21 April 2017
EMA/409209/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 30 of Directive 2001/83/EC

Etopophos and associated names

INN of the active substance: etoposide phosphate

Procedure number: EMEA/H/A-30/1417

Note:

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

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Table of contents

1. Background information

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 13 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.

2. Scientific discussion

2.1. Introduction

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
- 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.

2.2. Critical Evaluation

Submitted supporting data consisted of 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 complete information on the active substance.

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

Testicular cancer

Etoposide phosphate is approved for testicular cancer in all four member states (MSs) where is currently marketed, as monotherapy (FR, UK) and/or combination therapy (DE, FR, SE and UK).

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
Fitzharris et al. (1980)	Refractory testicular cancer	Prospective single arm	Etoposide phosphate 120 mg/m2 IV daily for 5 days repeated after 2-4 weeks (n=20); 100 mg/m2 IV daily for 5 days repeated after 4 weeks (n=6)	Of 24 evaluable patients, 3 (12.5%) CR, 33.5% PR
Hainsworth et al. (1985)	Refractory germinal neoplasms previously treated with cisplatin-containing regimens	Prospective single arm	Etoposide phosphate + cisplatin + bleomycin + doxorubicin (n=45)	Of 44 evaluable patients, 19 (43%) CR, 12 (27%) PR
Williams et al. (1987)	First-line disseminated germ cell tumour	Randomized Phase 3 study	244 patients randomly assigned to (1) cisplatin + vinblastine + bleomycin (PVB) or (2) bleomycin + etoposide + cisplatin (BEP)	Cure rate: 78% on BEP vs 66% on PVB
NCCN clinical practice guideline: testicular cancer	Metastatic testicular cancer	Guideline	Cisplatin + bleomycin + etoposide (BEP) is gold standard	For patients with good prognostic features, cure rates >90%.
NCCN clinical practice guideline: testicular cancer	Refractory or recurrent metastatic testicular cancer patients	Guideline	Etoposide monotherapy	Palliative

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

The marketing authorisation holder (MAH) refers to three studies from the literature to support the indication in testicular cancer. These include one randomised clinical trial (RCT), and provide evidence of response to monotherapy and combination therapy in the first-line metastatic and refractory settings. The MAH also refers to the NCCN guideline which supports the use of etoposide in these settings. Additional randomized 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).

According to the ESMO Guideline on Testicular Seminoma and Non-seminoma tumours, 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 although less data are available in this setting compared to the first-line setting. Effective approaches in post first-line 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 CHMP considered therefore that the indication for etoposide in testicular cancer, as combination therapy, is acceptable.

The role of etoposide monotherapy in the current treatment of testicular cancer is questioned. Although it is not currently specified in the Etopophos SmPCs of FR and UK 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). The CHMP therefore considered restricting the indication to combination therapy to treat testicular cancer in adults.

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 four MSs, as monotherapy (FR and UK) and/or combination therapy (DE, FR, SE and UK).

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.

Table 2: Literature evidence to support indication in SCLC

Reference	Disease setting	Design	Study treatments (patient numbers)	Outcomes
Tucker et al. (1987)	SCLC of bronchus	Prospective single arm	Etoposide phosphate 60 mg/m2/day for 5 days every 14 days, and etoposide 100 mg oral twice weekly between IV doses (n=47)	ORR 51% (24 out of 47). In these 24 patients, median survival was 225 days.
Jungi et al. (1975)	Solid tumours including lung cancer	Prospective single arm	Etoposide phosphate 60 mg/m2/day for 5 days every 21 days (2 course) followed by etoposide orally 60-120 mg/m2/day for 5 days every 21 days (n=30)	PR 42% in SCLC
Issell et al. (1985)	SCLC patients failing aggressive chemotherapy	Prospective single arm	Etoposide phosphate 80 mg/m2 IV days 1-5 every 3-4 weeks (n=116)	Of 95 evaluable patients, ORR 12%, median survival 12 weeks
Evans et al. (1985)	SCLC not responding to or relapsing after standard induction chemotherapy (cyclophosphamide, doxorubicin, vincristine); limited disease (n=24) and extensive disease (n=54).	Prospective single arm	Etoposide + cisplatin	6 (8%) CR; 37 (47%) PR; median DOR 22 weeks for limited disease and 18 weeks for extensive disease
Hainsworth et al. (1995)	Untreated SCLC	Randomized trial	Molar equivalents of etoposide and etoposide phosphate, in combination with cisplatin	Etoposide phosphate: ORR 61%; etoposide ORR 58%
NCCN Guideline: SCLC	SCLC	Guideline	Etoposide + cisplatin is the most commonly used initial combination; subsequent single agent therapy includes etoposide	
ESMO Guideline:	SCLC	Guideline	All patients with T1-	

SCLC			4, N0-3, M0 should be treated with 4 cycles of cisplatin + etoposide, or 4-6 cycles if a once daily radiotherapy schedule is used. In metastatic disease, combination chemotherapy is the main treatment option.	

Etoposide in combination with platinum is a standard of care treatment regimen in the first-line treatment of SCLC with localised disease (in combination with concurrent radiotherapy) or metastatic disease. In later lines, etoposide-platinum is also sometimes used, in patients who showed a good response in first-line treatment.

