21 April 2017
EMA/409248/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 30 of Directive 2001/83/EC

Vepesid and associated names

INN of the active substance: etoposide

Procedure number: EMEA/H/A-30/1425

Note:

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

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1. Background information

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 13 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.

2. Scientific discussion

2.1. Introduction

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 the Netherlands on 29/05/1981. The product was subsequently approved in AT, BE, DE, DK, EE, ES, FI, HR, IE, IT, LU, NO, RO, SE, SI and UK.

2.2. Critical Evaluation

The MAH has provided data from the literature and evidence from guidelines including the Network, National Comprehensive Cancer Clinical Practice Guidelines (NNCCP) and European Society for Medical Oncology guidelines (ESMO). The CHMP have reviewed all available data provided in the context of this Article 30 referral.

The main points discussed for the harmonisation of the different sections of the product information are summarised in the below report.

2.2.1. Product information

Summary of Product Characteristics

Sections 1 to 3

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Section 2 has been updated to include the qualitative and quantitative description of the 50 mg and 100 mg capsules.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.1 – Therapeutic Indications

Recurrent or refractory testicular cancer

Etoposide is approved for testicular carcinoma in 13 out of the 17 EU/EEA countries where is currently marketed, as monotherapy, combination therapy, or both. Etoposide is not currently approved for testicular cancer in AT, EE, HR or IT.

The below table summarises the data provided in support of this indication.

Table 1: Literature evidence to support indication in testicular cancer

Reference	Disease setting	Design	Study treatments (patient numbers)	Outcomes
Cavalli et al. (1981)	Advanced non-seminomatous testicular cancer, previous extensive chemotherapy and radiotherapy	Prospective single arm	Oral etoposide 175 mg/m2/day on days 1-3, repeated weekly (n=33)	Of 30 evaluable: 6 (20%) PR for median of 3.5 months 7 (23%) SD for median of 2.5 months
Miller et al. (1990)	Refractory germ cell tumours; previous treatment with cisplatin/etoposide combinations	Prospective single arm	Oral etoposide 50 mg/m2/day until progression/toxicity (n=22)	Of 21 evaluable: 3 (14%) PR 3 (14%) SD
Varini & Cavalli (1982)	Resistant testicular cancer, extensive treatment with chemotherapy and radiotherapy	Prospective single arm	Oral etoposide 175 mg/m2/day on day 1-3, repeat weekly for 6 weeks	Of 30 evaluable: 6 (20%) PR
Bremer (1982)	Refractory testicular cancer	Prospective two-arm study (unclear if randomised)	Oral etoposide 120 mg/m2 on days 1-5 every 4 weeks (n=37) IV etoposide 120 mg/m2 days 1,3 and 5 + IV ifosfamide 40 mg/kg days 1 and 5, every 3-4 weeks	Etoposide monotherapy: Response in 9 out of 37 (24.3%) Etoposide + ifosfamide: Response in 21 out of 36 (58.3%)
ESMO Guideline: Testicular Seminoma and Non-seminoma tumours; NCCN clinical practice guideline: testicular cancer	Metastatic testicular cancer	Review	Cisplatin + bleomycin + etoposide (BEP) is gold standard	For patients with good prognostic features, cure rates >90%.
Oldenburg et al. 2013 and NCCN clinical practice guideline: testicular cancer	Refractory or recurrent metastatic testicular cancer patients	Review	Etoposide monotherapy	Palliative

PR=partial response; SD=stable disease; PD=progressive disease

(Oldenburg et al. 2013)The MAH refers to four studies from the literature to support an indication in testicular cancer. These are small single-arm studies that provide evidence of response to monotherapy and combination therapy in the refractory and recurrent setting. Additional randomised studies have been conducted, which support the use of etoposide in testicular carcinoma in combination with other chemotherapy, as summarised in a systematic review by Feldman et al. (2008). The MAH also refers to the ESMO Guideline on testicular seminoma and non-seminoma tumours, as well as the relevant NCCN guideline. According to the ESMO guideline, 3 to 4 cycles with bleomycin, etoposide and cisplatin (BEP) is standard first line treatment for metastatic testicular cancer. In non-seminomas, BEP is used at stage I disease. Etoposide is also used in various combinations in the salvage setting. Effective approaches in the post first-line setting consist of either standard doses of 3-drug combinations based on ifosfamide and cisplatin or, alternatively, high-dose chemotherapy with two agents (e.g. with etoposide and carboplatin) with autologous stem-cell support.

The current European Society of Medical Oncology (ESMO) guideline recommends combination therapy therefore the indication is now restricted to combination therapy for the treatment of testicular cancer in adults. There is increased intra- and inter-patient variability for the oral formulation compared to the

intravenous (IV) formulation, which could result in an inadequate exposure. Since first-line therapy in testicular cancer is potentially curative, the indication has been limited to recurrent/refractory disease.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Small cell lung cancer

Etoposide is approved for small cell lung cancer (SCLC) in all 17 EU/EEA countries where is currently marketed, either as monotherapy, combination therapy, or both.

The literature evidence to support the proposed indication wording is summarised in the following table. Note that 'limited disease' is equivalent to T1-4, N0-3, M0 tumours, and extensive disease is equivalent to metastatic disease (ESMO Clinical Practice Guidelines).

Table 2: Literature evidence to support indication in SCLC

Reference	Disease setting	Design	Study treatments (patient numbers)	Outcomes
Smit et al. (1989)	Untreated SCLC ≥ 70 years age; extensive and limited disease	Prospective single arm	Oral etoposide 800 mg/m2 over 5 consecutive days, every 4 weeks (n=35)	Overall response rate 71%
Einhorn Bristol Laboratories. Document Control Number 910039633.	Previously treated, refractory SCLC	Prospective single arm	Oral etoposide 50 mg/m2/day (n=26)	1 (3.8%) CR 5 (19.2%) PR Duration 6 to 20 weeks
Hermes et al. (2008)	Extensive disease SCLC (Japan)	Randomised controlled trial	(1) carboplatin + irinotecan 175 mg/m2 IV (IC) day 1 (n=105) (2) carboplatin + etoposide 120 mg/m2/day PO (EC) days 1-5 (n=104); every 3 weeks for 4 cycles	Overall survival: HR 1.41 (95% CI 1.06 to 1.87; p<0.02) in favour of IC; median survival 8.5 months for IC vs. 7.1 months for EC
Johnson et al. (1991)	Recurrent SCLC after previous chemotherapy	Prospective single arm	Etoposide 50 mg/m2/day PO for 21 consecutive days (n=22)	10 (45%) CR, median duration 4 months
Matsui et al. (1987)	Limited and extensive disease SCLC	Prospective single arm	Etoposide 120 mg/m2 + cisplatin 60 mg/m2 + radiotherapy (n=56)	43 patients evaluable: Of 19 with limited disease, 63% CR, 32% PR; Of 24 with extensive disease, 34% CR, 54% PR
Hong et al. (1989)	Previously untreated SCLC (n=353)	Design to be confirmed	Cyclophosphamide 1,000 mg/m2 IV, vincristine 1.4 mg/m2 IV, and etoposide 50-100mg/m2 IV and oral (CEV regimen) or doxorubicin 50 mg/m2 IV (CAV regimen).	CEV superior to CAV (to be confirmed)

