Annex II

Scientific conclusions

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Vepesid contains etoposide, 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. Vepesid is available as 50mg and 100 mg capsules for oral use. Etoposide is used for the treatment of various neoplastic diseases. The first European approval was in NL on 29 May 1981. The product was subsequently approved in AT, BE, DE, DK, EE, ES, FI, HR, IE, IT, LU, NO, RO, SE, SI and UK.

Vepesid 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 Vepesid 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:

- Recurrent or refractory testicular cancer
- Small-cell lung cancer
- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma
- Acute myeloid leukaemia
- Ovarian cancer: non-epithelial ovarian cancer and platinum-resistant/refractory epithelial ovarian cancer

As regards the posology, all 17 SmPCs state in section 4.2 that the oral dose of etoposide capsules is based on the recommended intravenous (IV) dose and mention the need to consider bioavailability when prescribing, since it varies from patient to patient. The adult dosing section contains details on monotherapy, combination therapy, an alternative dosing schedule, and dosing adjustments for a low neutrophil count. The safety and efficacy of Vepesid and associated names in children below 18 years of age have not been established.

Based on data on bioavailability[1][2], the recommended oral dose is 100 to 200 mg/m2/day on day 1-5 in a cycle of 21 or 28 days; or 200 mg/m2/day on three days (most often days 1-3 or day 1, 3, and 5) in a cycle of 21 or 28 days.

The available efficacy data for etoposide in the different indications are based for the most part on studies in which etoposide was used intravenously. It has been found that with oral administration, within-patient variability in exposure (i.e. between cycles) is notably larger than after intravenous administration. The coefficient of variation is around 30% for oral administration, versus 10% for intravenous administration (between-patient variability is similar after intravenous or oral administration, i.e. 30-40%).

Increased within-patient variability in exposure may lead to greater variability in the dose-response relationship, i.e., leading to greater variability in patients' sensitivity to experience treatment-

[1] Hande KR, Krozely MG, Greco FA et al. Bioavailability of Low-Dose Oral Etoposide. J Clin Oncol 1993;11:374-377
[2] Johnson DH, Hainsworth JD, Hande KR, et al. Cancer 1999;67:231-244.

related toxicity from cycle to cycle, and potentially affecting overall efficacy of treatment in some patients. For this reason, it is critical that the advantages of the oral administration route are carefully weighed against the disadvantages of larger within-patient variability in exposure after oral administration, which should be evaluated on an individual basis. This is particularly relevant when patients are treated in the curative setting (e.g. for testicular cancer). For this reason, the CHMP agreed to include additional information in section 4.2 and 4.4 to inform physicians about the potential disadvantages of oral versus intravenous administration of etoposide.

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[3][4][5][6][7]. In renal impairment (creatinine clearance (CrCl) 15-5 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)[8]. This has been addressed by a warning in section 4.2 of the SmPC.

In section 4.3 of the SmPC Contraindications, the inclusions of hypersensitivity and concomitant use of live vaccines have been agreed as these are in line with the SmPC guidelines. In particular, for the concomitant use of live vaccines, immunosuppression is a common side effect of etoposide listed as very common in the SmPC. Lactation has been included as a contraindication, since breastfeeding women could replace breastfeeding by dairy products to feed their child.

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: within-patient variability, 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[9]. With regards to lactation, etoposide is excreted in the milk (Medications and Mothers' Milk: Thomas W. Hale) and it has been included as a contraindication. The text on breastfeeding 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.

[3] Kreusser W, Herrmann R, Tschope W, et al. Nephrological complications of cancer therapy. Contr Nephrol. 1982;33:223-238.
[4] Arbuck 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.
[5] Toffoli G, Corona G, Basso B et al. Pharmacokinetic Optimisation of Treatment with Oral Etoposide. Clin Pharmacokinet 2004; 43 (7): 441-446.
[6] Kintzel PE, Dorr RT. Anticancer drug reanl toxicity and elimination: dosing guidelines for altered renal function. Cancer Treatment Reviews 1995;21:33-64.
[7] 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.
[8] 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)].
[9] Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling – Appendix 3 (EMEA/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 Holders 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 Vepesid 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 Vepesid 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 Vepesid and associated names (see Annex I).

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