The MAH has cited a limited number of small single arm phase 2 studies. There are many more studies available in the public domain, as well as a systematic review, supporting the use of etoposide, in combination with platinum, for the treatment of SCLC. European clinical practice guidelines should also be considered.

The European Lung Cancer Working Party systematically reviewed published randomised clinical studies and the role of etoposide and cisplatin in the treatment of SCLC, summarizing 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 (0.72; 95% CI, 0.67–0.78; P<0.001).

The indication SCLC for etoposide, when used in combination with other chemotherapy, is considered approvable 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 the Etopophos SmPCs that etoposide is indicated as combination therapy, more recent decentralised 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). The current guidelines NCCN and ESMO recommend combination therapy for SCLC. Therefore, the CHMP considered restricting the indication in combination therapy to treat SCLC in adults.

The final agreed wording for this section of the SmPC 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, which is also mentioned in the NCCN guideline on NSCL, a comparative study by Albain et al. (2002) 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. 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 FR and SE. In DE, etoposide phosphate is only approved for re-induction. It is not currently approved for Hodgkin's lymphoma (HL) in the 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
Hagemeister et al. (1987)	Previously treated HL	Prospective single arm	Etoposide 100 mg/m2/day IV x 3 days in combination with methyl-GAG, ifosfamide, methotrexate (n=47)	CR 23%, PR 40%, median survival 50 weeks,
Perren et al. (1986)	First-line and relapsed HL	Prospective single arm	Vincristine + prednisolone + etoposide + chlorambucil (OPEC) n=39. In 30 patients this regimen was alternated with ChIVPP (O/C)	O/C: CR 71% (20/28) OPEC only: CR 56% (5/9)
Santoro et al. (1986)	HL refractory to MOPP and ABVD	Prospective single arm	Etoposide + lomustine + prednimustine (CEP) (number receiving CEP not provided)	CR 40% (median DOR > 15 months, median survival > 24 months), PR 14%
Santoro et al. (1986)	HL refractory to MOPP	Prospective single arm	CEP alternating with ABVD (n=21)	67% CR; median DOR > 24 months; median survival > 36 months
ESMO guideline: Hodgkin's Lymphoma	HL	Guideline	See assessor's comment below	

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

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.

The CHMP agreed that due to the very different treatment situations for which IV etoposide can be used in Hodgkin's lymphoma, specifications regarding the line of treatment should be left out of the indication.

Paediatric population

The MAH has identified published clinical studies including over 3000 paediatric HL patients treated with etoposide since 1989. As summarised by the MAH, several major study groups have included etoposide as a component of clinical trial chemotherapy regimens.

The German-Austrian Paediatric Hodgkin's Disease Study Group included etoposide in the OEPA (vincristine, prednisone, etoposide, and doxorubicin) induction regimen for 319 boys younger than 18 years old with previously untreated HL who were enrolled in study DAL-HD-90 between 1990 and 1995. Etoposide replaced procarbazine because the latter is known to be gonadotoxic. Etoposide was administered at a dose of 125 mg/m^2/day on days 3-6. At 5 years, the probability of event-free survival (EFS) and overall survival (OS) were 89% and 98% respectively.

The German Society of Paediatric Oncology and Haematology Hodgkin's Disease (GPOH-HD) 2002 study enrolled 573 patients younger than 18 years old with *de novo* classical HL between 2002 and 2005. Two courses of OEPA was given to all male patients (n=287) for induction. The dose of etoposide was 125 mg/m^2/day for 5 days. Girls received OPPA (OEPA with procarbazine substituted for etoposide). Haematotoxicity was more pronounced with OEPA than OPPA. EFS did not significantly differ between boys and girls (90.2% ± 2.3 v 84.7% ± 2.7, respectively; P = 0.12).

The French Society of Paediatric Oncology Study MDH90 enrolled 202 children with localised HL (stages IA to IIB) between 1990 and 1996, including 77 females. Patients were treated with vinblastine, bleomycin, etoposide (100 mg/m^2/day on days 1 to 5) and prednisolone (VBVP) for four cycles as induction therapy. A total of 83 patients (41%) achieved complete remission and a further 88 (44%) achieved at least 70% reduction in tumour size. The 5-year overall survival rate (mean ± SD) was 97.5% ± 2.1%, and the event-free survival rate (mean ± SD) was 91.1% ± 1.8%. The cumulative incidence of secondary leukaemia in the 202 patients is 0.9% at 5 years.

The United States (US) based Children's Oncology Group conducted a randomised study (AHOD0031) to investigate the role of early chemotherapy response in tailoring the role of subsequent therapy in 1712 *de novo* paediatric HL patients under 22 years. All patients received four cycles of doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone (ABVE-PC). Slow early responders were randomised to receive two cycles of DECA (dexamethasone, etoposide, cisplatin, and cytarabine), or no additional therapy, in conjunction with the 3rd and 4th ABVE-PC cycles. 4-year event-free survival (EFS) was 86.9% for rapid early responders. For slow early responders, 4-year EFS was 79.3% vs. 75.2% for DECA vs. no DECA (p=0.11).

ABVE-PC was also used in study P9425 (Children's Oncology Group) which enrolled 216 patients under 22 years with intermediate or high risk HL from 1997 to 2001. There were 76 females and 140 males.

