Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisations

Scientific conclusions

Overall summary of the scientific evaluation of Novantrone and associated names (see Annex I)

Novantrone contains mitoxantrone, a synthetic anthracenedione antineoplastic agent that has a cytocidal effect on both proliferating and non-proliferating cultured human cells, suggesting 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. Novantrone and associated names are approved for marketing as a 2mg/ml concentrate for solution for infusion for intravenous use in most European Union (EU) Member States (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.

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.

Clinical aspects

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

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. The CHMP considered that the efficacy of mitoxantrone has been demonstrated in these studies. 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)

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. These studies demonstrate the efficacy of mitoxantrone, in combination therapy, in the treatment of NHL. 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 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. Current guidelines for treatment of AML recommend an induction therapy with regimens containing an anthracycline (such as mitoxantrone) administered for 3 days and cytarabine administered for 7 days. The CHMP considered the clinical benefit of mitoxantrone demonstrated in adults and recommended the use of the term acute myeloid leukaemia rather than acute non-lymphocytic leukaemia.

Remission-induction treatment of blast crisis in chronic myeloid leukaemia, in combination regimen

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. 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, and accepted the indication.

Pain relief in patients with advanced, castrate-resistant prostate cancer, in combination with corticosteroids

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. The data 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. 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 intended specifically for palliation.

Palliation of non-resectable primary hepatocellular carcinoma

The MAH provided several phase II studies and case studies reported in the literature where mitoxantrone was given to patients with HCC. The CHMP concluded that the level of evidence provided is limited. In most studies no comparator was used or, when a comparator was used it appeared to be more effective. Further, mitoxantrone is not recommended in any treatment guidelines for hepatocellular carcinoma. 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

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). 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. In conclusion, 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)

The MAH presented an overview of studies of mitoxantrone, mainly in patients with relapsing remitting and secondary progressive multiple sclerosis. 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 risks of cardiotoxicity and leukaemia, 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. 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 agreed on an operational definition for the indication in the harmonised product information.

Section 4.2 – Posology and method of administration

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 dose reduction guidance for use in combination therapy and in case of myelosuppression. For acute myeloid leukaemia dosing recommendations were proposed as a single agent in relapses and in combination as induction, consolidation and salvage therapy. Separate dosing recommendations were also proposed for treatment of blast crisis and prostate cancer. These recommendations were considered appropriate.

In multiple sclerosis a flexible dosing schedule was agreed in order to reflect those used in clinical trials and practices in the different member states. In addition, due to the dose dependent risk of cardiotoxicity, the maximum lifetime cumulative dose was limited to 72 mg/m^2. 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. A dosing adjustment guide, based on bone marrow suppression was kept in the harmonised text 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.

The MAH proposed that only the administration via intravenous infusion should be retained, which was accepted. Dilution recommendation and guidance for the choice of veins as well as warning regarding extravasation, were considered adequate.

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. The CMHP considered that mitoxantrone should be contraindicated in breastfeeding mothers as it is a potential human teratogen. 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. As the harmonised indication is in the treatment of metastatic breast cancer, a warning in section 4.4 informing of the small risk of leukaemia and of the paucity of efficacy data in the adjuvant treatment of breast cancer was considered sufficient. The MAH also proposed to harmonise a contraindication present in a MS against the immunisation with a live attenuated vaccine. The CHMP was of the view that the scientific basis for this recommendation was weak and that information regarding vaccination schedule should rather be included in section 4.4 and 4.5, in line with clinical practice guidelines recommendations. Contraindications against the incorrect routes of administration, due to the risk of extravasation and other contraindications in place in a few

member states were also considered more adequately addressed by wording in other sections of the PI.

Section 4.4 – Special warnings and precautions for use

In addition to those described above, warnings related to incorrect route of administration, to cardiac risks, risk of leukaemia and bone marrow/haematological monitoring recommendations, reduced immunological response to infection, secondary AML and MDS were considered acceptable with some amendments. 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. In order to effectively minimise these risk the CMHP considered that in addition to the MAH proposal to evaluate the LVEF 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 be exceeded. 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 (RMP) with a particular focus on the use in multiple sclerosis to ensure a consistent minimum standard of management of the risks across MSs. The CMHP followed this advice and considered that given their importance for the safe use of the product, the RMP and educational materials should be imposed as a condition to the MA while the study should be included in the RMP as a category 3.

Finally, warnings relative to the mutagenic potential, to the potential discoloration of urine and other tissues, to the risk of tumour lysis syndrome and contraception recommendations, risk of transient or persistent amenorrhea, present in some members states were considered relevant. 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.

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

Most of the existing statements on interactions across the MSs were supported. 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. Further it was considered that the interaction with immunosuppressive medicines should be mentioned. In some member states, additional information was included on absence of interactions or pharmacokinetic and pharmacodynamic interactions without clinical relevance, this was not considered relevant to be included in the harmonised PI.

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. The restrictions regarding the use of mitoxantrone in pregnant women was harmonised to reflect the information available. Relevant information available on risks of infertility was also harmonised. Information on the need for

contraception in men was added to that already included for women and both were adjusted considering mitoxantrone half-life and respective gamete cycles length in men and women.

Section 4.7 – Effects on ability to drive and use machines

The CMHP was of the view that, in line with the SmPC guideline, as confusion and fatigue have been reported with mitoxantrone, it should be mentioned that the treatment has minor influence on those abilities.

Section 4.8 – Undesirable effects

This section was restructured according to guidelines. The MAH recalculated the frequencies as per the SmPC guideline and included details of the most important adverse reactions. The MAH was asked to discuss the relevance of including four ADRs, which have been reported and are listed in the PI of other mitoxantrone-containing products. Based on the data provided, the MAH was asked to add dysgeusia in the table listing the ARDs reported in oncology. The MAH considered relevant to list Tumour lysis syndrome. 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.

Section 4.9 – Overdose

No significant differences between the national SmPCs were present in this section. The MAH's proposal including the fatal cases reported with overdosage was accepted with the addition of the types of toxicities observed and general recommended actions.

Section 5 – Pharmacological properties

The proposal of the MAH for this section was accepted with minor amendments in line with the rest of the SmPC and rearrangement of the information taking into account the QRD requirements. Information of lesser relevance was removed in order to focus on the main information.

Other sections of the SmPC

Other sections have only been partially harmonised as it is considered that these should be adapted nationally.

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).

Grounds for the variation to the terms of the marketing authorisations

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.
- The Committee considered that additional risk minimisation measures in the form of educational materials for the use of Novantrone and associated names in multiple sclerosis were necessary. These should be included in a risk management plan.

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 set out in Annex IV, 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).