLL)/acute myeloid leukaemia (AML) in adults. This category includes myelogenous, promyelocytic, monocytic, and erythroid acute leukaemias*".

Four proof-of concept studies evaluated single-agent mitoxantrone in patients with refractory or relapsed AML or chronic myelogenous leukaemia in blast crisis (B-CML) at doses ranging from 10 to

14 mg/m$^2$ daily for 3-5 days. A dose-response effect was observed with optimal activity at a dose of 12 mg/m$^2$ daily for 5 days.

**Table 3. Largest published clinical trials with mitoxantrone in treatment combinations in AML**

| Source | Patients | Dose (mg/m$^2$) | Study design | Results |
|---|---|---|---|---|
| Arlin 1990 | 200 | M(12)+AraC[1,b]<br>DXR45+AraC[1,b] | RT | CR: 63% vs. 53%; p=0.15<br>remission, duration: 240d vs. 198d; p=0.27<br>OS: 328d vs. 247d; NS |
| Lowenberg 1998 | 489 | M(8)+AraC[1, b,f]<br>DXR30+AraC[1,b,f] | RT | CR: 47% vs. 38%; p=0.067)<br>DFS (at 5y): 8% vs. 8%; p=0.73<br>OS (at 5y): 6% vs. 9%; p=0.23 |
| Pavlovsky 1994 | 143 | M(12)+AraC[1,f]<br>DXR45+AraC[.f] | RT | CR: 53% vs. 43%<br>remission, duration: 185d vs. 165d; p=0.85<br>OS: 103d vs. 160d; p=0.85 |
| Mandelli 2009 | 2,157 | M(12)[e]+AraC[2]+ET[f]<br>DXR50+AraC[2]+ET[f]<br>IDR[e]+AraC[2]+ET[f] | RT | OS (at 5y):[c,d] 43.2% vs. 35.7% vs. 44.7% with<br>    HR 0.81 (p=0.03) vs. 1 vs. 0.77 (p=0.01)<br>CR: 69.8% (p=0.63) vs. 68.7% (co.) vs. 66.9%<br>    (p=0.49)<br>DFS (at 5y): 37% vs. 29% vs. 37% with<br>    HR 0.80 (p=0.02) vs. 1 vs. 0.83 (p=0.06) |
| Gibson 2011 | 504[a] | M(12)[e] +AraC[3]+ET[f]<br>DXR50+AraC[3]+ET[f] | RT | CR: 90% vs. 82%; p=0.4<br>DFS: 63% vs. 55%; p=0.03<br>relapse rate: 32% vs. 39%; p=0.05<br>OS:65% vs. 61%; p=0.2 |

AraC1 cytarabine (100 mg/m² d1-d7); AraC2 cytarabine (100 mg/m² d1-d10 plus bolus 25 mg/m²on d1); AraC3 cytarabine (100 mg/m² d1-d10); co. comparator for statistical analysis; d day; CR complete remission; DFS disease-free survival; DXR30 daunorubicin (30 mg/m² d1-d3); DXR45 daunorubicin (45 mg/m² d1-d3); DXR50 daunorubicin (50 mg/m² d1, d3, d5); ET etoposide (100 mg/m² d1-d5); HR hazard ratio; IDR idarubicin (10 mg/m²); M mitoxantrone (d1-d3); NS not significant; OS overall survival; PR partial response; RT randomized trial; y year.

[a] children 0-16 y (45% 2-9 y); [b] if needed (as in case of PR), a 2nd course was administered: AraC x 5d, M or DXR x 2d; [c] since complete remission; d without autologous stem-cell transplant; e on d1, d3, d5; f In case of PR, a 2nd remission induction course with the same drugs was given.

Current guidelines for treatment of AML recommend an induction therapy with regimens containing an anthracycline administered for 3 days and cytarabine administered for 7 days. Anthracyclines commonly studied and used include mitoxantrone. The CHMP considered the clinical benefit of mitoxantrone demonstrated in the treatment of acute myeloid leukaemia/acute non-lymphocytic leukaemia in adults and recommended the use of the term acute myeloid leukaemia rather than acute non-lymphocytic leukaemia. Insufficient information was provided in support of the different proposed categories; therefore, the CHMP considered that these should not be specified in the indication.

<u>Remission-induction treatment of blast crisis in chronic myeloid leukaemia, in combination regimen</u>

This indication is approved in a majority of the MS where Novantrone has a marketing authorisation. The MAH presented four studies of mitoxantrone administered in combination with other cytostatic agents in the treatment of a blast crisis in chronic myeloid leukaemia.

In a small study 40 evaluable patients were treated for blast crisis of chronic myelogenous leukaemia with mitoxantrone 12 mg/m$^2$/day for three days and 5-azacytidine 150 mg/m$^2$/day for 5 days (Dutcher, Eudey et al. 1992). The overall response rate was 23%, including five complete responders,

two partial responders, and two with haematologic improvement. Although response did not strongly correlate with survival, one third of responders were alive at one year.

These results were correlated in 14 patients with blastic phase chronic myelogenous leukaemia who received combination chemotherapy with mitoxantrone 5 mg/m$^2$/day for 3 days, cytosine arabinoside 100 mg/m$^2$ over 2 hours twice a day for 7 days and high dose methylprednisolone 1000 mg/day for 5 days (Bolaman, Koseoglu et al. 2002). Five patients (35%) achieved complete remission and four patients (28%) had a partial remission. The mean survival was 11.1 +/- 8.6 months for all patients, 19.4 +/- 4.0 months for those achieving a complete remission, 12.50 +/- 5.7 months for patients with partial remission and 1.8 +/- 1.8 months for the unresponsive patients.

A Phase I/II trial was performed in 16 patients with CML myeloid blast crisis (Fruehauf, Topaly et al. 2007). Patients were treated with imatinib plus mitoxantrone/etoposide in four cohorts: mitoxantrone 10 mg/m$^2$/day and etoposide 100 mg/m$^2$/day for 2 or 3 consecutive days and imatinib 600 mg/day from Day 15 (cohorts 1 and 2) or from Day 1 (cohorts 3 and 4). After haematological reconstitution after the cytopenic phase, cytarabine was given at a dose of 10 mg/m$^2$/day in addition to imatinib as maintenance treatment. All patients who received more intensive induction treatment (cohorts 3 and 4, n =7) achieved a haematologic response (HR). In contrast, HR was achieved in only 6 of 9 patients treated in cohorts 1 and 2. The induction treatment was well tolerated. The treatment-related mortality (TRM) rate of 12.5% (2 of 16 patients) observed in this study is similar to TRM rates observed with other intensive chemotherapy.

The Swedish CML group utilised an intensive chemotherapy protocol for 83 patients (aged 16–79 years) in accelerated (AP, n=22) or blastic phase (BC, n=61) (Axdorph, Stenke et al. 2002). Most patients received a combination of mitoxantrone (12 mg/m$^2$/day) and etoposide (100 mg/m$^2$/day) together with cytosine arabinoside (1 g/m$^2$ twice a day) for 4 days. Overall, 39 patients (47%) achieved a second complete phase (CP2)/partial remission (PR). Subsequent SCT/ASCT was feasible for half (n=34) of the responders (< 65 years). Responding patients <65 years were eligible for ablative chemotherapy followed by an allogeneic (SCT) or a double autologous stem cell transplant (ASCT). The 1 year survival was 70% for SCT/ASCT patients (median survival 21 months), 50% for responding patients overall, and 7% for non-responders (p<0.001).

Although the level of evidence is limited, the CHMP recognised that in selected cases and at the discretion of the treating physician the addition of mitoxantrone to combination regimens could be of benefit to this patient population. Therefore the proposed harmonised indication for the treatment of blast crisis in chronic myeloid leukaemia was considered acceptable.