The etoposide dose was 75 mg/m^2/day on days 0-4. Three to five cycles were administered prior to radiotherapy depending on initial response. Five-year EFS was 84% and 5 year OS was 95%. Study P9426 from the same group investigated 2-4 cycles of doxorubicin, bleomycin, vincristine and etoposide, with or without dexrazoxane (to reduce cardiopulmonary toxicity), according to a randomisation schedule. A total of 294 patients with low risk HL aged ≤ 21 years were enrolled between 1996 and 2000. The etoposide dose was 100 mg/m^2/day on days 1-5. The 8-year event free survival (EFS) between the treatment groups did not differ: 86.8% vs. 85.7% for dexrazoxane vs. no dexrazoxane.

The Children's Oncology Group have also investigated induction therapy with BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) in 99 children ≤ 21 years with advanced HL, from 1999 to 2002. The etoposide dose was 200 mg/m^2/day for 3 days. Seventy-two of 97 (74%) patients with institutional response evaluation achieved a complete response of partial response (≥ 70% reduction in tumour mass) after 4 cycles of BEACOPP. The 5-year EFS was 94% and the 5-year OS was 97%.

In conclusion, studies conducted by major groups provide evidence that etoposide is an established component of standard induction regimens for paediatric HL. Although some groups have used etoposide only for male patients, due to the risk of reproductive toxicity with procarbazine, other groups have used etoposide containing regimens in both males and females. The CHMP agreed that the MAH has submitted adequate evidence for the extension of the HL indication to the paediatric population and the adequate dose recommendation.

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

Non-Hodgkin's lymphoma

Etoposide phosphate is approved for non-Hodgkin's lymphoma (NHL) in DE, FR and SE, as part of combination therapy. It is not currently indicated for treatment of NHL in the UK. The MAH has provided a comprehensive review of the available evidence to support an indication in 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; and Peripheral T-cell lymphoma.

Diffuse large B-cell lymphoma (DLBCL)

According to ESMO guideline on diffuse large B-cell NHL and the NCCN guideline on NHL, etoposide is a treatment option for first line, relapsed and refractory patients. In young (< 61 years) high and high-intermediate-risk patients, R-CHEOP (rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone) is frequently used, although it has not been compared directly with R-CHOP in this setting. In relapsed /refractory disease, R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) and BEAM (carmustine, etoposide, cytosine-arabinoside, and melphalan) are options.

According to Schmitz et al. (2012), in the first line treatment of patients < 60 years with high-risk aggressive disease, eight cycles of R-CHEOP-14 (rituximab, cyclophosphamide, doxorubicin, vincristine, 100 mg/m2 of etoposide on days 1–3, and prednisone) every 2 weeks is associated with high remission rates. Adde et al (2006) reported high remission rates for R-CHEOP-14 in patients less than 65 years with high-risk aggressive disease. Gang et al. (2012) reported increased overall survival for R-CHEOP-14 vs. R-CHOP-14 in young high-risk patients, in a registry study.

In relapsed/refractory CD20+ DLBCL, R-ICE (rituximab, ifosfamide, carboplatin, and etoposide 100 mg/m2 day 1-3) was associated with a similar response rate to R-DHAP (rituximab, dexamethasone, high-dose cytarabine and cisplatin) in a randomised comparison by Gisselbrecht et al. (2010).

Follicular lymphoma

According to the ESMO guideline (Dreyling et al. 2016), CHVP-IFN (rituximab, cyclophosphamide, doxorubicin, etoposide, prednisone, interferon) is an option for the first-line treatment of symptomatic stage III-IV disease. Bachy et al. (2013) report the long-term follow-up of the FL2000 study comparing CHVP-IFN to CHVP-IFN plus rituximab. Median event-free survival was, 2.8 years (95%CI: 2.4-3.6 years) with CHVP-IFN compared to 5.5 years (95%CI: 3.9-8.8 years) with R-CHVP-IFN.

Mantle cell lymphoma

According to the ESMO guideline (Dreyling et al. 2014), PEP-C (prednisone, etoposide, procarbazine, and cyclophosphamide) may be considered in frail patients, aiming primarily at palliation. Damon et al. (2009) reported a single arm study of dose-intensified therapy in the first-line setting in 78 patients aged < 70 years. Two to three cycles of rituximab, methotrexate and augmented CHOP was followed by intensification with high doses of cytarabine and etoposide combined with rituximab and filgrastim. Patients then received high doses of carmustine, etoposide, and cyclophosphamide followed by autologous stem-cell transplantation (ASCT) and two doses of rituximab. The 5-year overall survival was 64% (95% CI, 50% to 75%) (Damon et al. 2009).

Peripheral T-cell lymphoma (PTCL)

The most common PTCL subtypes are PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AILT), and anaplastic large-cell lymphoma (ALCL), with or without expression of ALK. D'Amore et al (2012) reported the results of a study of ASCT in treatment-naïve patients (excluding ALK-positive ALCL). The induction regimen was CHEOP, including etoposide 100 mg/m2 IV on days 1 through 3 (etoposide was omitted in patients > 60 years). ORR was 82%; with 51% achieving a CR. Long-term PFS was achieved in 44%.

