

**Annex II**  
**Scientific conclusions**

## Scientific conclusions

Etoposide phosphate injection is supplied as a nonpyrogenic lyophilized powder intended for reconstitution and/or dilution with a suitable parenteral vehicle prior to intravenous (IV) administration and is available as 114 mg etoposide phosphate (100 mg etoposide equivalent) single dose sterile vial and 1140 mg etoposide phosphate (1000 mg etoposide equivalent) pharmacy bulk vial (Germany only).

Etopophos contains etoposide phosphate, a pro-drug of etoposide which is rapidly converted to etoposide in vivo. Etoposide is a semi-synthetic derivative of podophyllotoxin which ruptures double strand DNA by means of an interaction with DNA-topoisomerase II, or by the formation of free radicals. Etoposide is used for the treatment of various neoplastic diseases. The first European approval was in Sweden on 12 April 1996. Etopophos is currently approved in DE, FR, SE and UK.

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

Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product, the European Commission therefore notified the CHMP/European Medicines Agency on 14 October 2015 of a referral under Article 30 of Directive 2001/83/EC for Etopophos and associated names, in order to resolve divergences amongst the nationally authorised product information and thus harmonise the product information across the EU.

## Overall summary of the scientific evaluation by the CHMP

The revised indications in section 4.1 of the Summary of Product characteristics (SmPC) are:

- Testicular cancer: first line, recurrent or refractory testicular cancer
- Small-cell lung cancer
- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma
- Acute myeloid leukaemia
- Gestational trophoblastic neoplasia
- Ovarian cancer: non-epithelial ovarian cancer and platinum-resistant/refractory epithelial ovarian cancer

Paediatric indications were agreed in the following indications:

- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma
- Acute myeloid leukaemia

As regards the posology, section 4.2 of the SmPC, the doses were harmonised for all indications and patient populations – adult and paediatric.

The recommended dose in adult patients is 50 to 100 mg/m<sup>2</sup>/day on days 1 to 5 in line with the current clinical practice guidelines, however when administered on three days (e.g. days 1, 3, and 5) the daily dose that is most commonly used can be either 100 to 120 mg/m<sup>2</sup> every 3 to 4 weeks in combination with other drugs indicated in the disease to be treated.

In paediatric patients diagnosed with Hodgkin's lymphoma, non-Hodgkin's lymphoma or acute myeloid leukaemia, the CHMP recommended the range of 75 to 150 mg/ m<sup>2</sup>/day for 2 to 5 days in combination with other antineoplastic agents as supported in studies conducted by major international groups such as The German Society of Paediatric Oncology and Haematology Hodgkin's Disease, The Children's Cancer Group and The European Organization of Research and Treatment of Cancer Children Leukaemia Group among others. However, the treatment regimen and posology in these paediatric indications should be chosen according to the local standard of care.

In patients with renal impairment, the CHMP agreed not to recommend a dose reduction when creatinine clearance is > 50 mL/min as supported by available literature<sup>[1][2][3][4][5]</sup>. In renal impairment (creatinine clearance (CrCl) 15-50 mL/min) a dose reduction of 25% is recommended. The MAH also discussed a dose reduction for patients with end stage renal disease (CrCl < 15mL/min). The data in literature for patients with CrCl less than 15 mL/min and on dialysis strongly suggest that further dose reduction is required in these patients as reviewed by Inoue et al. (2004)<sup>[6]</sup>. This has been addressed by a warning in section 4.2 of the SmPC.

Hypersensitivity has been added as contraindication in section 4.3 of the SmPC in line with the guideline on SmPC. As immunosuppression is a very common side effect of etoposide, concomitant use of live vaccines has been added as a contraindication, which is in line as well with the guideline on SmPC. Finally, lactation has also been included as a contraindication with a reference to section 4.6 of the SmPC where lactation is further described.

The following special warnings and precautions for use have been harmonised in section 4.4 where they were already included in some or most of the national SmPCs: myelosuppression, secondary leukaemia, hypersensitivity, injection site reaction, low serum albumin, impaired renal and hepatic function, tumour lysis syndrome and mutagenic potential.

In section 4.5 of the SmPC the interactions that were documented in the majority of current national SmPCs have been retained in the harmonised text.

With regards to fertility, pregnancy and lactation section 4.6 of the SmPC, information addressed to women of childbearing potential with regards to contraception in males and females was included. The pregnancy section has been revised in line with the relevant guideline<sup>[7]</sup>. In relation to lactation, information on the fact that etoposide is excreted in the milk (Medications and Mothers' Milk: Thomas W. Hale) has been added. As breastfeeding women could replace breastfeeding by dairy products to feed their child the text has been amended accordingly. The CHMP also noted that etoposide may decrease male fertility. A text to consider preservation of the sperm has been included in this section.

Minor changes were included in the remaining sections of the SmPC. Changes introduced in the SmPC were consistently reflected in the labelling where relevant, however most sections were left to be completed nationally. The changes to the SmPC, when relevant for the user, have also been reflected in the PL and endorsed by the CHMP.

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<sup>1</sup> Kreusser W, Herrmann R, Tschöpe W, et al. Nephrological complications of cancer therapy. *Contr Nephrol.* 1982;33:223-238.

<sup>2</sup> Arbusk SG, Douglass HO, Crom WR et al. Etoposide Pharmacokinetics in Patients With Normal and Abnormal Organ Function. *Journal of Clinical Oncology* 1986; 4(11): 1690-1695.

<sup>3</sup> Toffoli G, Corona G, Basso B et al. Pharmacokinetic Optimisation of Treatment with Oral Etoposide. *Clin Pharmacokinet* 2004; 43 (7): 441-446.

<sup>4</sup> Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. *Cancer Treatment Reviews* 1995;21:33-64.

<sup>5</sup> Fissell WH, IV, Earl M. Pharmacokinetics of Anti-cancer Chemotherapy in Renal Insufficiency and Dialysis. *Renal Disease in Cancer Patients* 2014, Chapter 15, pp.251-269.

<sup>6</sup> Inoue, A. et al, Pharmacokinetic analysis of combination chemotherapy with carboplatin and etoposide in small-cell lung cancer patients undergoing hemodialysis. *Ann. Oncol.* 15, 51–54 (2004)].

<sup>7</sup> Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling – Appendix 3 (EMA/CHMP/203927/2005).

## **Grounds for the CHMP opinion**

Whereas

- The scope of the referral was the harmonisation of the product information,
- The product information proposed by the Marketing Authorisation Holder has been assessed based on the documentation submitted and the scientific discussion within the Committee,
- The Committee considered the referral under Article 30 of Directive 2001/83/EC
- The Committee considered the divergences identified in the notification for Etopophos and associated names, as well as the remaining sections of the product information.
- The Committee reviewed the totality of the data submitted by the MAH in support of the proposed harmonisation of the product information.
- The committee agreed on a harmonised product information for Etopophos and associated names.

The CHMP recommended the variation to the terms of the marketing authorisations for which the product information is set out in Annex III for Etopophos and associated names (see Annex I).

The CHMP as a consequence, concluded that the benefit-risk balance of Etopophos and associated names remains favourable, subject to the agreed changes to the product information.