<u>Pain relief in patients with advanced, castrate-resistant prostate cancer, in combination with corticosteroids</u>

This indication is approved in almost all the MS where Novantrone has a marketing authorisation, with minor variation in its exact wording. The MAH provided several phase III studies and a phase II study investigating the effect of mitoxantrone in combination with corticosteroids on pain relief and on overall survival. Relevant results are described below.

A phase III randomised multicentre trial compared the effectiveness of mitoxantrone (12 mg/m² every 3 weeks, up to a total dose of 140 mg/m²) plus low-dose (10 mg/day) prednisone to low-dose prednisone alone in 161 men with symptomatic, hormone refractory, progressive prostate cancer (Tannock, Osoba et al. 1996). The primary end point was a palliative response defined as a 2-point decrease in pain as assessed by a 6-point pain scale completed by patients without an increase in analgesic medication and maintained for two consecutive evaluations at least 3 weeks apart. Palliative response was observed in 23 of 80 patients (29%; 95% CI, 19%-40%) who received mitoxantrone

plus prednisone, and in 10 of 81 patients (12%; 95% CI, 6%-22%) who received prednisone alone (p=0.01). Similarly, the overall palliative response (defined as primary plus secondary responses) and the median duration of primary and overall palliative response were greater in the combination group (respectively 38% vs 21%; p=0.025; 7.6 vs 2.1 months, p=0.0009; 5.6 vs 1.9 months, p=0.0004). The median time to progression for all patients in the combination group was 4.4 months compared to 2.3 months in the prednisolone group (p=0.0001). Median time to death was 11.3 months for patients in the combination group compared to 10.8 months in the prednisolone group (p=0.2324). Nine of the 48 non-responder patients in the prednisolone group (19%) demonstrated a palliative response after crossover to the combination group. Out of 130 patients who received mitoxantrone, treatment was well tolerated, except for five episodes of possible cardiac toxicity (cumulative dose 116 to 214 mg/m$^2$). There were nine instances of fever with neutropenia (WHO grade 3 to 4) among 130 patients (including crossover) who received 796 courses of mitoxantrone chemotherapy; these infections resolved following antibiotic therapy.

In a second phase III study, combined treatment with mitoxantrone (14 mg/m² every 3 weeks) plus hydrocortisone (40 mg/day) was compared to hydrocortisone alone (40 mg/day) in 242 patients with hormone-refractory prostate cancer (Kantoff, Halabi et al. 1999). The primary endpoint was overall survival. Although there was a delay in time to treatment failure and disease progression in favour of the combination arm, there was no difference in overall survival (12.3 months in the combination arm and 12.6 months in the hydrocortisone arm; p=0.77). Partial remission (PR) was achieved in 10 patients (8.4%) in the combination arm and 2 patients (1.6%) in the hydrocortisone arm (p=0.018). The median time to progression (TTP) for patients in the combination arm was 7.3 months compared to 4.1 months in the hydrocortisone arm (p=0.0654). There was an indication that quality of life was better with the combined treatments, in particular with respect to pain control. Treatment in both arms was well tolerated, particularly considering the age of the patients. The most commonly reported grade 3 and 4 toxicities were haematopoietic toxicity in approximately 70% of patients in the combination arm. This did not result in undue morbidity.

In a third phase III trial 120 men with asymptomatic, progressive, hormone refractory prostate cancer were randomly assigned to treatment with mitoxantrone 12 mg/m$^2$ every 3 weeks and 5 mg twice daily prednisone or prednisone alone (Berry, Dakhil et al. 2002). Median follow up was 21.8 months. Median time to treatment failure and median time to progression were the same; 8.1 months in the mitoxantrone and prednisone group compared to 4.1 months in the prednisone alone group (respectively p=0.017 and p=0.018). More patients (48%) treated with mitoxantrone and prednisone achieved a 50% or greater reduction in prostate specific antigen levels than those who received only prednisone (24%, p=0.007). There was no significant difference in median survival between the 2 groups, which was 23 and 19 months, respectively. Toxicity was considered low. Leukopenia and neutropenia were the most commonly observed WHO grade 3 and 4 toxicities. Cardiac toxicity grade 3 and 4 was not observed.

The data provided by the MAH and reported in the literature clearly indicate an effect of mitoxantrone, in combination with corticosteroids, for the palliation (e.g. pain relief) of patients with advanced castrate-resistant prostate cancer (CRPC). However, no benefit in overall survival or other clinically relevant endpoints has been reported. In the last decades several anti-cancer medicinal products acting on clinically relevant endpoints (e.g. OS, PFS, TTP, ORR) have been approved in the EU for the treatment of patients with HRPC. Considering the above points, highlighted by the CHMP, the MAH proposed to specify in the indication that mitoxantrone is intended specifically for palliation (and not for improvement of survival, nor other clinical endpoints) in advanced castrate resistant prostate cancer. The toxicity of mitoxantrone appears to be acceptable in this patient population at the proposed cumulative dose of less than 140 mg/m$^2$. It is recognised that mitoxantrone is currently

given in clinical practice to patients with CRPC to achieve palliation after exhaustion of other available treatment options. Therefore the CHMP agreed to the proposed indication in CRPC.

Palliation of non-resectable primary hepatocellular carcinoma

This indication is approved in a majority of the MS where Novantrone has a marketing authorisation, with minor variation in its specificity (e.g. general indication in hepatocellular carcinoma (HCC) or specifically in non-resectable primary hepatocellular carcinoma). The MAH provided several phase II studies (including one comparative study) and case studies reported in the literature where mitoxantrone was given to patients with HCC. Relevant results are described below.

In a clinical study, 38 patients were divided into two groups after hepatectomy for hepatocellular carcinoma with high risk factors for recurrence: one group (n=19) was treated with mitoxantrone by hepatic arterial infusion (3-weekly cycles of 6-10 mg/m² for three days), and the other group (n=19) received no treatment (Takagi, Koyama et al. 1998). The survival rates after 1 and 3 years were 94.7% and 54.7% for the group treated by hepatic arterial infusion chemotherapy and 53.9% and 32.8% for the non-treated group (p=0.012). The non-recurrence rates after 1 year and 3 years were 94.7% and 44.2% for the treated group and 52.6% and 23.6% for the non-treated group (p=0.005), respectively. The survival rates and non-recurrence rates after 3 years in the treated group were significantly higher (p=0.012 and p=0.005, respectively).

In a phase II study comparing mitoxantrone 14 mg/m² and cisplatin 75 mg/m² every 3 weeks in primary liver cancer, 69 patients were eligible (Falkson, Ryan et al. 1987). Two patients treated with cisplatin had partial responses. The upper limit of the 95% confidence interval in the response rate to mitoxantrone was (0%, 8%), and to cisplatin (0%, 17%). The median survival time was 14 weeks on both drugs. One patient had a severe cardiac reaction. In the mitoxantrone group 12 patients had a severe haematological reaction.

In a phase II non-comparative study, 35 patients with HCC were treated with mitoxantrone 12 mg/m² infused intravenously every 21 days, adjusted by increment of 2 mg/m² depending on toxicity and response (Dunk, Scott et al. 1985). One complete and five partial responses were seen in 22 evaluable patients and in a further 4 patients tumour size remained static for lengths of time ranging from 13 to 42 weeks. Bone marrow suppression was dose-limiting but managed by dose reduction. Other acute toxicity was rare, vomiting and hair loss being reported only once each. Cardiac events occurred in 5 patients, 3 of whom had received high total cumulative doses of mitoxantrone.

In another phase II study 49 patients with histologically confirmed primary liver cancer were administered mitoxantrone 14 mg/m² every 3 weeks (Falkson and Coetzer 1985). Estimated median survival time was 12 weeks for the 36 patients evaluable. The survival time of the two patients who exhibited partial response was 20 and over 28 weeks respectively. Among the patients evaluable for toxicity, leukopenia (including two grade 4) and thrombocytopenia were the most important side-effects encountered.