According to the ESMO guideline (d'Amore et al. 2012), CHEOP has shown some benefits over CHOP in the first-line treatment of patients < 60 years with nodal PTCL (PTCL-NOS, AITL, ALCL ALK+, ALCL ALK−). Dose-dense CHOEP schedule followed by ASCT is an evidence-based approach. In the relapsed setting, an option is ICE, aiming at ASCT. In enteropathy-associated T-cell lymphoma (EATL), IVE/ MTX (ifosphamide, vincristine, etoposide, and methotrexate) followed by ASCT has shown promising results in the first-line setting. In addition, CHOEP-14 consolidated with ASCT has shown improved outcomes compared with standard CHOP. In natural killer/T-cell lymphoma (NKTCL), SMILE (dexamethasone, methotrexate, ifosphamide, L-asparaginase, etoposide) is an option in the first-line and relapse settings. For hepatosplenic T-cell lymphoma (HSTCL), regimens such as ICE and CHEOP have been proposed in the first-line setting.

Schmitz et al. (2010) also reviews evidence which suggests that CHEOP is associated with better efficacy than CHOP for younger patients with ALK-positive ALCL, and to some extent other T- cell lymphomas.

Overall, the MAH has provided sufficient evidence to support the clinical use of etoposide in the above NHL subtypes, which make up the majority of NHL sub-types. The CHMP agreed that there is evidence

of efficacy and acceptable safety in first-line and/or relapse settings, in combination with other agents. The MAH has removed specifications regarding line of treatment from the indication wording.

Paediatric population

The MAH has identified published clinical studies including over 1000 paediatric NHL patients treated with etoposide since 1989. As summarised by the MAH, several major study groups have included etoposide as a component of clinical trial chemotherapy regimens. Selected examples are described below.

The Children's Cancer Group (CCG) study CCG-5912 used DECAL (dexamethasone, etoposide, cisplatin, cytarabine, and L-asparaginase) in 68 children ≤ 21 years with recurrent NHL. The etoposide dose was 100 mg/m^2 at hours 0, 12, 24 and 36. A response was reported for 29 (42%), including 23 complete responses. Maintenance therapy also included etoposide (100 mg/m^2/day on days 1-5 in combination with ifosfamide and mesna. 5-year EFS was 23% and 5 year survival was 30%.

An international study group consisting of CCG, Société Française d'Oncologie Pédiatrique (SFOP) and UK Children's Cancer Study Group (UKCCSG) evaluated 217 children ≤ 18 years with higher-risk B-cell NHL (Cairo et al. 2007). After induction therapy, patients responding to induction therapy received standard or reduced intensity intensification therapy with cytarabine, etoposide and Ara-C. The dose of etoposide was 100 mg or 200 mg/m^2/day on days 2-5, according to the randomisation schedule. The 4 year EFS was 90% (±3.1%) for the standard regimen compared to 80% (±4.2%) for the lower intensity regimen.

The BFM Group study NHL-BFM95 was designed to investigate two methotrexate regimens in children with B-cell NHL and acute B-cell leukaemia (B-ALL). From 1996 to 2001, 505 eligible patients were enrolled. Lower risk groups received induction therapy which included etoposide 100 mg/m^2/day on days 4-5. Higher risk groups received induction therapy which included etoposide 100 mg/m^2/day on days 3-5. The 3-year EFS was 89% ±1% for the total group.

The COG reported the results of a study of rituximab in combination with standard chemotherapy (FAB/LMB 96) in 40 evaluable children (age 3-23, 80% of patients were between 4 and 15 years) with Burkitt lymphoma and combined CNS and bone marrow involvement (Goldman et al. 2014). This study included etoposide + cytarabine as the consolidation regimen. The 3-year EFS/OS was 90% (95% CI: 76–96%) in the entire cohort.

Kung et al. (1999) reported the use of ICE (ifosfamide, carboplatin, etoposide) as a salvaging regimen in recurrent NHL. The etoposide dose was 100 mg/m^2/day on days 1-3. From 1990 to 1993, 21 evaluable patients aged 2 to 20 years were treated. The overall remission rate was 71% (15 patients), with 43% CRs and 28% PRs.

The Berlin–Frankfurt–Münster (BFM) group conducted trial NHL-BFM 90 to investigate tailored intensification of therapy. A total of 431 children ≤ 18 years with B-NHL or B-ALL were enrolled from 1990 to 1995. All patients received induction treatment that included etoposide (100 mg/m^2/day on days 4-5). Consolidation for higher risk patients included etoposide 100 mg/m^2/day on days 3-5. At a median follow-up of 4.2 years, the estimate for EFS was 88% ± 2%. In the same trial, 89 children ≤ 18 years with anaplastic large-cell lymphoma (ALCL) were treated with induction therapy included etoposide as part of combination chemotherapy. The dose of etoposide was 100 mg/m^2/day on days 4-5. For high risk patients, higher dose therapy was also given, including etoposide 150 mg/m^2/day for days 3-5. The Kaplan-Meier estimate for a 5-year event-free survival was 76% ± 5% for all patients.

Cairo et al. 2016 reports the outcome of the 5th international symposium on childhood, adolescent and young adult NHL. In recurrent/refractory B-NHL, rituximab has been successful in combination with ICE (ifosfamide, carboplatin, etoposide).

The submitted evidence demonstrates that etoposide is an established component of chemotherapy regimens used in B-NHL, recurrent/refractory NHL, Burkitt lymphoma, and ALCL. The MAH also refers to the NIH guideline which recommends DECAL or ICE for recurrent Burkitt and Burkitt-like lymphoma/leukaemia and Diffuse Large B-cell Lymphoma (DLBCL). In addition, DA-EPOCH-R (including etoposide) is currently being studied in children with primary mediastinal B-cell lymphoma (ClinicalTrials.gov number, NCT01516567).