CR=complete partial; PR=partial response; SD=stable disease; PD=progressive disease; DOR=duration of response

The MAH states that for the management of SCLC, etoposide and cisplatin are the most commonly used initial combination chemotherapeutic agents. Based on Phase 2 study data, active 2nd and 3rd

line (subsequent) chemotherapy includes oral etoposide (NCCN Guideline). All patients with T1-4 N0-3 M0 tumours with good performance status should be treated with concurrent chemotherapy and thoracic radiotherapy (Fruhl et al. 2013). The chemotherapy schedule consists of four cycles of cisplatin–etoposide or 4–6 cycles if a once-daily radiotherapy schedule is used. In metastatic disease, first-line treatment of stage IV SCLC is palliative, and combination chemotherapy has been the main treatment option for more than three decades. No chemotherapy doublet has yet been shown to be superior to IV etoposide–platinum in a Western population (Fruhl et al. 2013).

The data to support the indication in SCLC is based mainly on single arm studies. In one randomised clinical trial (n=220) (Hermes et al. 2008) the combination of etoposide and carboplatin is inferior to irinotecan and carboplatin based on overall survival. However this study was conducted in Japan. The MAH makes reference to a large study (n=353) by Hong et al. (1989) which appears to show that CEV is superior to CAV in previously untreated SCLC. The European Lung Cancer Working Party systematically reviewed published randomised clinical studies and the role of etoposide and cisplatin in the treatment of SCLC, summarising at least 17 studies evaluating the role of etoposide. This analysis showed that etoposide-containing regimens resulted in superior overall survival compared to non-etoposide containing regimens (HR = 0.65, 95%CI: 0.61-0.69), and that regimens with etoposide (without cisplatin) resulted in superior overall survival in comparison with a regimen without either etoposide or cisplatin (HR = 0.72; 95% CI, 0.67–0.78; P<0.001).

The MAH also refers to the ESMO Clinical Practice Guidelines for SCLC (Frhul et al. 2013). The guideline recommends that T1, 2 N0, 1 M0 stage should be treated with 4 cycles of adjuvant chemotherapy. All other T1-4, N0-3 M0 with good performance status should receive chemotherapy (and concurrent radiotherapy), such as 4 cycles of cisplatin-etoposide (or 4-6 cycles if once daily radiotherapy used). Treatment of stage IV SCLC is palliative. Based on meta-analyses, etoposide-cisplatin has been adopted as a standard treatment regimen. A recent meta-analysis showed improved overall survival with irinotecan-platinum compared with etoposide-platinum, but the results were primarily driven by Asian studies. No chemotherapy doublet has yet been shown to be superior to IV etoposide–platinum in a Western population. Relapsed patients with sensitive disease derive benefit from re-challenge with platinum-etoposide.

The CHMP considered the indication for SCLC, when used in combination with other chemotherapy, based in the available data in literature supporting the efficacy of etoposide, and further taking into account European guidelines on the management of SCLC in clinical practice.

The role of etoposide monotherapy in the current treatment of SCLC is questioned. Although it is not currently specified in most Vepesid SmPCs that etoposide is indicated as combination therapy, more recent procedures of etoposide generics do specify that etoposide is indicated only as combination therapy (Etoposide Fresenius Kabi, NL/H/2469/001 and Etoposide Accord, SE/H/1330/001).

As the current ESMO guideline recommends combination therapy, the CHMP has restricted the indication to combination therapy for the treatment of SCLC in adult patients.

The final agreed wording of the product information can be found in Annex III of the CHMP opinion.

Non-small cell lung cancer

An indication in non-small lung cancer (NSCLC) was proposed for the harmonised SmPC following a request to discuss current nationally authorized indications that were not initially proposed for the harmonised text. The MAH referred to one clinical study by Albain et al. (2002), which is also mentioned in the NCCN guideline on NSCLC, a comparative study showing that cisplatin (CDDP) administered together with etoposide and carboplatin (CBDCA) administered together with etoposide

are comparable with regard to efficacy. This study does not directly support the efficacy of etoposide in NSCLC. Additional data are available in the public domain in which the efficacy of etoposide in NSCLC was studied:

Additional data are available in the public domain in which the efficacy of etoposide in NSCLC was studied. A comparative study by Bonomi et al. (2000) shows that etoposide administered together with platinum is inferior to paclitaxel administered together with platinum. This study shows that etoposide as part of combination therapy is inferior to other available therapies and therefore does not support the efficacy of etoposide in NSCLC. A randomised phase III study by Cardenal et al. (1999) shows that etoposide-cisplatin is inferior to gemcitabine-cisplatin in the first-line treatment of NSCLC. A single-arm study by Waits et al. (1992) shows that as monotherapy, etoposide has only moderate activity in NSCLC. This study does not allow conclusions regarding the efficacy of etoposide in NSCLC.

Overall, these studies do not support the indication NSCLC for etoposide and therefore a harmonised indication was not agreed by the CHMP.

Hodgkin's lymphoma

This indication is currently approved in 14 out of the 17 EU/EEA countries where it is marketed. Etoposide is not approved for the treatment of Hodgkin's lymphoma (HL) in EE, NL and UK.

The literature evidence to support the proposed indication wording is summarised in the following table.

Table 3: Literature evidence to support indication in Hodgkin's Lymphoma

Reference	Disease setting	Design	Study treatments (patient numbers)	Outcomes
Hainsworth et al. (1990)	Refractory lymphoma, at least one combination chemotherapy regimen	Prospective single arm	Etoposide 50 mg/m2/day PO for 21 consecutive days, repeated every 28-35 days (n=23)	13 (62%) PR; median response duration 5 months;
Taylor et al. (1982)	Relapsed advanced lymphomas resistant to standard chemotherapy (HL: n=13)	Prospective single arm	Etoposide 120 mg/m2/day IV for 5 days or orally for 7-10 days, repeated 3-weekly	Of 12 evaluable: 3 (23%) CR; 5 (38%) PR; median DOR 20 weeks
Perren et al. (1986)	First-line and relapsed HL	Prospective single arm	Vincristine+prednisolone+etoposide+chlorambucil (OPEC) alternating with ChIVPP (n=30); OPEC alone (n=9)	OPEC/ ChIVPP: CR 20/28 (71%); OPEC only: CR 5/9 (56%)
Santoro et al. (1986)	3rd line treatment of HL refractory to MOPP and ABVD (n=58)	Prospective single arms	CCNU or etoposide, lomustine, and prednimustine (CEP). CEP alternating with ABVD in patients resistant to MOPP (patient numbers to be confirmed)	CR 40% median DOR 15 months, median survival 24 months), PR 14% In CEP / ABVD, CR 76%, median DOR 24 months, median survival 36 months

CR=complete partial; PR=partial response; SD=stable disease; PD=progressive disease; DOR=duration of response

The MAH states that for intermediate stage HL, patients < 60 years who are eligible for intensive treatment, combinations including etoposide (e.g. BEACOPP) are established. In advanced stage HD aged < 60 years, BEACOPP is an option (NCCN Clinical Practice Guidelines, Eichenauer et al. 2014).