Twenty-three patients with were treated by hepatic arterial infusion (HAI) of mitoxantrone 6 to 10 mg/m²/day by continuous hepatic artery infusion for three consecutive days, repeated every 4 weeks (Shepherd, Evans et al. 1987). A partial response was seen in six patients, with a median duration of 20 weeks (range, 18 to 38 weeks). Five patients achieved stable disease, with a median duration of 20 weeks (range, 11 to 42 weeks). The median survival of the overall group was 22 weeks. Survivals of responding, stable, and nonresponding patients were 32 weeks, 24 weeks, and 9 weeks, respectively. Granulocytopenia was frequent at both dose schedules. Myelosuppression was seen in all patients. Two patients developed neutropenia-associated fever.

Colleoni reported on two case studies respectively including 18 and 40 patients treated with 12 mg/m$^2$ for 3 weeks combined with interferon beta or alone. Four partial responses occurred in the first one (6 stable disease, 7 disease progression) and 9 in the second (15 stable disease, 14 disease progression) (Colleoni, Nole et al. 1992, Colleoni, Bajetta et al. 1993).

Intra-tumoural injection of mitoxantrone as palliative local treatment of malignant hepatic lesions was conducted in 9 patients previously treated with primary or secondary liver tumours (Farres, de Baere et al. 1998). Fifteen lesions (8 hepatocellular carcinoma, 7 metastatic lesions) were treated with mitoxantrone 10 mg (for lesions less than or equal to 3 cm) or 20 mg (for lesions greater than 3 cm) in 0.5 ml of contrast media using computed tomography guidance. Tumour response based on size was minor (25% to 50% size reduction), unchanged (< 25% size reduction) or progressive (>25% increase in size) in 1, 11, and 3 lesions, respectively. Within 2 to 9 months after mitoxantrone, 9 lesions showed an increase in size.

The CHMP concluded that the level of evidence provided is limited to few series of patients with high heterogeneity in terms of dose administered, route of administration and disease settings (e.g. primary metastatic tumours not resectable, or resectable with mitoxantrone given after resection). In most studies no comparator was used or, when a comparator was used (i.e. cisplatin) it appeared to be more effective when compared to mitoxantrone. The more compelling evidence is in the adjuvant use in resected hepatocellular cancer at high risk of recurrence, but this is also from a limited number of patients (19 patients treated with mitoxantrone and 19 with placebo). Further, mitoxantrone is not recommended in any treatment guidelines for hepatocellular carcinoma. The evidence discussed shows evidence of some activity for mitoxantrone in hepatocellular carcinoma, which would warrant further evaluation in larger trials. The CHMP considered the level of evidence currently available insufficient to support the use of mitoxantrone in hepatocellular carcinoma, which the MAH accepted and therefore withdrew this indication from the proposed harmonised PI.

Treatment of acute lymphocytic leukaemia

This indication is approved in a few MS where Novantrone has a marketing authorisation. The MAH provided a phase III study and several uncontrolled phase II studies in induction therapy as well as studies of mitoxantrone in combination regimens in relapsed/refractory ALL (including a study in children). Relevant results are described below.

In a multicentre, prospective, randomised trial the ALL-2 regimen (cytarabine 3 g/m$^2$ daily for 5 days with mitoxantrone 80 mg/m$^2$ plus GM-CSF and methotrexate) was compared with a standard 4-drug induction (L-20 regimen: vincristine, prednisone, cyclophosphamide, and doxorubicin plus GM-CSF and methotrexate) in previously untreated ALL patients (Lamanna, Heffner et al. 2013). Patients also received consolidation, maintenance therapy, and central nervous system prophylaxis. Responses were evaluated in 164 patients. The frequency of complete remission for the ALL-2 regimen was 83% compared to 71% in the L-20 regimen (p=0.06). More patients on the L-20 arm failed with resistant disease (21% vs 8%; p=0.02). Induction deaths were comparable at 9% (ALL-2) versus 7% (L-20). The median survival was similar; and, at 5 years, the survival rate was 33% alive on the ALL-2 arm versus 27% on the L-20. The incidence of severe adverse events was similar in both arms. In the ALL-2 arm a second wave of myelosuppression was noted between days 60 and 120, which the authors attributed to the high-dose mitoxantrone.

In a multicentre, open-label, randomised study in 216 paediatric patients aged 1-18 years with first relapse of ALL were randomly assigned to induction treatment with either idarubicin or mitoxantrone (Parker, Waters et al. 2010). Estimated 3-year progression-free survival was 35.9% (95% CI, 25.9–45.9) in the idarubicin group versus 64.6% (95% CI, 54.2–73.2) in the mitoxantrone group

(p=0.0004), and 3-year overall survival was 45.2% (95% CI, 34.5–55.3) versus 69.0% (95% CI, 58.5–77.3; p=0.004). Overall the number of toxic effects at grade 3 or higher was significantly lower for patients given mitoxantrone than for those given idarubicin (incidence rate ratio mitoxantrone:idarubicin 0.86, 95% CI 0.75–0.98, p=0.02). However significantly higher toxicity level was reported at the end of the trial in patients given mitoxantrone, although the number of adverse events was low.

In a clinical phase II study the combination of high dose cytosine arabinoside and mitoxantrone (HAM) was applied to 24 patients with refractory acute lymphoblastic leukaemia (ALL) (Hiddemann, Buchner et al. 1990). Therapy consisted of HD-araC 3 g/m$^2$ every 12h Days 1-4 and mitoxantrone 10 mg/m$^2$/d Days 2-5 or 2-6. Twelve of the 24 patients (50%) achieved a complete remission, one patient had a partial remission, and five patients were non-responders. Median time to complete remission was 33 days. Nausea, vomiting, diarrhoea, and mucositis were the most frequent side effects, except for infectious complications accounting for the majority of grade 3 and 4 toxicities. In addition, in another study 14 patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia (ALL, in good early responders with corticosensitive and chemosensitive ALL) who received imatinib and HAM (mitoxantrone 10 mg/m$^2$ with intermediate-dose cytarabine 2000 mg/m$^2$/12h) all had complete remission (de Labarthe, Rousselot et al. 2007).

Sequential fludarabine, cytarabine, and mitoxantrone (FLAM) showed efficacy in relapsed and refractory adults with ALL in phase II study with 50 patients (Giebel, Krawczyk-Kulis et al. 2006). Complete remission (CR) rate was 50% and was significantly higher for patients in whom FLAM was administered as a second-line therapy compared to those more heavily pre-treated (66 vs 13%, p=0.02). Seventeen patients had leukaemia regrowth after initial cytoreduction, whereas, eight patients died in aplasia (six of septic infections and two of fatal cardiac complications). At 3 years, the probability of disease-free survival for patients who achieved CR was 16%. In another study 55 adults patients, including 12 with relapsed or refractory acute leukaemia received salvage therapy with the FLAM regimen, which consisted of fludarabine, cytarabine, and increasing doses of mitoxantrone (Koller, Kantarjian et al. 1999). Overall, the complete response rate was 27.3% (15 of 55 patients, including 4 of 17 with acute myelogenous leukaemia (AML), 4 of 12 with acute lymphocytic leukaemia (ALL), and 7 of 26 with the blastic phase of CML). Dose-limiting toxicity was not observed, including at doses of mitoxantrone escalated to 60 mg/m$^2$ over 4 days. Significant myelosuppression was observed in all patients. No clinical cardiac dysfunction was observed.