The CHMP agreed that the MAH has submitted adequate evidence for the extension of the NHL indication to the paediatric population and the adequate dose recommendation.

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

Acute myeloid leukaemia

Etoposide is approved for the combination treatment of acute myeloid leukaemia (AML) in DE, FR and SE. Etoposide is not currently marketed for AML in UK. The MAH provided a comprehensive review of the available evidence to support an indication in AML.

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 MRD-negative intermediate risk AML, and for whom autologous 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. as discussed by the MAH and as mentioned in a recent review article on the treatment of AML Döhner et al. (1995).

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 agreed that the available evidence supports an indication in adult AML, both in the first-line and relapsed/refractory settings. The MAH has removed specifications regarding line of treatment from the indication wording.

Paediatric population

The MAH has identified published clinical studies including almost 10,000 paediatric AML patients treated with etoposide since 1979. This includes induction and consolidation therapy in *de novo*, refractory and relapsed patients. As summarised by the MAH, several major study groups have used etoposide as an established component of clinical trial chemotherapy regimens.

The Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) AML 2002/01 trial enrolled 504 children aged 0-18 years with *de novo* AML. High risk patients were treated with haematopoietic stem cell transplant (HSCT). All patients, irrespective of the risk group, were given 2 courses of induction chemotherapy, including ICE (idarubicin, cytarabine, and etoposide 100 mg/m^2/day on days 1-5). Consolidation therapy also included etoposide (125 mg/m^2/day on days 2-5).

The BFM group have conducted several studies in paediatric AML, including AML-BFM 83, AML-BFM 87 and AML-BFM 93, in which the induction cycle consisted of ADE (cytarabine, daunorubicin, and etoposide 150 mg/m^2/day on days 6-8) for a total of 960 patients aged 0-17. Although these studies were not designed to investigate the efficacy of etoposide, an improvement in long-term survival was observed after introduction of the ADE regimen. More recently, this group also conducted a randomised trial of liposomal daunorubicin in relapsed or refractory AML in 394 patients less than 21 years. High intensity consolidation therapy, if required, included cytarabine and etoposide (100 mg/m^2 twice daily for 4 days).

During 2006-2010, the Children's Oncology Group (COG) conducted trial AAML0531 which enrolled 1070 patients aged 0-29 years with untreated primary AML. Patients were randomised to standard therapy with or without gemtuzumab ozogamicin (GO). All patients received ICE (including etoposide 100 mg/m2/day on days 1-5) as induction therapy and cytarabine + etoposide (150 mg/m^2/day on days 1-5) as intensification course. 3-year overall survival was 69.4% for the GO arm compared to 65.4% for the non-GO arm.

The Japanese Childhood AML Cooperative Study Group (JPLSG) conducted trial AML99 which enrolled 240 children with *de novo* AML. Low risk children were treated with chemotherapy alone (not HSCT). The induction regimen included etoposide 150 mg/m^2/day on days 1-5. The 5-year overall survival was 75.6%.

The UK Medical Research Council (MRC) enrolled 359 children aged < 15 years with AML (*de novo* and secondary) into the MRC AML10 trial between 1988 and 1995. This study included a randomised comparison of etoposide versus thioguanine for 286 children: patients were randomised to receive 2 induction courses of DAT (daunorubicin, Ara-C and 6-thioguanine) or ADE (daunorubicin, Ara-C and etoposide). The etoposide dose was 100 mg/m^2/day on days 1-5. All patients who went into remission received consolidation that also included etoposide. Survival 7 years after entry was 58% for DAT vs. 50% on ADE (p=0.2). Although not formally a non-inferiority study, this study provides evidence that ADE has comparable efficacy to DAT in paediatric AML. The 'MRC AML10' regimen is current standard of care for induction (Rubnitz et al. 2017).

The MRC AML12/DCOG ANLL97 protocol which enrolled children with AML between 2000 and 2004 consisted of randomised allocation to induction with 2 courses of ADE or MAE (mitoxantrone, Ara-C, etoposide). This was followed by a 3rd course of MACE (amsacrin, Ara-C, etoposide).

The Nordic Society of Paediatric Haematology and Oncology (NOPHO) conducted study NOPHO-AML 93 in 243 children with AML between 1993 and 2001 in which induction was with ATEDox (Ara-C, 6-thioguanine, etoposide 100 mg/m^2/day on days 1-4, doxorubicin). The consolidation regimen also included etoposide. The 5-year survival was 65%.

The European Organization of Research and Treatment of Cancer (EORTC) Children Leukaemia Group conducted study 58921 which was a randomised comparison of the combination idarubici, etoposide, Ara-C and of mitoxantrone, etoposide, Ara-C for induction in 177 patients with childhood AML between 1992 and 2002. Etoposide was also included in the intensification regimen. The dose of etoposide was 150 mg/m^2/day on days 6-8 for induction and 125 mg/m^2/ day on days 2-5 for consolidation. The 5-year survival rate was 62%.

In conclusion, studies conducted by major groups provide evidence that etoposide is an established component of standard induction and intensification regimens for paediatric AML. The CHMP agreed that the MAH has submitted adequate evidence for the extension of the HL indication to the paediatric population and the adequate dose recommendation.