The MAH submitted evidence from small prospective single arm studies, which overall demonstrate that etoposide has activity in Hodgkin's lymphoma (HL). The MAH also makes reference to the ESMO

Clinical Practice Guidelines for Hodgkin's lymphoma. According to the ESMO guideline, two cycles of bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone in escalated dose (BEACOPP escalated) and two cycles of doxorucibin, bleomycin, vinblastine and dacarbazine (ABVD) is an option in intermediate-stage patients younger than 60 years old who are eligible for intensive treatment. In advanced stage patients, six cycles of BEACOPP escalated is a recognised option. BEASCOPP escalated includes etoposide 200 mg/m2 IV days 1-3. According to the guideline, several trials have shown superior tumour control with BEACOPP escalated vs. ABVD in a randomised comparison.

The ESMO guideline also refers to a systematic review and network meta-analysis of the effect of initial treatment strategy on survival of patients with advanced-stage HL. This network analysis found that the survival advantage of six cycles of BEACOPP escalated is 7-10% at 5 years compared to ABVD.

For relapsed disease, the ESMO guideline includes salvage regimens such as ifosfamide, carboplatin, etoposide (ICE) and BEACOPP escalated (Eichenauer et al. 2014).

Since first-line therapy in Hodgkin's lymphoma is potentially curative, it will be important to ensure adequate exposure. High intra-individual variability and dose dependence of the oral bioavailability is reported. Therefore in individual patients, it may not be possible to predict the optimum dose. The MAH was asked to discuss whether a first-line indication in Hodgkin's lymphoma can be supported, based on the available pharmacokinetic and efficacy data for oral etoposide.

There is increased intra- and inter-patient variability for the oral formulation compared to the IV formulation, which could result in an inadequate exposure. Since first-line therapy in HL is potentially curative, the indication is limited to second-line treatment.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Non-Hodgkin's lymphoma

Currently Vepesid is approved for Non-Hodgkin's lymphoma (NHL) as monotherapy in Austria and approved as combination therapy in Austria, Germany, Slovenia and Spain. In Belgium, Luxembourg, Denmark, Norway, Romania, and Sweden the current SmPC does not specify if etoposide is approved as monotherapy or combination for NHL.

As per current ESMO guidelines etoposide is a part of combination therapy for the following four indications: Diffuse large B-cell lymphoma (DLBCL), Follicular lymphoma, Mantle cell lymphoma (MCL), and Peripheral T-cell lymphoma.

Kroschisnky et al. (2008) investigated the pharmacokinetic equivalency of oral and intravenous etoposide in ten patients with aggressive lymphomas to address the logistic issue of intravenous administration of etoposide on three consecutive days. Standard CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) was given plus etoposide 100 mg/m2 intravenously on day 1, and 200 mg/m2 orally on days 3 and 4. The mean bioavailability of oral etoposide was 58 ± 15% with an inter-patient variability of 26%. Significant differences in bioavailability of oral etoposide between the used dose levels (350, 400 and 450 mg) were not observed. Mean area under the plasma concentration-time curve (AUC) after a 100 mg/m2 intravenous and a 200 mg/m2 oral dose of etoposide were 74.0 ± 18.3 and 84.9 ± 29.6 µh/ ml (P = 0.481). Inter-patient variability of AUC was 25% for the IV route and 35% after oral intake. The authors concluded that the equivalency of AUC after 200 mg/m2 of oral and 100 mg/m2 of intravenous etoposide support the use of the oral preparation in patients treated with the CHOEP regimen (Matsui et al 1987).

For the treatment of patients older than 60 years of age with DLBCL that are not able to receive the recommended rituximab (R)-CHOP due to cardiac dysfunction; doxorubicin could be substituted with gemcitabine, etoposide or liposomal doxorubicin. Therefore, etoposide is a treatment option as per ESMO and NCCN guidelines. Moccia et al. (2009) reported the efficacy of R-CEOP (rituximab, cyclophosphamide, etoposide, vincristine and prednisone) in R-CHOP-ineligible first-line DLBCL patients and compared their outcomes to a historical cohort receiving RCHOP. Etoposide is administered at a dose of 50 mg/m2 IV on day 1 and 100 mg/m2 PO on days 2 and 3 of each cycle. They performed a retrospective analysis in their institution from December 2000 to March 2009, 81 patients were identified treated with R-CEOP. The control group included 162 randomly chosen patients matched for age, stage and IPI score and treated with R-CHOP. Although patients treated with R-CEOP had a lower 5-year overall survival (OS) rate than the RCHOP group (49% vs. 64%, respectively) reflecting the underlying co-morbidities and frailty of this population, the 5-year time to progression rate was similar in both groups (57% for R-CEOP vs. 62% for R-CHOP; p=0.21) (NCCN Guideline).

Coleman et al. (2012) conducted a study to determine if the oral PEP-C regimen (prednisone, etoposide 50 mg, procarbazine, cyclophosphamide) given in either a daily, alternate day, or fractionated basis, is effective in a variety of lymphomas. One hundred twenty two patients were studied although the majority had low grade or mantle cell lymphoma. All had received at least two or more prior therapies. Overall, 75% achieved an objective response (OR) with 38% complete responses (CRs) or CRs unconfirmed, and 37% PR. ORs were achieved in mantle cell (85%), follicular (88%), marginal zone (71%), and small lymphocytic (67%) lymphomas (ESMO Guideline).

Ruan et al. (2010) reported the results of a small single arm study of the RT-PEPC regimen. This included rituximab, thalidomide and daily PEPC (including etoposide 50 mg). Of 22 evaluable patients, who had all received at least one previous therapy, the overall response rate (ORR) was 73% (95% CI, 50%-89%), and the median progression-free survival (PFS) was 10 months (95% CI, 5-23 months) (ESMO Guideline).

The CHMP considered that there is adequate evidence to support the use of etoposide in NHL. The concern for Vepesid is whether an indication in first-line NHL, when therapy is potentially curative, is appropriate given the more variable exposure for oral vs. IV formulations of etoposide. In view of the wide range of oral bioavailability in a small sample of patients, and the lack of robust clinical efficacy data in the first-line setting, it is concluded that there is insufficient evidence to support the first-line indication for oral etoposide, when therapy is potentially curative. The CHMP therefore agreed to restrict the indication to relapsed/refractory setting.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Acute myeloid leukaemia

According to the applicant, etoposide is approved for the treatment of acute myeloid leukaemia (AML) in 14 out of the 17 countries where it is currently marketed. Etoposide is not currently marketed for AML in DE, EE or UK.