The phase III study provided showed that outcome of patients treated with cytarabine/mitoxantrone (ALL-2 regimen) is comparable to outcome of patients treated with L-20 (vincristine, prednisone, cyclophosphamide, doxorubicin). However the CMHP was of the view that overall the evidence provided was insufficient, in particular considering the large heterogeneity among acute leukaemia patients. This indication is currently authorised in only two MSs and current clinical practice guidelines do not support the use of mitoxantrone in ALL, neither in untreated patients nor in the refractory/relapsed setting. As anthracycline-based regimens in ALL are supported by current guidelines and in view of the overlapping mechanism of action of mitoxantrone and anthracyclines, the efficacy of mitoxantrone may be similar, however no data could be identified in literature that would sufficiently support a comparable efficacy of mitoxantrone and anthracycline-based regimens in the indication ALL. In conclusion, in view of the limited data available, the CHMP considered that the indication was not acceptable. This was accepted by the MAH which therefore withdrew it from the proposed harmonised PI.

Treatment of multiple sclerosis (MS)

This indication is approved in almost all the MS where Novantrone has a marketing authorisation, with some differences in the exact patient population. Multiple sclerosis is a non-fatal disease, but a chronic progressive and disabling condition. Three different clinical courses of multiple sclerosis have been defined: relapsing/remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (PPMS). Progressive/relapsing multiple sclerosis (PRMS) was first defined as a fourth category but is no longer used, those patients would now be considered primary progressive.. While both pivotal studies with mitoxantrone were initiated prior to the first classification of the four multiple sclerosis disease categories, it is considered that the effects were mainly investigated in patients with SPMS and RRMS (Edan 1997 and Hartung 2002). The MAH presented studies in support of a proposed harmonised indication, initially worded as *"mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e. patients whose neurologic status is significantly abnormal between relapses)"* and re-worded during the procedure as a second proposal intended to address CHMP comments *"in induction therapy in patients with worsening secondary progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (with evidence of persistent inflammatory activity), for reducing neurologic disability and/or the frequency of clinical relapses in particular when followed by a maintenance therapy with a disease-modifying immunomodulatory drug"*. Relevant results are described below.

In the MIMS study, a placebo-controlled, double-blinded, randomised trial, 194 patients with RRMS or SPMS were assigned placebo or mitoxantrone 5 mg/m$^2$ or 12 mg/m$^2$ (intravenously) every 3 months for 24 months (Hartung, Gonsette et al. 2002). Eligibility criteria included, secondary progressive or remitting-progressive (patients with relapsing-remitting disease with residual deficits after relapse) multiple sclerosis, Expanded Disability Status Scale (EDSS) between 3 and 6 points, and active disease progression as defined by EDSS deterioration of at least 1.0 point in the preceding 18 months. Mitoxantrone 12 mg/m$^2$ was significantly better than placebo in all five primary variables (changes in the EDSS: -0.13(1.24) with high dose mitoxantrone versus 0.23(1.01) in the placebo group, p=0.02), ambulation index (AI), and Standard Neurological Status (SNS: -1.07(8.61) with high dose mitoxantrone versus 0.77(6.79) in the placebo group) values at 24 months compared to baseline values; number of relapses requiring corticosteroid treatment; and time to first relapse requiring corticosteroid treatment) and in secondary efficacy parameters evaluating neurologic disability, relapse, quality of life and hospitalisation. The annualised relapse rate was also notably lower in the mitoxantrone 12 mg/m$^2$ group, with a 66% reduction in relapse rate over 2 years. In the subset of 110 patients who underwent T1-weighted Gd-enhancing and T2-weighted MRI scans at baseline, Month 12 and Month 24, results supported the hypothesis that mitoxantrone decreases the inflammatory process in the central nervous system. The effect of mitoxantrone 5 mg/m$^2$ was intermediate between mitoxantrone 12 mg/m$^2$ and placebo. This suggests a dose-response effect which forms supporting evidence of biological activity of mitoxantrone in multiple sclerosis. This is further supported by the results of the Vollmer studies in RRMS patients, where a lower cumulative dose was administered to 40 RMS patients (36 mg/m$^2$) and less pronounced effects were observed.

In a randomised, open-label study, 85 patients were first treated with 1 g/month methylprednisolone for 2 months to screen patients with active disease thus eligible for the second part of the study, a 6-month treatment period with either methylprednisolone 1 g/month or mitoxantrone 20 mg/month (cumulative dose 72mg/m$^2$) combined with methylprednisolone 1 g/month (Edan, Miller et al. 1997). To be eligible for randomisation (second part of the study), patients must have developed at least one new Gd-enhancing MRI brain lesion during the screening period. Patients randomised in this study had

RRMS (71%) or SPMS (29%). On average, patients had been diagnosed with multiple sclerosis for approximately 6 years prior to enrolment, with an average of about 2-3 relapses in the year prior to enrolment. The primary endpoint of the study was met, with significantly more patients randomised to the combination group improving, as defined by negative Gd-enhancing scans at Month 6 compared to methylprednisolone alone (31% (5/16) vs. 90% (19/21), p=0.001). Mitoxantrone in combination with methylprednisolone was consistently statistically better than methylprednisolone alone from Month 2 to 6. The gradual improvement of the MRI scans from Month 2 to 6 in the combination group suggests a direct effect of mitoxantrone on the pathological lesions of multiple sclerosis rather than an effect on the blood-brain barrier. The combination treatment showed also significant better results than methylprednisolone alone in the secondary endpoints (number of new and persisting Gd-enhancing lesions on MRI scan, clinical results assessed by EDSS score, and number of relapses). The strong and rapid reduction in the inflammatory process suggests a potential role for mitoxantrone in rapidly deteriorating patients with multiple sclerosis. These results were confirmed in a randomised controlled study in 109 patients with aggressive RMS comparing the effect of a 6 months pre-treatment with mitoxantrone 12mg/m$^2$ (cumulative dose 72mg/m$^2$) combined with methylprednisolone to that of interferon-beta-1b (INF) with the same dose of methylprednisolone, followed in both arms by INF for two years and a half (Edan, Comi et al. 2011). The time to worsening by at least one EDSS point (from the score confirmed at 3 months) was delayed by 18 months in the mitoxantrone group compared with the IFN group (p<0.012). Patients in the mitoxantrone group had a reduced number of Gd-enhancing lesions at month 9 (83% reduction) and a slower accumulation of new T2 lesions at each time point. In addition, the risk of sustained accumulation of disability at 3 years was reduced by 64.9% and the annualised relapse rate per patient by 61.7%, in the mitoxantrone group compared to the INF group. A 5-year follow-up observational study in 100 patients with aggressive RMS showed similar results (Le Page, Leray et al. 2008).

A Cochrane analysis concluded that mitoxantrone shows a significant partial efficacy in reducing the risk of multiple sclerosis progression and the frequency of relapses in patients affected by worsening RRMS, PRMS and SPMS in the short-term follow-up (two years) with no major neoplastic events or symptomatic cardiotoxicity related to mitoxantrone being reported (Martinelli Boneschi, Vacchi et al. 2013). The authors noted that studies with longer follow-up have raised concerns about the risk of systolic dysfunction and therapy-related acute leukaemia, occurring in about 12% and 0.8% of mitoxantrone-treated patients respectively. In summary, the authors suggested that mitoxantrone could be a treatment options for patients with worsening RRMS and SPMS and with evidence of persistent inflammatory activity after a careful assessment of the individual patients' risk-benefit profile and alternative treatment options. A more favourable risk-benefit profile of mitoxantrone was considered when the drug is used for a short-term induction treatment followed by a maintenance immunomodulatory treatment given the evidence of a dose-effect relationship for adverse events.