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

Gestational trophoblastic neoplasia

An indication in gestational trophoblastic neoplasia (GTN) 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 harmonised text.

According to the current ESMO guidelines since 2002 all GTN patients should be staged using FIGO system. For patients with high risk > or = 7 several multidrug different multiagent therapies have been developed including: Methotrexate (MTX), folinic acid (FA) and actinomycin D (ActD): MFA ; MTX, ActD, cyclophosphamide, doxorubicin, melphalan, hydroxyurea and vincristine: CHAMOCA; MTX, ActD and cyclophosphamide: MAC; etoposide, MTX and ActD: EMA and others. At Charing Cross Hospital a regimen was developed consisting of EMA alternating weekly with cyclophosphamide and vincristine (EMA-CO). This has been widely adopted worldwide. A retrospective comparison in 227 patients from the Korean GTD centre's experience of MFA, MAC, CHAMOCA with EMA-CO demonstrated a remission rate of 63.3% (31 of 49), 67.5% (27 of 40), 76.2% (32 of 45) and 90.6% (87 of 96), respectively Kim et al. (1998). In the 272 cases at Charing Cross Hospital treated between 1979 and 1995, OS was 86.2% [95% confidence interval (CI) 81.9% to 90.5%].While these results were good, the presence of liver or brain metastases correlated with only 27% or 70% long-term survival Bower et al. (1997).This was associated with death from haemorrhage or metabolic complications of overwhelming disease within 4 weeks of admission and/or before adequate chemotherapy could be given. To reduce early deaths in patients with very advanced disease, they found that commencing chemotherapy gently with low-dose etoposide 100 mg/m2 and cisplatin 20 mg/m2 on days 1 and 2 repeated weekly for 1–3 weeks has virtually eliminated this problem. Indeed, low-dose induction etoposide and cisplatin combined with genetic testing to exclude non gestational trophoblastic tumors (nGTTs) has helped to improve long-term OS data to over 94% in high-risk patients. About 20% of high-risk GTN patients will progress on or after primary chemotherapy, but these individuals will still have an excellent outcome with ~75%–80% being salvaged. Patients receiving etoposide, methotrexate, and dactinomycin alternating weekly with cyclophosphamide and vincristine (EMA/CO) were identified using the Charing Cross GTN database. Four hundred thirty-eight patients received EMA/CO between 1995 and 2010. Six patients had nGTTs and all died. GTN patients OS was 94.3% in high-risk patients and 99.6% in the low-risk group, with a median follow-up time of 4.2 years. Seven patients with high-risk GTNs died as a result of drug-resistant disease. Etoposide and cisplatin (EP) induction chemotherapy was given to

23.1% of high-risk patients (33 of 140 patients) with a large disease burden, and the early death rate was only 0.7% compared with 7.2% in the pre-1995 cohort. 432 GTN patients were evaluated, 171 patients received the EMA/CO in first line setting and 261 patients received the EMA /CO regimen in second line setting, 423 out of 432 patients were considered cured (Alifrangis et al. 2013).

The combination of EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine) is currently the most widely used first-line combination chemotherapy regimen for high-risk gestational trophoblastic neoplasia (GTN), although this regimen has not been rigorously compared to other combinations such as MAC (methotrexate, actinomycin D and chlorambucil) or FAV (5-FU, actinomycin D and vincristine) in randomised controlled trials (reviewed in Deng et al. 2013, Cochrane Database Syst Rev. 2013 Jan 31;[1]:CD005196). It is recognised, however, that given the low incidence of GTN randomised controlled trials in this field are difficult to conduct.

In conclusion, the CHMP agreed that there is adequate evidence to support an indication in gestational trophoblastic neoplasia for etoposide as part of combination chemotherapy.

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 authorised indications that were not initially proposed for the harmonised 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, randomized 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

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

Table 4: Current dosage recommendations, by country

Country	Dosage Recommendation
France	Doses shall be between 50 and 150 mg/m^2 per 24 hours, most often over 1 to 3 days depending on the protocol used. In therapeutic intensification protocols (acute leukaemia, malignant lymphoma): -40 to 60 mg/kg in a single daily dose when ETOPHOS® is combined with fractionated total body irradiation -40 mg/kg in a single daily dose or between 300 mg and 400 mg/m^2 over three consecutive days when ETOPHOS® is combined with other chemotherapies, 3 to 8 days prior to transplant, in an infusion over 4 hours
Germany	In children and adults, ETOPOPHOS 1000 mg is given at the following dosage: -56.8 to 113.6 mg etoposide phosphate/m^2 body surface/day (corresponding to 50 to 100 mg etoposide/m^2 body surface) on days 1 to 5 or -136.2 to 170.4 mg etoposide phosphate/m^2 body surface (corresponding to 120 to 150 mg etoposide/m^2 body surface) on days 1, 3 and 5.
Sweden	The dosage of Etopofos is 50-100 mg/m^2 body surface area daily for five days or 100 mg/m^2 per day on days 1, 3 and 5 every 3-4 week in combination with other suitable chemotherapy.
United Kingdom	The recommended course of Etopophos Injection is 60-120 mg/m², (etoposide equivalent) i.v. daily for five consecutive days. As Etopophos produces myelosuppression, courses should not be repeated more frequently than at 21 day intervals.

