21 March 2013
EMA/CHMP/203219/2013
Committee for Medicinal Products for Human Use (CHMP)

Caelyx

(Doxorubicin hydrochloride)

Procedure No. EMEA/H/C/000089/0008

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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ADMINISTRATIVE INFORMATION

Name of the medicinal product:	Caelyx 2 mg/ml concentrate for solution for infusion
Marketing Authorisation Holder:	Schering-Plough Europe
Active substance:	Doxorubicin hydrochloride (in a pegylated liposomal formulation)
Pharmaco-therapeutic group (ATC Code):	Cytotoxic agents (anthracyclines and related substances) L01DB
Therapeutic indications:	Caelyx is indicated: As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk. For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen. In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant. For treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD_4 counts (< 200 CD_4 lymphocytes/mm^3) and extensive mucocutaneous or visceral disease. Caelyx may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline).
Pharmaceutical form:	Concentrate for Solution for Infusion
Strengths:	2 mg/ml
Routes of administration:	Intravenous

I. INTRODUCTION

Caelyx is indicated in patients with breast cancer, ovarian cancer, multiple myeloma and AIDS-related Kaposi Sarcoma (KS). Common adverse events include palmar-plantar erythrodysesthesia (PPE), myelosuppression, stomatitis, mucositis, nausea, vomiting and asthenia.

The active ingredient of Caelyx is doxorubicin hydrochloride, a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius*. The exact mechanism of the antitumour activity of doxorubicin is not known. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic effects. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix thus preventing their unwinding for replication.

Caelyx is a long-circulating pegylated liposomal formulation of doxorubicin hydrochloride. Pegylated liposomes contain surface-grafted segments of the hydrophilic polymer methoxypolyethylene glycol (MPEG). These linear MPEG groups extend from the liposome surface creating a protective coating that reduces interactions between the lipid bilayer membrane and the plasma components. This allows the Caelyx liposomes to circulate for prolonged periods in the blood stream. Pegylated liposomes are small enough (average diameter of approximately 100 nm) to pass intact (extravasate) through defective blood vessels supplying tumours. Evidence of penetration of pegylated liposomes from blood vessels and their entry and accumulation in tumours has been seen in mice with C-26 colon carcinoma tumours and in transgenic mice with KS-like lesions. The pegylated liposomes also have a low permeability lipid matrix and internal aqueous buffer system that combine to keep doxorubicin hydrochloride encapsulated during liposome residence time in circulation

This FUM (008) relates to the obligation to submit paediatric data, in response to an EMEA letter dated 25/03/2005. The EMEA letter was sent to all Marketing Authorisation Holders (MAH) as part of an exercise to remind MAH of their legal obligations.

Area	**Description**	**Due date**
Clinical	FUM 008: Resulting from MAH obligation to submit Paediatric Data (in response to EMEA letter dated 25/03/2005): Study: "Caelyx in combination with oral Topotecan in children and young adults with High grade malignant Gliomas and Pontine Gliomas refractory to standard therapy" supported by SP (in Germany) is ongoing. The German HIT- Glioblastoma group conducts the phase I/II dose escalation study. The study will enrol 20 patients. The expected time of completion of the enrolment would be 10 months.	30/09/2010

II. SUMMARY OF MAH'S SUBMISSION

The MAH states the following:

This study, to which reference was made in our May 2005 company's response in reply to the EMEA letter dated 25 March 2005 requesting information on paediatric data, was an Investigator Initiated Study (IIS) conducted in Germany.

There was no formal Clinical Study Report (CSR) prepared / finalized for this particular IIS study, but instead of such a CSR the company received from the investigators the following official publication regarding the study: "Pegylated-liposomal doxorubicin and oral topotecan in eight children with relapsed high-grade malignant brain tumors" (*J Neurooncol (2008) 86: 175-181*).

The CHMP herewith confirm that the above data does not require an update of the Product Information.

Brief summary of the submitted study

The MAH has submitted a copy of a published study by Wagner et al., 2008. The publication relates to a retrospective review of children with relapsed malignant brain tumours who were given individualised treatment with pegylated (PEG)-liposomal doxorubicin and topotecan. Eight patients were included in the study. The authors concluded that the schedule of PEG-liposomal doxorubicin (30 - 40 mg/m^2 every 4 weeks) in combination with oral topotecan results in tumour response, but the toxicity was high. An individualised increasing dose of PEG-liposomal doxorubicin 10 - 20 mg/m^2 every 2 weeks is now recommended.

CHMPs' Assessment

The MAH has submitted a copy of a published retrospective review of treatment of eight children with relapsed malignant brain tumours. No indication for children with relapsed malignant brain tumour is sought and the study provided by the Applicant is not considered sufficient to support one.

In terms of fulfilment of the FUM, the CHMP considers that FUM 008 has been adequately fulfilled and considers that the submitted data do not require an update to the Product Literature

III. CHMP'S OVERALL CONCLUSION AND FURTHER ACTION IF REQUIRED

FUM 008

Overall Conclusion:

In conclusion, the information provided by the MAH, after assessment, is considered adequate:

☒ PAC fulfilled (all commitments fulfilled) - No further action required

☐ PAC not fulfilled (not all commitments fulfilled) and further action required