In the studies presented, albeit, limited in number and in heterogeneous populations, mitoxantrone demonstrated a consistent effect on relapses as well as disability. The results suggested a dose-response effect which forms supporting evidence of biological activity of mitoxantrone in multiple sclerosis. Considering the mechanism of action of mitoxantrone, its efficacy is believed to be mediated by an effect on inflammation, hence the use of mitoxantrone in SPMS patients is not considered justified. Further, the terms in the second proposal of the MAH "worsening secondary progressive multiple sclerosis", "progressive relapsing multiple sclerosis" or "worsening relapsing remitting multiple sclerosis" do not correspond to official categories and are not clearly defined. For these reasons, the CHMP did not consider this wording proposal acceptable. Mitoxantrone demonstrated efficacy as a short course treatment, however it is unclear whether subsequent treatment with disease modifying agent would be beneficial as this has not been evaluated in controlled settings. Considering the risks of

cardiotoxicity and leukaemia (see 2.2.4), the CHMP was of the view that mitoxantrone use should be limited to the population in which the benefits would outweigh these serious risks. The CHMP sought the advice of the SAG Neurology in order to gain insight into the current clinical use of mitoxantrone and clearly define the patient population which can benefit from this treatment (see 2.3.1). The SAG considered that mitoxantrone could be used in treatment of inflammatory active multiple sclerosis associated with accumulation of disability where no other treatment option is available. The CMHP followed the advice of the SAG and included a shortened wording providing an operational definition for the indication in the harmonised product information "*treatment of patients with highly active relapsing multiple sclerosis associated with rapidly evolving disability where no alternative therapeutic options exist*", cross referring to sections 4.2, 4.4 and 5.1.

## 2.2.2. Section 4.2 – Posology and method of administration

The general dosing recommendations were globally aligned between member states, with minor variations in schedules of administration and dose adaptation (including dose lowering for patients receiving other myelosuppressant or cytotoxic medicinal products as well as for elderly and possibly for patients with renal or hepatic impairment) or additional indication-specific recommendation. In addition, in some MS a maximum cumulative dose was given for use in multiple sclerosis. The MAH proposed harmonised dosing recommendations based on the doses studied in clinical trials and a general recommendation to monitor cardiac toxicity in cancer patients. Common dosing recommendations were proposed for metastatic breast cancer and non-Hodgkin's lymphoma including a guide for dose adjustment in case of myelosuppression and dose reduction guidance for use in combination therapy. For acute myeloid leukaemia dosing recommendations were proposed as a single agent in relapses and in combination with cytarabine and etoposide (only for refractory AML) as induction, consolidation and salvage therapy. Separate dosing recommendations were also proposed for treatment of blast crisis and prostate cancer (in combination with corticosteroids). These recommendations were considered appropriate.

In multiple sclerosis the MAH initially proposed 12 mg/m$^2$ dose every 3 months up to a maximum dose of 100 mg/m$^2$, however in order to reflect the schedules used in clinical trials and practices in the different member states, a range of 1-3 months was considered more appropriate. In addition, due to the dose dependent risk of cardiotoxicity, the maximum lifetime cumulative dose was limited to 72 mg/m$^2$; dose at which mitoxantrone was found efficacious but the cardiotoxicity was minimised (please refer to 2.2.4). For this reason also, it was specified that Novantrone should not be initiated for treatment of multiple sclerosis in patients who have already been treated with it. Further dosing adjustment guide was re-introduced, based on the extent and duration of bone marrow suppression within 21 days after and 7 days before mitoxantrone infusion in order to minimise the risk of leukaemia. General dose lowering for other serious toxicity, including recommendation to discontinue treatment in case of WHO grade 4 toxicity, were also accepted.

With regards to the paediatric population, the proposed statement that the safety and efficacy of Novantrone have not been established in this population was considered adequate, further specifying that Novantrone is not a relevant treatment in this age group.

Concentrate for solution for intrapleural or intraperitoneal use as well as concentrate for solution for injection/infusion were authorised in a few MS, however in the harmonisation, the MAH proposed that only the administration via intravenous infusion should be retained, which was accepted, therefore other route of administration will not be discussed here. Dilution recommendation and guidance for the choice of veins as well as warning regarding extravasation, already included in some member states, were considered adequate.

## 2.2.3. Section 4.3 – Contraindications

The standard contraindication in case of hypersensitivity to the active substance or any of the excipients (including sulphite, as already mentioned in some member states) was kept in the harmonised text.

Information on the risks to the babies of pregnant and breastfeeding mothers treated with mitoxantrone was inconsistently reflected across the different section of the PI in the different MS. Mitoxantrone is excreted in human milk and significant concentrations (18 ng/ml) have been reported for 28 days after the last drug administration (6 mg/m$^2$) (Azuno, Kaku et al. 1995). Mitoxantrone is considered a potential human teratogen because of its mechanism of action and the developmental effects demonstrated by related agents. No teratogenic effects were observed in studies in rats and rabbits, but the maximum doses tested were below the equivalent of the recommended dose in humans. Six cases of exposure to mitoxantrone during pregnancy were described in the literature so far. Two cases of exposure in early pregnancy resulted in a case of a male baby with Pierre-Robin Sequence and growth retardation without evidence of congenital malformations in the other case. Two cases of exposure to mitoxantrone and other cytotoxic agents in the second trimester of pregnancy reported a stillborn without apparent congenital malformations, one growth-retarded preterm newborn and two healthy newborns. No late teratogenic effects were observed in a French post-marketing study in multiple sclerosis (Le Page, Leray et al. 2011). Twenty-seven women between 1 and 7 years after their last course of mitoxantrone gave birth to 32 healthy babies. In view of the above, the CMHP considered that mitoxantrone should be contraindicated in breastfeeding mothers. In addition, as multiple sclerosis is not a life threatening disease, mitoxantrone should be contraindicated in the treatment of multiple sclerosis in pregnant women.

In some MS Novantrone was contraindicated for use as an adjuvant treatment for breast cancer, in relation to the possible risk of leukaemia. In breast cancer, the risk of developing AML after mitoxantrone has been reported at incidences ranging from 0.5% to 7% depending on studies (mean 2.5%). As the harmonised wording in section 4.1 specifies that mitoxantrone is indicated in the treatment of metastatic breast cancer, a warning was included in section 4.4 informing of the small risk of leukaemia and of the absence of sufficient efficacy data in the adjuvant treatment of breast cancer.

The MAH also proposed to harmonise a contraindication present in a MS against the immunisation with a live attenuated vaccine during and for up to 6 months after end of mitoxantrone therapy. The CHMP was of the view that the scientific basis for this recommendation was weak. Clinical practice guidelines recommend to leave a period of 3 months between end of treatment and vaccination. It is acknowledged that these recommendations are based on low quality evidence; however, listing this contraindication would preclude the use of live vaccines in specific situations in which the anticipated benefits of vaccination are considered to outweigh the potential risks. Therefore, this information should be included in section 4.4 and 4.5, in line with the clinical practice guidelines.

Contraindications against the intrathecal, subcutaneous, intramuscular or intra-arterial routes of administration were also in place in some member states, due to the risk of extravasation and as neuropathy and neurotoxicity, both central and peripheral nervous system have been reported. These and other contraindications in place in a few member states were considered more adequately addressed by wording in other sections of the PI.

## 2.2.4. Section 4.4 – Special warnings and precautions for use

In addition to those described above (e.g. immunisation with live virus vaccines), several warnings were in place in all (or all but one or two) member states with slightly different wordings and level of details (risks linked to inappropriate routes of administration, cardiac risks including risk factors and monitoring recommendations, risk of leukaemia and bone marrow/haematological monitoring recommendations, reduced immunological response to infection, secondary AML and MDS) and the harmonised proposal of the MAH was considered acceptable with some amendments as described below.

It was considered relevant to specify adverse events that occurred in case of incorrect administration (i.e. other than intravenous) and that cancer patients who received cumulative doses of 140 mg/m$^2$ had a cumulative 2.6% probability of clinical congestive heart failure and that the overall cumulative probability rate of moderate or severe decreases in LVEF at this dose was 13%.

The cardiovascular and leukaemia risks were considered key to the benefit-risk balance in the multiple sclerosis indication and were reviewed in details as well as risk minimisation measures proposed to manage those. In addition, the CMHP requested the advice of the SAG and of the PRAC regarding the need for additional risk minimisation measures (see 2.3). Relevant results are described below.