Chemotherapy is used in the treatment of AML as induction, consolidation, or (rarely) maintenance therapy. Standard first-line of AML is with cytarabine and an anthracycline for induction treatment. For consolidation, there is no single best regimen, but it often incorporates high-dose cytarabine. Etoposide is not part of the most widely used standard first-line induction or consolidation regimens. However, there are a number of studies which support the efficacy of etoposide as part of combination chemotherapy in subsets of patients with AML. The Dutch Haemato-Oncology Foundation for Adults (HOVON) uses a combination of etoposide with mitoxantrone as part of their standard of care for consolidation of patients in CR1 who are under 65 years of age, who have good risk AML or minimal

residual disease (MRD)-negative intermediate risk AML, and for whom autologous stem-cell translplantation (SCT) is not possible (HOVON treatment guideline AML, 2014). This practice is based on a study by Vellenga et al. (2011) which showed that overall survival was similar for this subset of patients when randomised to either autologous SCT or intensive chemotherapy with etoposide and mitoxantrone (44% vs 41% at 5 years, p=0.86). An additional study shows that response-based treatment with cycles of mitoxantrone plus etoposide after standard induction treatment with idarubicin and cytarabine, leads to additional complete responses in the subset of patients who did not achieve complete response upon standard induction treatment (Van Der Jagt et al. 2006).

The NCCN AML guideline mentions that etoposide can be used as part of the MEC regimen (mitoxantrone, etoposide, cytarabine) in relapsed/refractory AML, which is based on the study by Amadori et al. (1991) as discussed by the MAH and as mentioned in a recent review article on the treatment of AML (Döhner et al. 2015).

In paediatric patients, etoposide is often used as the third drug in addition to cytarabine and an anthracycline in the first-line treatment of AML. This is supported by a limited amount of data in literature (Tsukimoto et al. (2009); Rubnitz et al. (2010); Treatment guideline of the “Foundation for Pediatric Oncology the Netherlands“ [SKION], 2012).

Overall, there are limited comparative data available which directly demonstrate the efficacy of etoposide in AML. It is recognised, however, that in current clinical practice etoposide is used as part of induction and consolidation treatment in subsets of patients with AML, as part of combination chemotherapy. Of note, in another recent Article 30 procedure of Novantrone (mitoxantrone), efficacy of the combination of mitoxantrone and etoposide was also recognised to support the indication of AML for mitoxantrone.

The CHMP considered that there is adequate evidence to support the use of etoposide in AML. The concern for Vepesid is whether an indication in first-line AML, when therapy is potentially curative, is appropriate given the more variable exposure for oral vs. IV formulations of etoposide. In view of the wide range of oral bioavailability in a small sample of patients, and the lack of robust clinical efficacy data in the first-line setting, it is concluded that there is insufficient evidence to support the first-line indication for oral etoposide, when therapy is potentially curative. The CHMP therefore agreed to restrict the indication in AML to the relapsed/refractory setting.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Ovarian cancer

An indication in ovarian cancer is proposed for the harmonised SmPC following in response to a request to discuss current nationally authorized indications that were not initially proposed for the harmonized text.

Between 1984 and 1989, 20 patients with incompletely resected ovarian dysgerminoma were treated on two protocols of the Gynecologic Oncology Group (GOG). All patients received cisplatin, bleomycin, and either vinblastine or etoposide. More recent patients also received consolidation chemotherapy with vincristine, dactinomycin, and cyclophosphamide (VAC). Eleven patients had clinically measurable disease, and 10 responded completely. Fourteen second look procedures were done, and all were negative. It was concluded that cisplatin-based chemotherapy was highly effective in patients with advanced dysgerminoma. Researchers believed at that time that the standard approach should be three courses of bleomycin, etoposide, and cisplatin (BEP) (Williams et al. 1991).

Bajorin et al. (1993) performed a randomised phase III clinical trial to evaluate the efficacy of etoposide plus carboplatin (EC) versus etoposide plus cisplatin (EP) in good risk germ cell tumor (GCT)

patients. Between October 1986 and December 1990, 270 patients were randomised to receive four cycles of either EP or EC. The etoposide dose in all patients was 100 mg/m2 on days 1 through 5. EP patients received cisplatin at 20 mg/m2 on days 1 through 5 and therapy was recycled at 21- day intervals. For EC patients, the carboplatin dose was 500 mg/m2 on day I of each cycle and the EC recycling interval was 28 days. Two hundred sixty-five patients were assessable: 131 patients treated with EC and 134 treated with EP. One hundred fifteen of 131 assessable patients (88%) treated with EC achieved a CR versus 121 of 134 patients (90%) treated with EP (P = .32). Sixteen patients (12%) treated with EC relapsed from CR versus four patients (3%) treated with EP. Therefore, 32 patients (24%) who received carboplatin experienced an event (incomplete response [IR] or relapse) compared with 17 of 134 patients (13%) who received cisplatin (P =0 .02). At a median follow-up of 22.4 months, event-free and relapse-free survival were inferior for patients treated with EC (P =0 .02 and P =0.005, respectively). No difference in overall survival was evident (P = 0.52). It was concluded that two-drug therapy with EC using this dose and schedule was inferior to therapy with EP. Cisplatin remains as the standard platinum analog in the treatment of patients with good-risk GCTs.

Homesley et al. (1999) performed a phase II study to assess efficacy and toxicity of the combination of BEP as first-line therapy for ovarian stromal malignancies. Patients with incompletely resected Stages II–IV or recurrent cancer underwent surgical debulking. The final dose schedule was 20 units/m2 bleomycin IV push day 1 every 3 weeks 3 x 4, 75 mg/m2 etoposide days 1–5 every 3 weeks 3 x 4 and 20 mg/m2 cisplatin days 1–5 every 3 weeks 3 x 4. The frequency of negative second-look surgery was the primary outcome measure. Seventy-five women were entered; 18 were excluded. Grade 4 myelotoxicity occurred in 61% of the patients. Thirty-seven percent (14/38) of the patients undergoing second look laparotomy had negative findings. The six complete responders were of long median duration (24.4 months). In this study BEP appeared to be an active combination regimen for first-line chemotherapy of malignant tumors of the ovarian stroma. Myelotoxicity was tolerable.

Pautier et al. (2008) performed a study to investigate the activity and toxicity of BEP regimen in ovarian granulosa cell tumors. Twenty consecutive patients with initial metastatic (5 patients) or recurrent (15 patients) ovarian granulosa cell tumors were treated; BEP regimen: B: 30 mg intravenously or intramurally on days 1, 8, and 15; E: 100 mg/m2/day on days 1–5; and P: 20 mg/m2/day on days 1–5; median follow-up: 45 months (range: 3–112). The overall response rate was 90% (nine clinical complete response [CR], nine clinical partial response) with a median duration of 24 months (range: 4–77). A second-look laparotomy performed in 11 patients showed a pathologic CR in 7 cases and microscopic disease in 1 case. Seven patients were free of disease (at 4–84 months); 11 patients relapsed (median: 24 months, range: 13–58), 12 patients were alive at the time of the analysis, and 9 patients were without disease (2 patients in second CR). At 4 years, overall survival and event-free survival were respectively 58% and 30%. BEP regimen appeared to be an active regimen for ovarian granulosa cell tumors in first-line chemotherapy.