The harmonised, proposed text reflects the recommendations of the MAH. The MAH refers to a Phase 1 study (Budman et al 1994) evaluating etoposide phosphate given as a 5-minute infusion on days 1, 3 and 5 every 21 days in patients with solid tumours. The doses evaluated were 50, 75, 100, 125, 175 and 200 mg/m2/day. The MTD was 179 to 200 mg/m2/day. Slevin et al. (1989) conducted a randomized trial to evaluate the effect of schedule on the activity of etoposide in SCLC. 500 mg/m2 as a continuous IV infusion over 24 hours was compared to five consecutive daily 2-hour IV infusions of 100 mg/m2. Both regimens were repeated every 3 weeks for a maximum of 6 cycles. The 5-daily schedule was superior to the 24-hour infusion: response rate 89% vs. 10%

The MAH was requested to further justify the dosing recommendations in light of the data that support the different indications, and relevant guidelines. The proposed dosing recommendation of 50 to 100 mg/m2 /day on days 1-5, every 3 to 4 weeks, is considered to be in line with the current clinical practice guidelines and the most widely used treatment regimens in which etoposide is administered on days 1-5. However, when etoposide is administered on three days (e.g. day 1, 3, and 5), the daily dose that is most commonly used can be either 100 or 120 mg/m2.

Paediatric population

The paediatric posology has been adequately justified, based on literature data, for the HL, NHL and AML indications as described in section 4.1 above.

Renal impairment

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

The SmPCs of DE and SE recommend a starting dose reduction (75% of the normal dose) in patients with moderate renal impairment (15 - 50 ml/min). These sub-populations are not mentioned in the posology section of the SmPCs of France or the United Kingdom.

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 $\geqslant$ 10ml/min. Arbuck et al 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 $\geqslant$ 70 ml/ min/ 1.73 m2 and nine patients with a creatinine clearance of < 70 ml/ min/1.73 m2. 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 Fissell 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. It is agreed with the MAH that the totality of the available evidence supports the proposal not to recommend a dose reduction when creatinine clearance is > 50 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. D'Incalci et al (1986), Pfluger et al. (1993) and Joel (1996) have generated data which demonstrates a lower clearance, longer half-life and increased the area under the plasma concentration-time curve (AUC) in patients with renal impairment compared to those

with normal renal function. In a review, Joel et al. (1994) presents evidence that steady state plasma concentrations, AUC and clearance correlate with haematological toxicity. A dose reduction of 25% in renal impairment (creatinine clearance 15-50 mL/min) 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.

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 phosphate use, by country

Contraindication	Countries
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.	France, Germany, Sweden, United Kingdom
Concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients (see section 4.5).	Germany, Sweden
Myelosuppression	
Severe hepatic impairment	Germany, United Kingdom
Severe renal impairment (Creatinine-clearance <15 ml/min)	Germany
Pregnancy	France, Germany
Lactation	France, Sweden
Myocardial infarction	Germany
Low serum albumin	Germany
Active infection	Germany
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 use of live vaccines as a contraindication is agreed, as immunosuppression is a common side effect of etoposide (listed as very common in the proposed SmPC). 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, in line with the national SmPC of DE. 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

Myelosuppression

Myelosuppression is the dose limiting toxicity of etoposide. The SmPCs of DE and SE include warnings that severe myelosuppression with resulting infection or bleeding may occur. The SmPC of SE also includes the warning that fatal myelosuppression has been reported, and that patients should be monitored for myelosuppression; this warning is stated in the SmPC of DE under 'contraindications'. In the SmPC of the UK, a warning to monitor peripheral blood counts and liver function is included in section 4.8. 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 the national SmPCs of DE, SE and UK.

Hypersensitivity

Text regarding the risk of hypersensitivity is included in all current national SmPCs except UK.

Injection site reaction

The SmPC of SE states that *"ETOPOPHOS should be given only by slow intravenous infusion (usually over a 30 to 60 minute period) since hypotension has been reported as a possible side effect of rapid intravenous injection."* The SmPCs of FR, DE and the UK also include language about the potential for hypotension in other sections of their SmPCs.

All SmPCs include warnings regarding the possibility of extravasation.

Low serum albumin

Text regarding the association of low serum albumin with increased toxicities is included in current national SmPCs of DE and SE.

Impaired renal and hepatic function

Etoposide is partially metabolized 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.

Section 4.4 of the current national SmPC of SE states 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 SmPC of DE. Severe hepatic dysfunction is a contraindication in the UK. Section 5.2 of the SmPC of FR includes information about reduced clearance in renal impairment.

The latest proposals for warnings regarding impaired renal and hepatic function are acceptable.

Tumour lysis syndrome

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

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 DE, SE and UK already include a statement regarding mutagenic potential. The warning is acceptable.

The final agreed wording for section 4.4 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. The text proposed for section 4.5 has also been included in section 4.5 of the final core safety profile (CSP) following the PSUR review under the worksharing procedure with Denmark as the P-RMS (DK/H/PSUR/0029/001), except the paragraph related to the administration of etoposide phosphate with drugs that are known to inhibit phosphatase activity.

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 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."* No statement regarding fertility is provided in section 4.6 of the SmPCs of DE or UK.

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.