Over the 3 years study duration in the MIMS study, left-ventricular ejection fraction (LVEF) was decreased to less than 50% in two patients in the 5 mg/m$^2$ group and two in the 12 mg/m$^2$ group. No congestive heart failure (CHF) or other clinically significant cardiac dysfunction occurred during 3 years of monitoring (Hartung, Gonsette et al. 2002). No cardiotoxicity was observed in the second pivotal study (Edan, Miller et al. 1997). In the pivotal trials no case of therapy-related acute leukaemia was observed.

A cohort of 509 patients (395 SPMS, 81 worsening RRMS, 33 PRMS) treated with mitoxantrone (12 mg/m²) every 3 months was followed in a long-term study in the United-States (RENEW study Rivera, Jeffery et al. 2013). The patients received laboratory workups and cardiac monitoring (symptoms of CHF, cardiac structure-activity relationship, LVEF measured using echocardiogram or a multiple gated acquisition scan (MUGA)) every 3 months during the treatment phase and then annually for a total of 5 years. LVEF reduction under 50% was reported in 27 (5.3%) patients during the treatment phase (n=509) and 14 (5.6%) patients during the annual follow-up phase (n=250). Signs and symptoms of congestive heart failure were observed in 10 (2.0%) patients (six during treatment phase and four during the annual follow-up phase). Serious adverse reactions included reduced LVEF (<50%) in 3% of the patients and symptomatic CHF in 0.4%. The median latency of CHF events from the first dose of mitoxantrone was 24.2 months (range 9.5–35.6 months). The median latency of LVEF reductions below 50% from the first dose of mitoxantrone during the treatment phase was 29 months (range 13.3–44.6 months). Among patients with cardiac events, 74.2% of patients received doses >75 mg/m² compared with 25.8% of patients who received ≤75 mg/m$^2$ (p<0.0001). Post-hoc analyses of the risk for cardiotoxicity outcomes revealed that cumulative dose exposure is the primary risk factor associated with the risk of cardiac toxicity with mitoxantrone. Therapy-related leukaemia was reported in three (0.6%) patients who received total cumulative Mitoxantrone doses of 73.5 mg/m², 107.3 mg/m², and 97.1 mg/m² respectively.

In the French mitoxantrone cohort study, which followed 802 multiple sclerosis patients (352 SPMS, 308 worsening RRMS, 142 PPMS) for at least 5 years after initiation of mitoxantrone therapy, 1/802 patients (0.1%) presented with acute congestive heart failure and 39/ 794 patients (4.9%) presented with asymptomatic LVEF reduction under 50% (persistent in 11 patients (28%), transient in 27 patients (69%), on the last scan at year 5 in 1 patient) (Le Page, Leray et al. 2011). Two cases of

therapy-related leukaemia (0.25%) were detected 20 months after treatment initiation (one death and one with 8 years confirmed remission). The authors of concluded that the use of mitoxantrone in multiple sclerosis patients should be limited to a cumulative dose 72 mg/m$^2$ instead of 96 mg/m$^2$.

A multicentre retrospective cohort study evaluating the cardiac side effects attributed to mitoxantrone analysed in 639 multiple sclerosis patients (102 RRMS, 441 SPMS, and 96 PPMS) in Germany found similar incidence rates (Fleischer, Salmen et al. 2014). The authors concluded that the odds of cardiac dysfunction were 1.019 times higher (95% CI; 1.006-1.032) for every mg/m$^2$ body surface area increase in mitoxantrone cumulative dose, and that the 95% confidence interval for the odds ratio was.

A recent Cochrane review (Martinelli Boneschi, Vacchi et al. 2013) and a literature review by Edan and Le Page came to similar conclusion (Edan and Le Page 2013).

A recent literature review of 11 studies in 716 patients by the American Academy of Neurology confirmed a low incidence of systolic dysfunction (decrease in LVEF (>10%) was estimated to occurs in approximately 12% of patients and congestive heart failure in 3 (0.4%) of patients) and therapy-related acute leukaemia (TRAL) with mitoxantrone therapy in patients with multiple sclerosis though higher than indicated by earlier analysis (Marriott, Miyasaki et al. 2010). However, the definition of cardiotoxicity by a decrease of the LVEF is inconsistent between studies and due to possible variations of the measure a decrease of the LVEF >50% might be a more reliable indicator of the risk of cardiac side effects.

Further, active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity (Posner, Dukart et al. 1985). Multiple sclerosis itself has been inconsistently associated with cardiac abnormalities (Olindo, Guillon et al. 2002) and a more severe stage of the disease may predispose for more severe and established cardiac abnormalities under treatment.

In order to effectively minimise these risk the CMHP considered that in addition to the MAH proposal to evaluate the LVEF by echocardiogram or MUGA prior to each dose of mitoxantrone in multiple sclerosis patients, it should also be monitored yearly for up to 5 years after the end of therapy and the maximum cumulative dose should not exceed 72mg/m$^2$. It should also be monitored at regular interval for cancer patients. In addition, a complete blood count should be obtained before each dose of mitoxantrone and 10 days following each administration. Patients should be advised to seek medical attendance if signs or symptoms develop, including over five years after end of treatment. In addition, due to the risk of development of secondary malignancies, the benefit-to-risk ratio of mitoxantrone therapy should be determined before starting therapy.

These measures were considered adequate by the SAG and the PRAC, who further considered the numerous requirement and their importance for the safe use of the product in multiple sclerosis, educational material should be developed and a study should be conducted to ensure they are adhered to. These should be included in a risk management plan with a particular focus on the use in multiple sclerosis to ensure a consistent minimum standard of management of the risks across MSs.

Finally, warnings relative to the mutagenic potential observed in bacterial and mammalian tests systems as well as in rats, to the potential discoloration of urine and other tissues, monitoring recommendations linked to the risk of tumour lysis syndrome, contraception recommendations in males and in females and risk of transient or persistent amenorrhea, present in some members states were considered relevant. Persistent amenorrhea was observed in approximately 17-22% of women with regular menses in post-authorisation studies (Rivera, Jeffery et al. 2013 and Le Page, Leray et al. 2011). Further, as the potential additive risks of mitoxantrone in patients with long term exposure also

to other immunosuppressants are not known, the CHMP was of the view that it should be mentioned that the safety and efficacy of mitoxantrone have not been demonstrated after other multiple sclerosis treatments approved more recently (i.e. natalizumab, fingolimod, alemtuzumab, dimethyl fumarate or teriflunomide).

## 2.2.5. Section 4.5 – Interaction with other medicinal products and other forms of interaction

Most of the existing statements on interactions across the MSs were considered supported (increased the risk of cardiac toxicity in combination with potentially cardiotoxic active substances, risk of AML and MDS with concomitant antineoplastic agents and/or radiotherapy, risk of increased myelosuppression when used in combination with other myelosuppressive agent, risks with live virus vaccines during and after treatment, potential risks with concomitant use of inhibitors of the breast cancer resistance protein (BCRP) transporter and limited knowledge of excretion of mitoxantrone with a cross reference to section 5.2) and the MAH's proposed harmonised wording was accepted by the CHMP.

In addition, the increased thrombotic or haemorrhage risk with concomitant Vitamin K antagonists with tumoural disease, widely described in the literature was considered relevant to be added by the CHMP, together with recommendations to closely monitor prothrombin time ratio or International Normalised Ratio (IRN, indicative of the time blood takes to clot). Further it was considered that the interaction with immunosuppressive medicines should be mentioned, due to the risk of excessive immunodepression and of lymphoproliferative syndrome.

In some member states, additional information was included in this section on absence of interactions or pharmacokinetic and pharmacodynamic interactions with mitoxantrone observed in vitro or in laboratory animals (including interaction with phenytoin) without clinical relevance, this was not considered relevant to be included in the harmonised PI.