For GCTs advanced stages and recurrent, platinum-based regimens are the treatment of choice with BEP regimen the most widely used, generally, three cycles of BEP in completely resected disease and four to five cycles for patients with macroscopic residual disease seem appropriate. For early stages SCSTs, BEP is the most commonly used regimen. Alternative chemotherapy options include: etoposide plus cisplatin; cyclophosphamide, doxorubicin and cisplatin; paclitaxel and carboplatin; or platinum agent alone (Colombo et al. 2012).

As the treatments of epithelial and non-epithelial types of ovarian cancer differ substantially, the CHMP considered that a distinction between these two entities with regard to formulation of the indication should be made.

Non-epithelial ovarian cancer

Etoposide is used as part of the standard of care for different subtypes of non-epithelial ovarian cancer as part of combination therapy with bleomycin and platinum (BEP). BEP is used as first-line treatment both in early and advanced stages of disease (ESMO guideline on treatment of non-epithelial ovarian cancer, 2012; and NCCN guideline ovarian cancer, 2015).

In the recurrent setting, etoposide is also used as part of combination therapy (particularly in sex cord-stromal tumours).

Thus, the use of etoposide as part of combination therapy in non-epithelial ovarian cancer, both in first-line and later lines of treatment, is evidence-based and considered standard of care.

Epithelial ovarian cancer

The current standard of care first-line treatment of early stage epithelial ovarian cancer consists of surgery followed by adjuvant chemotherapy (Winter-Roach et al. 2009, Cochrane Database Syst Rev 2009; CD004706; ESMO guideline newly diagnosed and relapsed epithelial ovarian carcinoma, 2013). In advanced stage disease, debulking surgery followed by chemotherapy with paclitaxel and platinum (or vice versa; i.e. chemotherapy followed by surgery) are considered standard of care treatments. Docetaxel-carboplatin or pegylated liposomal doxorubicin-carboplatin are considered alternative treatment options. Addition of bevacizumab to chemotherapy has been shown to improve PFS.

Etoposide is not commonly used in the first-line treatment of epithelial ovarian cancer.

In recurrent platinum-resistant/refractory epithelial ovarian cancer, four different chemotherapeutic agents have shown to have activity in phase III trials, i.e. paclitaxel, topotecan, pegylated liposomal doxorubicin, and gemcitabine. Etoposide has been demonstrated to have activity in the recurrent setting in a number of phase II studies. No single agent has been found to be superior to another in the recurrent platinum-resistant/refractory setting. Furthermore, randomised clinical trials of combinations have not demonstrated clinical benefit for combinations compared to single agent. Therefore, selection of therapy should be guided by the clinical situation of the patient, quality of life, and convenience of administration. Single agent orally administered etoposide has an important advantage compared to available intravenously administered agents, i.e., that hospitalisation for intravenous administration is not required.

In conclusion, the CHMP considered that the benefit-risk of etoposide in the first-line or later-line treatment of non-epithelial ovarian cancer, as well as in the treatment of platinum-resistant/refractory epithelial ovarian cancer, remains favourable.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.2 – Posology and method of administration

Posology

All 17 SmPCs state that the oral dose of etoposide capsules is based on the recommended IV dose and mention the need to consider bioavailability when prescribing, since it varies from patient to patient.

The current dose recommendations vary, as indicated the table below:

Table 4: Current dosage recommendations, by country

Country	Dosage Recommendation
Austria	[22]
Belgium/Luxembourg	100 - 200 mg/m²/day for 5 days or 200 mg/m²/day on days 1, 3 and 5 every 3 to 4 weeks
Croatia	100 – 200 mg/m²/day, days 1 to 5, or 200 mg/m²/day, days 1, 3 and 5 every 3 to 4 weeks
Denmark	Unspecified
Estonia	100-200 mg/m²/day on days 1 to 5 or 200 mg/m²/day on days 1, 3 and 5 every 3-4 weeks
Finland	100-200 mg/m² daily for five days (days 1-5), or 200 mg/m² daily for three days (days 1, 3 and 5) at intervals of 3-4 weeks
Germany	100 and 200 mg etoposide/m² body surface on days 1 to 5
Ireland	120-240 mg/m²/day, for five consecutive days
Italy	100 200 mg/m²/day for the first five days, or 200 mg/m²/day on days 1, 3 and 5, with an interval of 3 4 weeks
Netherlands	100-200 mg/m²/day for 5 consecutive days or 200 mg/m²/day on days 1, 3 and 5 every 3 to 4 weeks
Norway	100-200 mg/m² body surface daily for five days (day 1-5) or 200 mg/m²/24 hours for three days (day 1, 3 and 5) with intervals of 3-4 weeks
Romania	100 - 200 mg/m²/day, days 1 to 5 or 200 mg/m²/day, days 1, 3 and 5 every 3-4 weeks
Slovenia	100 – 200 mg/m²/day, days 1 to 5, or 200 mg/m²/day, days 1, 3 and 5 every 3 to 4 weeks
Spain	100 and 200 mg/m²/day, during consecutive days 1 to 5 of the cycle, or 200 mg/m²/day during days 1, 3 and 5 of the cycle every 3-4 weeks
Sweden	100-200 mg/m² body surface area daily for five days (day 1 to 5) or 200 mg/m² daily for three days (day 1, 3 and 5) every 3rd - 4th week
United Kingdom	120-240 mg/m² orally daily, for five consecutive days.

The harmonised, proposed text reflects the recommendations of the Company. The adult dosing section contains details on monotherapy, combination therapy, an alternative dosing schedule, and dosing adjustments for a low neutrophil count.

The national SmPCs of AT, BE/LU, HR, DK, EE, FI, DE, IE, IT, NL, NO, RO, SI, ES, and SE also indicate that for daily doses of over 200 mg, the dose should be divided (taken twice daily).

The SmPCs of HR, EE, FI, IT, NL, NO, RO, ES, SI and SE state that etoposide should be administered in combination with other drugs approved for use in the disease to be treated, but this is not specified in the other national SmPCs.

Eleven countries (all except DK, EE, FI, IE, SE, and UK) also provide an alternative dosage schedule for etoposide capsules.

The core safety profile (CSP) and the SmPCs of AT, BE/LU, DK, FI, DE, IT, NL, NO, RO, SI, and SE state that doses subsequent to the initial dose should be adjusted if a neutrophil count less than 500 cells/mm3 occurs for more than 5 days or is associated with fever or infection, if platelet count less than 25,000 cells/mm3 occurs, if any other grade 3 or 4 toxicity develops or if renal clearance is less than 50 ml/min.

Hande et al. (1993) determined the bioavailability (BA) of oral etoposide capsules administered at doses of 100 mg and 400 mg [38]. The AUC following IV etoposide was compared to the AUC following

an oral dose administered 48 hours later to the same patient. The BA of a 100 mg dose was measured on 16 occasions in 11 patients. The BA of a 400 mg dose was determined on 12 occasions in 6 patients. The mean (±SD) BA of the 100 mg dose was 76% ± 22%. The mean (±SD) BA of the 400 mg dose was 48% ± 18%. The coefficient of variation in oral etoposide BA was 29% with a 100 mg oral dose and 37% with a 400 mg oral dose. In a review of etoposide in the treatment of small cell lung cancer by Johnson et al. (1999), the bioavailability of an oral hydrophilic gelatin capsule averages 50% although there is significant inter-patient variability [40]. With increasing oral dose (e.g. doubling from 200 mg to 400 mg) there is a less than proportional increase in AUC.