Pregnancy

The use of etoposide during pregnancy is contraindicated in the SmPCs of FR and SE. The labels of DE 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 paragraph on pregnancy should start with clinical information. Adequate and well-controlled studies are not expected, and their absence is not informing the prescribers. A very limited number of outcomes are available, which might reflect that we do not really know what the toxicological effects during pregnancy are.

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).

Breastfeeding

The administration of Etopophos during lactation is contraindicated in FR and SE. All 4 national SmPCs indicate that it is not known whether these drugs are excreted in human milk. The SmPC of DE states that during treatment with Etopophos, mothers must not nurse their babies because it is unknown whether etoposide is excreted into human milk.

Etoposide is excreted in the milk (Medications and Mothers' Milk by Thomas W. Hale, 1998). Lactation should be included as a contraindication, since breastfeeding women could replace breastfeeding by dairy products to feed their child (see also section 4.3). A recommendation to discontinue breast-feeding or discontinue etoposide is appropriate.

The breast-feeding text has been amended in line with the *Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling – Appendix 3.*

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 section 4.6 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 phosphate 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 SmPCs of FR and SE indicate that it has not been demonstrated that the administration of etoposide phosphate modifies the ability to drive vehicles or use machines. The SmPC of SE also states 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 to operate machines. The SmPC of UK provides no information in this section.

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 harmonized 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 utilized single agent etoposide therapy.

Some national SmPCs include adverse drug reactions (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, headache, chest pain, hyperkinesia, akinesia, hyperuricaemia and metabolic acidosis. 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 allergic reactions has been expanded to include information on the occurrence of apnoea with spontaneous resumption of breathing following cessation of infusion. This information is already available in the SmPCs of FR and UK. As such cases have indeed been reported in the context of hypersensitivity reactions with etoposide phosphate, the inclusion of this information in section 4.8 of the harmonised SmPC is justified. The paragraph of Haematological Toxicity has been expanded with information that bleeding has been reported, information that 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. Signs/ symptoms of hypersensitivity reaction have also been added. The justification for not including headache and confusional state is agreed.

The MAH has completed a review of the published studies for etoposide in an attempt to estimate the frequency for all ADR terms. The MAH has re-calculated the frequencies for some ADRs where previously the frequency was unknown. This is based on the Integrated Safety Summary (ISS) for etoposide monotherapy. This approach is acceptable. Frequencies have been re-calculated for infection, haemorrhage, alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, and bilirubin increased (see attached annotated product information document).

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. The MedDRA LLT “rigors” is considered to be covered by the PT “chills” and has therefore been omitted, while the term “fever” is not a MedDRA term and has been replaced by the PT “pyrexia”. The 3 paragraphs under *Hypersensitivity* have been re-ordered in order of decreasing 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”. “Loss of consciousness” has been replaced by the PT “syncope”.

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 SmPCs of all MSs state that no antidote is available and suggest symptomatic, supportive treatment in case of overdose, with close monitoring of patients during treatment. Also, all SmPCs

indicate that metabolic acidosis and cases of serious hepatic toxicity have been reported in patients receiving higher than recommended intravenous doses of etoposide phosphate.

The sentence *"Etoposide and its metabolites are not dialysable"* appears in the SmPC of FR, and has been retained for the harmonized SmPC based on results published by Sauer et al. who assayed in vitro cytostatic drugs for their dialyzability. They determined that effective removal of epipodophyllotoxins including etoposide by any extracorporeal therapy cannot be expected because of high volume of distribution, very long plasma half-lives, high metabolic rates and poor in vitro dialysability. Failure of hemodialysis to remove etoposide in a dialysis patient was reported by 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 SmPCs of DE, SE and UK state that following intravenous administration, etoposide phosphate is rapidly and completely converted to etoposide in plasma. All 4 SmPCs state the following. A direct comparison of the pharmacokinetic parameters (AUC and CMAX) of etoposide following intravenous administration of molar equivalent doses of Etopophos and etoposide was made in two randomised cross-over studies in patients. Results from both studies demonstrated no statistically significant differences in the AUC and CMAX for etoposide when administered as Etopophos or etoposide. No differences were seen in haematological toxicity after the administration of Etopophos compared to Vepesid.

All 4 MS SmPCs report that in vitro, etoposide is highly protein bound (94-97%) to human plasma proteins. The UK SmPC describes a study that investigated the effects of other therapeutic agents on in vitro binding of 14C etoposide to human serum proteins. In that study, only phenylbutazone, sodium salicylate, and aspirin displaced protein-bound etoposide at concentrations generally achieved in vivo.

In the SmPCs of DE and FR, the AUC is described as increasing linearly with the administered etoposide-dose, after intravenous administration.

Currently, the biotransformation of etoposide phosphate is only discussed in the SmPC of DE.

The fact that etoposide is cleared by both renal and non-renal processes is reflected in each of the 4 national SmPCs. The SmPCs of SE and UK further explain that metabolic conversion accounts for the main portion of the non-renal elimination of etoposide.

Section 5.2 has been updated as it addressed poor overall structure and duplicate information, and is now 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 Etopophos 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:

- 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^2/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^2 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^2/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 (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) 15-50 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). This has been addressed by a warning in section 4.2 of the SmPC.

Hypersensitivity has been added as a 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 on risk assessment of medicinal products on human reproduction and lactation: from data to labelling – Appendix 3*. 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.

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 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.

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