## 2.2.6. Section 4.6 – Fertility, pregnancy and lactation

Information on the excretion of mitoxantrone in breast milk and the need to interrupt breastfeeding prior to treatment initiation was consistently reflected across member states. However different levels of restriction were given regarding the use of mitoxantrone in pregnant women. The wording was harmonised to reflect the limited information available, contraindicate the use in the treatment of multiple sclerosis and recommend against the use in pregnant women in other indications (see also 2.2.3). Relevant information available on risks of infertility in men and women, already included in some member states was also harmonised. Information on the need for contraception in men was added to that already included for women and moved under a dedicated subsection. The periods during which contraception should be continued after end of treatment were adjusted based on estimates considering mitoxantrone half-life and respective gamete cycles length in men and women.

## 2.2.7. Section 4.7 – Effects on ability to drive and use machines

In a few member states it was mentioned in this section that caution should be exercised when driving and using machines but in most it was stated that no studies had been conducted and no data was available. As confusion and fatigue have been reported with mitoxantrone, the CMHP was of the view that, in line with the SmPC guideline, it should be mentioned that the treatment has minor influence on those abilities.

## 2.2.8. Section 4.8 – Undesirable effects

Divergences were noted in this section regarding the way the information was presented, the event listed (indication dependant) and the frequencies. This section was restructured according to guidelines. The MAH recalculated the frequencies based on 27 published clinical trials with a total of 4,377 patients treated with mitoxantrone as monotherapy and in combination therapy, of which 314 were multiple sclerosis patients. In case where an ADR had not been reported in the reviewed trials but identified in spontaneous reports, its frequency was estimated as 0.95%, as per the SmPC guideline. In line with the QRD requirement, the MAH was asked to include details of the most important adverse reactions, e.g. myocardial toxicity, myelosuppression and haematologic toxicities. The MAH was asked to discuss the relevance of including the ADRs conjunctivitis, tumour lysis syndrome, taste disturbances, and rhinitis, which have been reported and are listed in the PI of other mitoxantrone-containing products.

In clinical trials, dysgeusia was observed in mitoxantrone monotherapy treatment for oncology indications only and in the literature, taste changes are mentioned as most frequently reported side effect in breast cancer patients who received mitoxantrone treatment, therefore the MAH was asked to add dysgeusia in the table listing the ARDs reported in oncology with the frequency uncommon. Tumour lysis syndrome, already listed under section 4.4, has been associated with mitoxantrone treatment in the literature, therefore the MAH considered relevant to list it in this section. Reports of "conjunctivitis" and "rhinitis" in the MAH's safety database (data lock point 09 December 2014) do not provide sufficient details for an assessment of the reported event, therefore at present this was considered sufficiently covered under the preferred term "infection" and "upper respiratory tract infections".

The CHMP also considered that in the table of ADR in multiple sclerosis the footnote specifying that the events amenorrhea may be consistent with premature menopause and that the causal relationship between the cases of sudden death and mitoxantrone administration is uncertain should be left in the harmonised PI. A Cochrane review in multiple sclerosis found that amenorrhea and persistent amenorrhea were developed during therapy by 35% of the female treated with mitoxantrone and by none of the women in the placebo group (Martinelli Boneschi, Vacchi et al. 2013). For most of the participants the amenorrhea disappeared after discontinuation treatment; however, in six women (12% of the total) amenorrhoea was still present after the end of treatment (one year after end of treatment (5) and at an undefined follow up visit (1)). Women treated with mitoxantrone had an OR of 22.3 (95% CI 4.03 to 123.47; P=0.0004) of developing amenorrhoea compared with placebo-treated participants. Of the 6 reports of sudden death retrieved in the safety database of the MAH, only one of those was explicitly assessed as possibly related to mitoxantrone treatment by the reporter.

## 2.2.9. Section 4.9 – Overdose

No significant differences between the national SmPCs were present in this section. The MAH's proposal including the lack of antidote, the fact that dialysis would likely not help due to mitoxantrone's properties, the fatal cases reported at ten-fold the recommended dose and potential treatment needed was accepted with the addition of the types of toxicities observed and general recommended actions.

### 2.2.10. Section 5.1 – Pharmacodynamic properties

The proposal of the MAH for this section was accepted with minor amendments in line with the agreed text in other sections of the SmPC and rearrangement of the information under the appropriate subleaders. Information related to indications that were not considered acceptable was removed.

### 2.2.11. Section 5.2 – Pharmacokinetic properties

The MAH's proposed wording was accepted with some additional changes and reorganisation of the information taking into account the QRD requirements. In line with SmPC guideline, data in animals was removed. It was specified that the pathways leading to the metabolism of mitoxantrone have not been elucidated, but that there does not seem to be relevant differences in pharmacokinetics of mitoxantrone between elderly and young patients.

### 2.2.12. Section 5.3 – Preclinical safety data

The CHMP endorsed the content of the proposed text for this section, however information of lesser relevance to humans or duplicated was removed in order to focus on the main information.

### 2.2.13. Other sections of the SmPC

Sections 1 (name of the medicinal product), 2 (qualitative and quantitative composition), 3 (pharmaceutical form), 6 (pharmaceutical particulars), 7 (marketing authorisation holder), 8 (marketing authorisation number(s)), 9 date of first authorisation/renewal of the authorisation and 10 (date of revision of the text) have only been partially harmonised as it is considered that these should be adapted nationally.

### 2.2.14. Labelling

Changes introduced in the SmPC were consistently reflected in the labelling, however most sections were left to be completed nationally. Sections related to the unique identifier were added in line with the current QRD template (dated February 2016).

### 2.2.15. Package Leaflet

The package leaflet (PL) was amended in accordance with the changes made to the SmPC, adapting the language and taking into consideration the relevance of the information for the patient. At the time of CHMP opinion, the MAH had not conducted the user readability testing on the harmonised Package Leaflet. The MAH committed to complete the test within 8 weeks of CHMP opinion, and to provide the corresponding report to the relevant NCA when it becomes available.

## 2.3. Expert consultation

### 2.3.1. Consultation of the Scientific Advisory Group (SAG) in Neurology

A meeting of the Scientific Advisory Group in Neurology was convened on 6 November 2015, at the request of CHMP, to gain insight into the current clinical use of mitoxantrone in patients with multiple sclerosis.

The expert group reported that mitoxantrone is used in the EU, with some variability across MS, as second or third line, in a restricted population of patients with relapsing multiple sclerosis sharing features of high inflammatory status and rapid deterioration, with the intend to prevent irreversible disability progression. This indication is everywhere balanced with the clear perception of the potential for severe side effects of mitoxantrone. Nevertheless, the experts considered that mitoxantrone has its place in the treatment of multiple sclerosis, in inflammatory active multiple sclerosis associated with accumulation of disability, where no other option is available. The SAG members recommended repeated infusion of 12mg/m$^2$ doses up to a maximum cumulative dose of 72mg/m$^2$. The experts were of the view that the risk minimisations measures described in the product information were appropriate and complete, however they considered that educational material may be useful, especially in multiple sclerosis where this indication is not currently authorised.

## 2.3.2. Consultation of the Pharmacovigilance Risk Assessment Committee (PRAC)

The CHMP sought the advice of the PRAC on the need for additional risk minimisations measures regarding the risk of leukaemia and cardiotoxicity in multiple sclerosis.

Based on the available data, the PRAC considered that the risks of cardiomyopathy and leukaemia associated with mitoxantrone are well known. Nevertheless, it was considered that additional risk minimisation measures were needed to ensure physicians' awareness of the risks and highlight the importance of complying with the monitoring requirements, as included in the SmPC, as well as patients' understanding of the risks and of the monitoring needs during and after treatment. Therefore the PRAC recommended the development of educational materials, to be included in a RMP to ensure a consistent minimum standard of management of the risks of mitoxantrone. In addition, the PRAC advised that the adherence to the risk minimisation measures should be monitored via a post-authorisation study.