The most widely used dosing regimens for intravenous etoposide are: 50-100 mg/m2 on five consecutive days, on day 1-5 in a cycle of 21 or 28 days; or 100-120 mg/m2 on three days (most often days 1-3 or day 1, 3, and 5) in a cycle of 21 or 28 days. The bioavailability of etoposide is dose-dependent, i.e., around 75% at a dose of 100 mg and 50% at a dose of 400 mg.

Based on these data on bioavailability, 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.

This is in line with the current product information of Vepesid and the dosing recommendation is therefore considered acceptable.

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-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, it was proposed 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. Sections 4.2 and 4.4 have been updated accordingly.

Renal impairment

Etoposide is eliminated by renal clearance of unchanged drug and by biliary excretion of the glucuronide metabolite.

The SmPCs of AT, BE/LU, HR, DK, EE, IE, NL, NO and RO recommend a starting dose reduction (75% of the normal dose) in patients with moderate renal impairment (15 - 50 ml/min). The German SmPC recommends that treatment courses of etoposide be carried out only in patients with normal kidney function.

The MAH proposed no dose reduction for patients at the higher end of moderate renal impairment (creatinine clearance > 50 mL/min) based on recommendation provided by Kreusser et al. (1982) and based on data presented by Arbuck et al (1986). Kreusser et al. (1982) recommended that no dose

reduction was required for GFR ≥ 10ml/min. Arbuck et al. (1986) published a study performed in 17 patients, some with moderate renal dysfunction. No difference was observed in pharmacokinetic parameters in eight patients with a creatinine clearance of ≥ 70 ml/ min/ 1.73 m^2 and nine patients with a creatinine clearance of < 70 ml/ min/1.73 m^2. In addition, Toffoli et al. (2004) recommended dose reduction to avoid haematological toxicity in patients with renal dysfunction (creatinine CL < 50 ml/min). Other authors recommended different dose reduction cut off values. Kintzel & Dorr (1995) recommended only a ~15 -20 % decrease in dose when a patient's creatinine clearance in the range from 60 to 45 mL/min, respectively. In a recent review by Fisselli et al. (2014) on the PK of anti-cancer chemotherapy in renal insufficiency and chronic kidney disease, it is summarized that the PK of etoposide is similar in end-stage renal disease (ESRD) as in normal subjects and any dose adjustments in chronic kidney disease is largely empiric. Therefore, in totality, these investigations support that there is no need for a dose reduction in patients with a creatinine clearance within 50 to 60 ml/min.

The basis for a 25% dose reduction in moderate and severe renal impairment (creatinine clearance 15-50 mL/min) has been further justified. In a review by Joel et al. (1994) it is presented evidence that steady state plasma concentrations, AUC and clearance correlate with haematological toxicity. A dose reduction of 30% in renal impairment is recommended. In a review by Kintzel & Dorr (1995), a dose reduction of 25% is recommended at a creatinine clearance of 30 mL/min, but no recommendation is given for lower CrCl values. Sinkule et al. (1984) review the PK of etoposide in paediatric patients with solid tumours. The creatinine clearance was a significant predictor of renal clearance. D'incalci et al. (1986) reported the results of a study of the PK of etoposide in patients with abnormal renal function. The PK was investigated in 18 cancer patients with normal renal function and 8 patients with renal impairment, after a single IV dose of etoposide 100 mg. There was a clear relationship between etoposide clearance and creatinine clearance, and dose adjustment was recommended in relation to creatinine clearance values. There is no clinical data to support an alternative dosing recommendation in severe renal impairment to that recommended by the MAH for CrCl 15-50 ml/min. Bearing in mind that this is a harmonisation procedure, and that the current national SmPC already include the MAH proposed dosing recommendation with regard to renal impairment (a 25% dose reduction in patients with CrCl 15-50 ml/min), the response is accepted.

The MAH was also asked to discuss the possibility of recommending 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, A. et al. (2004). This has been addressed by a warning in section 4.2 of the SmPC.

The MAH was asked to provide pharmacokinetic data to support the requirement to take Vepesid capsules in the fasted state.

In 1985, Harvey et al showed that food does not interfere with the bioavailability of etoposide at 100 mg dose in 11 patients. Mean AUC in the fed state was comparable to the fasted state. There was considerable inter-patient variation in exposure which was not related to the fed or fasted state. There was a small sample size (n=11), the study did not include statistical analyses, and the study appeared not to have information on being statistically powered.

Subsequently, the bioavailability of oral etoposide capsules at doses of 100 mg and 400 mg was determined in a study by Hande et al. (1993) Etoposide was administered orally 1 hour before or 2 hours after food in the study. Hande concluded that the mean bioavailability of a 100-mg oral dose was 76 ± 22% and of a 400-mg dose was 48 ± 18%. Additionally, the study confirmed wide inter-patient and intra-patient variability in oral etoposide bioavailability. This study was the basis for the MAH to administer etoposide orally on an empty stomach.

Given these data, 16 out the 17 SmPCs (DE as the exception) currently recommend that oral etoposide is to be administered on an empty stomach.

Based on the results of these two studies and the approved SmPCs, the CHMP agreed that the available evidence does not support administration without regard to food. Given the high intra-patient and inter-patient variability in bioavailability it is prudent to recommend administration in the fasted state. The CHMP therefore considered to maintain the recommendation to administer oral etoposide in the fasted state.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.3 – Contraindications

Table 5: Current contraindications to etoposide use, by country

Contraindication	Countries
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.	Austria, Belgium /Luxembourg, Croatia, Denmark, Estonia, Finland, Germany, Ireland, Italy, Netherlands, Norway, Romania, Slovenia, Spain, Sweden, United Kingdom
Concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients (see section 4.5).	Austria, Belgium /Luxembourg, Croatia, Denmark, Finland, Germany, Ireland, Italy, Netherlands, Norway, Romania, Slovenia, Sweden
Severe myelosuppression	Austria, Belgium /Luxembourg, Denmark, Germany, Romania, Spain
Severe hepatic impairment	Austria, Belgium /Luxembourg, Croatia, Denmark, Germany, Italy, Romania, Spain, United Kingdom
Severe renal impairment (Creatinine-clearance <15 ml/min)	Austria, Croatia, Denmark, Germany
Pregnancy	Austria, Belgium /Luxembourg, Croatia, Denmark, Spain
Lactation	Austria, Belgium /Luxembourg, Netherlands, Spain, Sweden
Myocardial infarction	Germany
Low serum albumin	Germany
Active infection	Germany, Romania
Abnormal peripheral nervous system	Germany

The inclusion of the hypersensitivity contraindication is agreed as it is in line with the SmPC guideline.

The rationale to include concurrent the use of live vaccines of a contraindication is agreed, as immunosuppression is a common side effect of etoposide (listed as very common in the proposed SPC). Although the cited Advisory Committee on Immunization Practices (ACIP) recommendations do not mention etoposide specifically, it is stated:

Drugs with known immunosuppressive or immunomodulatory properties include high-dose systemic corticosteroids, alkylating drugs, antimetabolites, TNF-α inhibitors (e.g., etanercept), IL-1 blocking agent (e.g., anakinra), and other monoclonal antibodies targeting immune cells (e.g., rituximab, alemtuzumab). No specific data exist on the use of YF vaccine in persons receiving these therapies. However, these persons are presumed to be at an increased risk for YF vaccine-associated serious adverse events, and the use of live attenuated vaccines in these persons is contraindicated according to the package insert for most of these therapies.

The contraindication is in line with the SmPC guideline, which states:

Other medicines or classes of medicine, which must not be used concomitantly or consecutively should be stated, based on either data or strong theoretical reasons.

The concomitant use of live vaccines contraindication is therefore agreed.

A contraindication in severe renal impairment (creatinine clearance <15 ml/min) was initially included. Etoposide is used to treat life-threatening conditions. Warnings in section 4.2 and 4.4, including advice to lower the dose, are considered more appropriate. In line with the inclusion of dose reduction advice in section 4.2, the contraindication has been deleted.

Lactation has been included as a contraindication, since breastfeeding women could replace breastfeeding by dairy products to feed their child.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.4 – Special warnings and precautions for use

Within-patient variability

Additional text has been included at the request of CHMP regarding the larger intra-patient variability with oral vs IV etoposide.

Myelosuppression

Myelosuppression is the dose limiting toxicity of etoposide. The majority of EU/EAA SmPCs include warnings that severe myelosuppression with resulting infection or bleeding may occur, that fatal myelosuppression has been reported, and that patients should be monitored for myelosuppression.

The SmPCs of AT, BE/LU, DK, FI, IT, NL, NO, RO, SI and SE states that etoposide *'should not be administered to patients with neutrophil counts less than 1,500 cell/mm3 or platelet counts less than 100,000 cells/mm3, unless caused by malignant disease.'* All SmPCs include the recommendation to measure the following haematological parameters at the start of therapy and prior to each subsequent dose: platelet count, haemoglobin, white blood cell count and differential.

Secondary leukaemia

Epipdophyllotoxins including etoposide have been linked to the development of secondary leukaemia since the 1980s. The proposed harmonised wording for secondary leukaemia is already included in all 17 national SmPCs.

Low serum albumin

Text regarding the association of low serum albumin with increased toxicities is included in all current national SmPCs except IE and UK.

Impaired renal and hepatic function

Etoposide is partially metabolised into inactive forms in the liver and cleared by both the liver and the kidneys. Mild to moderate liver dysfunction does not affect the pharmacokinetics of etoposide, but severe hepatic impairment could contribute to greater toxicity because of reduced hepatobiliary metabolism. In this setting, regular monitoring of renal and hepatic function is justified to allow the optimal dose of etoposide to be administered to the individual patient.

The current national SmPCs of BE/LU, DK, FI, IT, NO, RO, and SI, and state that patients with impaired hepatic and renal function should regularly have their renal and hepatic function monitored due to the risk of accumulation. Hepatic and renal impairment are listed as contraindications in the German SmPC.

A warning covering moderate and severe renal impairment has been included as requested, given the effect of renal impairment on etoposide PK, and consequently, haematological toxicity.

The hepatic impairment warning has been re-instated.

Tumour lysis syndrome

A warning regarding tumour lysis syndrome has been added similar to the wording included in the national SmPC of DE.

Mutagenic potential

Due to its mechanism of action, etoposide has mutagenic potential. Mutations induced in somatic cells may lead to the development of secondary cancer. Mutations induced in germ cells may be transmitted to future generations. The current national SmPCs of AR, BE/LU, DK, FI, IT, NL, NO, RO, SI, ES and SE already include the statement regarding mutagenic potential.

The SmPCs of Croatia, Denmark, Germany, Netherlands, Romania, and Slovenia state that etoposide capsules contain excipients sodium propyl parahydroxybenzoate (E217) and sodium ethyl parahydroxybenzoate (E215), which may cause allergic reactions (possibly delayed). This paragraph has been added to the proposed harmonised SmPC in accordance with the European Commission Guideline "Excipients in the label and package leaflet of medicinal products for human use" Revised 1 July 2003.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

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

Interactions that are documented in the majority of current national SmPCs have been retained in the proposed harmonised text. Minor amendments have been made toimprove clarity.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

The CHMP noted that it has been reported in the literature that etoposide is a P-glycoprotein substrate however information on P-glycoprotein was not included in any of the current SmPCs of etoposide. The MAH is therefore encouraged to review the available information with regards to the impact on drug interactions by induction or inhibition and submit a variation, as appropriate.

Section 4.6 – Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

The French SmPC of FR states that women of child-bearing age must be informed that the use of a method of contraception is in their best interests. The SmPC of SE provides the following statement regarding fertility. *"Given the mutagenic potential of etoposide, an effective contraception is required for both male and female patients during treatment and up to 6 months after ending treatment. Genetic consultation is recommended if the patient wishes to have children after ending the treatment. As etoposide may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood. Etoposide may possibly lead to irreversible sterility."*

The SmPC Guideline of September 2009 recommends that contraceptive measures should be mentioned in a separate paragraph for women of childbearing potential in combination with a cross-reference to section 4.4. The text has been updated accordingly and is now agreed.

Pregnancy

The use of etoposide during pregnancy is contraindicated in the SmPCs of AT, DK, RO and ES. The labels of DE, IE and UK indicate a conditional contraindication. It is agreed that a contraindication is not appropriate, since there may be situations for which use in pregnancy is necessary.

The MAH has revised the pregnancy section in line with *Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling – Appendix 3* (EMEA/CHMP/203927/2005). Adequate and well-controlled studies are not expected, and their absence is not informing the prescribers. In addition, it is already stated that there are no or limited data on use in pregnant women. Therefore the sentence *'There are no adequate and well-controlled studies in pregnant women.'* has been deleted.

Breastfeeding

Lactation is contraindicated in the current national SmPCs of AT, BE/LU, NL, FI, RO and SE. It is not known whether etoposide is in human milk. The SmPC of DK states that etoposide should not be used during lactation. The SmPC of DE states that during treatment, nursing must be discontinued, because it is unknown whether etoposide is excreted in human milk.

Etoposide is excreted in the milk (Medications and Mothers' Milk: Thomas W. Hale). Lactation should be included as a contraindication, since breastfeeding women could replace breastfeeding by dairy products to feed their child (see LoOI: section 4.3). A recommendation to discontinue breast-feeding or discontinue etoposide is appropriate.

The MAH has amended the breast-feeding text in line with *Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling – Appendix 3* (EMEA/CHMP/203927/2005).

Fertility

The CHMP noted that etoposide may decrease male fertility. A text to consider preservation of the sperm has been included.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.7 – Effects on ability to drive and use machines

The MAH has not conducted studies on the effect of etoposide administration on the ability to drive or operate machines. However several adverse reactions of etoposide do affect a patient's ability to concentrate and react.