## *2.4. Risk Management*

The CHMP, having considered the data submitted in the application, the SAG and the PRAC advice, was of the opinion that the below pharmacovigilance and risk minimisation activities are necessary for the safe and effective use of the medicinal product. The CHMP considered that these measures would be relevant to be applied for other products containing mitoxantrone, including generics.

**Risk Management Plan**

The CHMP considered that in order to allow for a consistent minimum standard of management of the risks associated with mitoxantrone treatment across Member States the MAH shall incorporate the below educational materials and study protocol in the risk management system they operate. The RMP describing the risk management system with a particular focus on the use in multiple sclerosis shall be submitted to the Reference Member State (RMS) for assessment within 2 months following the Commission Decision. The RMP should be focused on the cardiotoxicity (considering jointly cardiac function and myocardial toxicity) and haematotoxicity (considering jointly acute myeloid leukaemia and myelodysplastic syndrome) as important identified risks and on the risk minimisation measures for these risks. Safety specifications can also include other important identified risks such as bone marrow suppression/myelosuppression and teratogenicity/reproductive toxicity, however no other elements are considered relevant to be added to the safety specifications (see table 4).

**Table 4. Summary of safety concerns to be included in the RMP for Novantrone containing products**

| Summary of safety concerns | |
|---|---|
| Important identified risks | • Cardiac function/myocardial toxicity |
| | • Secondary acute myeloid leukaemia and myelodysplastic syndrome |
| | • Bone marrow suppression/myelosuppression |
| | • Teratogenicity/reproductive toxicity |

**Educational materials**

Educational programme should be developed in order to inform healthcare professionals and patients of the risks of cardiotoxicity and leukaemia and related monitoring requirements during and after treatment for multiple sclerosis, with the aim to facilitate treatment initiation decision-making and ensure the risks are adequately minimised. The educational programme shall be constituted of a targeted prescriber guide, a checklist for pre-treatment screening and ongoing monitoring requirements during and after treatment, a targeted patient guide focussing on the key risks and monitoring requirements as well as other relevant key risk minimisation measures and a patient alert card reminding of key signs and symptoms regarding cardiotoxicity and leukaemia risk. These materials should include the following key elements and be submitted for evaluation to the relevant National Competent Authorities within two months of Commission Decision:

The targeted prescriber guide should include the following key-elements:

- Novantrone could cause cardiotoxicity

    o signs and symptoms

    o need for echocardiogram or MUGA evaluation of the left-ventricular ejection fraction (LVEF) prior to administration of each dose and yearly for up to 5 years after the end of therapy.

- Novantrone could cause haematotoxicity, including secondary acute myeloid leukaemia and myelodysplastic syndrome

    o signs and symptoms

    o the need for monitoring at the start and prior to each treatment administration

HCP checklist should include the following key-elements:

- evaluation of the left-ventricular ejection fraction (LVEF)

- life-time maximum dose

- full blood count including platelets

Patient information document should include the following key-elements:

- signs and symptoms of cardiotoxicity and haematotoxicity

- Information on the need of regular monitoring, and when it should be carried out, for cardiotoxicity and haematotoxicity

Patient alert card should include the following key-elements:

- key signs and symptoms regarding cardiotoxicity and haematotoxicity

The MAH shall ensure that in each Member State where Novantrone and associated names are marketed for use in multiple sclerosis, all healthcare professionals and patients who are expected to prescribe and dispense or use Novantrone are provided with the above educational package. The MAH should agree about the exact content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authorities.

**Post-Authorisation Safety Study**

Considering the multiple monitoring requirements that should be complied with in order to minimise the risks associated to mitoxantrone, the MAH is required to conduct a study to monitor the adherence to these measures, and therefore the effectiveness of the educational material. The MAH proposal to conduct this study using a survey focusing on obtaining information on the understanding, knowledge and behaviour of the treating physicians on the screening and monitoring requirement for multiple sclerosis patients to minimise the cardiotoxic and malignancy risk associated with the use of Novantrone is considered appropriate (see table 5). The exact details of the proposed survey should be submitted to the RMS for assessment within 2 months of European Commission Decision. The survey will be added as a category 3 study to the RMP and a descriptive analysis of the results will be provided in future PSURs. The submission date of the final study report will be agreed with the RMS.

**Table 5. Overview of post-authorisation safety study for Novantrone**

| Study/activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| Novantrone for the treatment of patients with highly active relapsing multiple sclerosis associated with rapidly evolving disability (drug utilisation study, 3) | To evaluate the awareness of treating physicians' to risk minimisation measures in patients with highly active relapsing multiple sclerosis. | Cardiotoxicity (i.e. deterioration of LVEF, congestive heart failure) and haematotoxicity (i.e. secondary acute myeloid leukaemia and myelodysplastic syndrome) in patients with highly active relapsing multiple sclerosis. | Planned start upon agreement of survey with the RMS (2016). | Interim results in PSURs. Submission date of final study report to be agreed with the RMS. |

## 2.5. Recommendation

The CHMP recommended the revision and harmonisation of the Product Information for Novantrone and associated names and adopted the following harmonised indications:

- *Mitoxantrone is indicated in the treatment of metastatic breast cancer.*

- *Mitoxantrone is indicated in the treatment of non-Hodgkin's lymphoma.*

- *Mitoxantrone is indicated for the treatment of acute myeloid leukaemia (AML) in adults.*

- *Mitoxantrone in combination regimens is indicated in the remission-induction treatment of blast crisis in chronic myeloid leukaemia.*

- *Mitoxantrone is indicated in combination with corticosteroids for palliation (e.g. pain relief), related to advanced castrate resistant prostate cancer.*

- *Mitoxantrone is indicated for treatment of patients with highly active relapsing multiple sclerosis associated with rapidly evolving disability where no alternative therapeutic options exist (see sections 4.2, 4.4 and 5.1).*

The indications palliation of non-resectable primary hepatocellular carcinoma and treatment of acute lymphocytic leukaemia proposed by the MAH were not accepted by the CHMP due to the scarcity of robust clinical trials adequately supporting the use of mitoxantrone in these conditions. The other (non-)clinical sections of the SmPC were also harmonised. In conclusion, the revised and harmonised of the Product Information for Novantrone was considered acceptable by the CHMP.

At the time of opinion, the MAH had not conducted the user readability testing on the harmonised Package Leaflet. The MAH committed to conduct the test and to provide the corresponding report within 8 weeks of the opinion. In addition, the MAH shall submit a RMP including educational material and a post-authorisation study protocol for assessment to the Reference Member State/relevant National Competent Authorities within 2 months of Commission Decision.

## 2.6. Conclusions

The basis for this referral procedure was a harmonisation of the SmPC, labelling and package leaflet.

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC.

- The committee considered the identified divergences for Novantrone and associated names, for the indications, posology, contraindications, special warnings and precaution for use, as well as the remaining sections of the SmPC, labelling and package leaflet.

- The committee reviewed the data submitted by the MAH in support of the proposed harmonisation of the Product Information, including clinical trials, open studies, published studies and reviews as well as evidence based and consensus guidelines. In addition, the committee considered the advice of the Scientific Advisory Group Neurology and of the Pharmacovigilance Risk Assessment Committee.

- The committee agreed the harmonisation of the summary of product characteristic, labelling and package leaflet.

In view of the above, the Committee concluded that the benefit-risk balance of Novantrone and associated names remains favourable, subject to the agreed condition to the marketing authorisations, and taking into account the agreed amendments to the product information and other risk minimisation measures.

The CHMP as a consequence, recommends the variation to the terms of the marketing authorisations for Novantrone and associated names (see Annex I).