The majority of SmPCs (AT, BE/LU, DK, FI, IE, IT, NL, NO, RO, SE and SI) state that if the patient experiences side effects such as fatigue and somnolence they should avoid driving or operating machines. The SmPC of DE states that nausea and vomiting, as well as acute hypersensitivity reactions with hypotension, may occur leading indirectly to an impairment of the ability to drive or operate machines. The SmPC of ES indicates that driving and operating machines are not recommended immediately after etoposide administration, as it could lead to nausea, vomiting, fatigue or transitory cortical blindness.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.8 – Undesirable effects

The proposal for section 4.8 of the harmonised SmPC is based on the CSP finalised following procedure DK/H/PSUR/0029/001, and it is in line with the majority of national SmPCs. Generally, the rationale that resulted in the listed reactions was based on the incidences of adverse events (AEs) derived from studies that utilised single agent etoposide therapy. References to etoposide phosphate have been removed, but are included in the SmPC of Etopophos.

Some national SmPCs include ADRs that are considered synonyms or symptoms of terms already included. Other AE terms included in national SmPCs, but not in the CSP, were considered by the MAH for inclusion in the harmonized text. A comprehensive search, cumulative to 31 August 2015 of the Corporate Safety Database was performed to identify all events reported by Health Care Professional (HCP) spontaneous, literature and related clinical trials cases in which etoposide was considered a suspect or interacting drug. Additionally, separate searches were conducted using preferred terms (PTs) for the national AEs not included in the CSP: confusional state, dizziness, headache, syncope/ presyncope, hyperuricaemia, hyperhidrosis, metabolic acidosis, phlebitis, tongue oedema/ swollen tongue, face oedema/ swelling face/ angioedema, female infertility. The relative incidence rates of the national AEs as compared to the total number of HCP confirmed events contained in the safety database for etoposide were low. As a result of this review, the MAH is not proposing to add these terms to section 4.8 of the harmonised SmPC.

The paragraph on haematological toxicity now includes information that bleeding has been reported. This information is also included in section 4.4 of the proposed harmonised SmPC.

Section 4.8 was updated to include a summary of safety profile and to add a number of additional ADRs to the table: infection, haemorrhage, pyrexia, bronchospasm, tumour lysis syndrome, aspartate amino transferase increased, alkaline phosphatase increased, bilirubin increased and infertility. Alanine aminotransferase increased has also been added to the table in addition to aspartate aminotransferase increased, as both are sensitive indicators for liver injury.

The MAH has initiated a review of the published studies for etoposide in an attempt to estimate the frequency for all ADR terms. Only frequencies from MAH-sponsored randomised controlled clinical trials should be used for the estimation of frequencies. The MAH should make sure that the estimated frequencies are incorporated in the ADR table once this analysis has been finalised.

A proposed correction to the haematological toxicity paragraph is acceptable. The heading “Allergic reactions” in section 4.8 has been replaced by “Hypersensitivity” in line with section 4.4. This sub-paragraph has been updated to include information on the events reported with anaphylactic reactions, such as chills, pyrexia, tachycardia, bronchospasm, dyspnoea and hypotension, which can be fatal. The event 'bronchospasm' has also been added to the ADR table given its seriousness. The events of face oedema, swelling face, tongue oedema and swelling tongue have been moved to the description of ADRs in the subparagraph of “hypersensitivity”. The PT ‘syncope’ has also been added.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 4.9 – Overdose

The current national SmPCs of all EEA/EU countries recommend that no antidote is available and suggest symptomatic, supportive treatment in case of overdose, with close monitoring of patients during treatment. The proposed harmonised text is in line with national SmPCs and also the agreed CSP following procedure DK/H/PSUR/0029/001. The MAH has added wording that similar toxicities are expected to occur with the oral formulation, based on evidence from the literature that oral etoposide is associated with comparable toxicity to IV etoposide when oral etoposide is administered at twice the dose of IV (Sauer et al. 1990). The MAH has also added wording that etoposide and its metabolites are not dialyzable based on in vitro assays of cytostatic drugs. The high volume of distribution and long half-life also affects dialysability (Holthuis et al. 1985). Dialysis of Drugs (Johnson et al. 2010) also indicates that dialysis does not have a clinically important effect on plasma clearance of etoposide.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.1 – Pharmacodynamic properties

The pharmacotherapeutic group and Anatomical Therapeutic Chemical (ATC) code have been assigned using the 2nd, 3rd and 4th levels of the ATC classification system as follows:

L - Antineoplastic and immunomodulating agents (1st level, anatomical main group)

L01 - Cytostatics (2nd level, therapeutic subgroup)

L01C - Plant alkaloids and other natural products (3rd level, pharmacological subgroup)

L01CB - Podophyllotoxin derivatives (4th level, chemical subgroup)

L01CB01 - etoposide (5th level, chemical substance)

The mechanism of action wording has been consolidated from various current national SmPCs.

The proposed ATC classification and mechanism of action wording are acceptable.

The MAH has not proposed a wording for 'pharmacodynamic effects', 'clinical efficacy and safety' or 'paediatric population'. The MAH states that no information is provided in section 5.1 of the national SmPCs under these sub-headings. Etoposide has been authorised in Europe since 1981. It would be very challenging to summarise the available pharmacodynamics, efficacy and safety data in such a way as to be useful for prescribers. The omission is therefore acceptable.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.2 – Pharmacokinetic properties

The concept that etoposide is administered in the active form is captured in all SmPCs. Furthermore, peak plasma levels, bioavailability, metabolic pathway and plasma protein binding are described in most of the national labels. This section has not been systematically updated by all countries, thus not always reflecting all relevant information.

The proposed wording for the pharmacokinetic properties section of the harmonised SmPC has been derived from the CCDS and the various EU country SmPCs.

Section 5.2 has been updated as it addressed poor overall structure and repeated information. The proposed text is agreed.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Section 5.3 – Preclinical safety data

All national labels provide similar preclinical safety data. The carcinogenic potential of etoposide has not been studied. Considering the mechanism of action, etoposide is a potentially carcinogenic and genotoxic substance. It has been demonstrated that etoposide was mutagenic on mammal cells and it is to be expected that etoposide phosphate would have identical mutagenic effects.

Section 5.3 has been updated to include a statement on comparative systemic exposure.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Sections 6 to 10

Sections 6 – 10 of the proposed harmonised SmPC have been updated in line with the CHMP comments.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

Package Leaflet (PL)

The changes to the SmPC, when relevant for the user, have also been reflected in the PL and endorsed by the CHMP.

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

3. Recommendation

Based on the review of all available data, the CHMP recommended the revision and harmonisation of the product information for Vepesid and associated names. The final agreed wording of the product information can be found in Annex III of the CHMP opinion.

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 (Hande et al. 1993; Johnson et al. 1999), 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-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 (Kreusser et al. (1982); Arbuck et al. (1986); Toffoli et al. (2004); Kintzel et al. (1995); Fissell et al. (2014)). 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). 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 on risk assessment of medicinal products on human reproduction and lactation: from data to labelling – Appendix 3*. 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.

4. Grounds for 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.

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