TENIPOSIDE

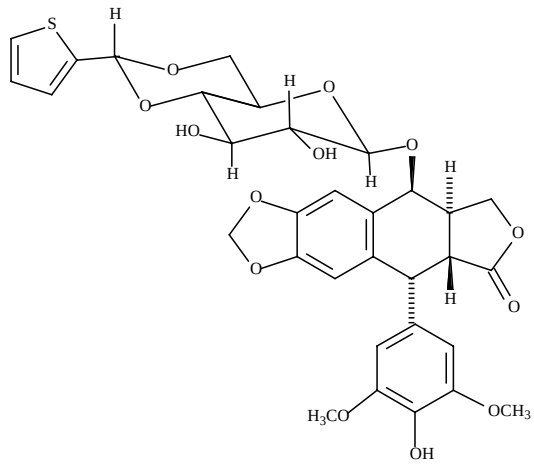
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 29767-20-2
Chem. Abstr. Name: (5*R*,5a*R*,8a*R*,9*S*)-5,8,8a,9-Tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-{[4,6-*O*-[(*R*)-2-thienylmethylene]-β-D-glucopyranosyl]oxy}-furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one
IUPAC Systematic Name: 4′-Demethylepipodophyllotoxin, 9-(4,6-O-2-thenylidene-β-D-glucopyranoside)
Synonyms: Epipodophyllotoxin; EPT; teniposide VM-26; VM 26; 5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-{[4,6-*O*-(2-thienylmethylene)-β-D-glucopyranosyl]oxy}furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{32}H_{32}O_{13}S$ Relative molecular mass: 656.67

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White, crystalline solid (Gennaro, 1995; Budavari, 1996)

(*b*) *Melting-point*: 242–246 °C (Gennaro, 1995; Budavari, 1996)
(*c*) *Spectroscopy data*: Ultraviolet, infrared, fluorescence emission, nuclear magnetic resonance (proton and ^{13}C) and mass spectral data have been reported (Kettenes-van den Bosch *et al*., 1990).
(*d*) *Solubility*: Insoluble in water and diethyl ether; slightly soluble in methanol; very soluble in acetone and dimethylformamide (Medical Economics Data Production, 1999)
(*e*) *Optical rotation*: $[\alpha]_D^{20}$, –107° (9:1, chloroform/methanol) (Budavari, 1996)
(*f*) *Dissociation constant*: pK_a, 10.13 (Budavari, 1996)

1.1.4 *Technical products and impurities*

Teniposide is available as a 10-mg/mL injection solution. It is poorly soluble, and the 50-mg intravenous preparation typically also contains benzyl alcohol (0.15 g), *N*,*N*-dimethylacetamide (0.3 g), polyethoxylated castor oil (2.5 g), maleic acid to a pH of 5.1 and absolute ethanol to 5 mL (Gennaro, 1995; American Hospital Formulary Service, 1997; Canadian Pharmaceutical Association, 1997; LINFO Läkemedelsinformation AB, 1998; Rote Liste Sekretariat, 1998; Thomas, 1998; Medical Economics Data Production, 1999).

Trade names for teniposide include Vehem, Vehem-Sandoz, Vumon and Vumon Parenteral (Royal Pharmaceutical Society of Great Britain, 1999; Swiss Pharmaceutical Society, 1999).

1.1.5 *Analysis*

Standard analytical methods have not been established for teniposide. The methods for the analysis of teniposide in various matrices include high-performance liquid chromatography, thin-layer and paper chromatography and radioimmunoassay (Kettenes-van den Bosch *et al*., 1990).

1.2 Production

Teniposide is prepared from etoposide by reaction with 2-thiophene carboxaldehyde, with zinc chloride as the catalyst (Kettenes-van den Bosch *et al*., 1990).

Information available in 1999 indicated that teniposide is manufactured and/or formulated in 24 countries (CIS Information Services, 1998; Royal Pharmaceutical Society of Great Britain; 1999; Swiss Pharmaceutical Society, 1999).

1.3 Use

Teniposide is a semi-synthetic derivative of podophyllotoxin, an extract of the roots and rhizomes of two plant species that have been used in folk medicine for

several hundred years. It inhibits DNA topoisomerase II (Imbert, 1998). During early clinical trials for cancer chemotherapeutic use, podophyllotoxin itself proved to be too toxic, and, in the 1960s, two epipodophyllotoxins, teniposide and etoposide (see monograph, this volume), were described (Keller-Juslén *et al.*, 1971). The first clinical trial of teniposide in cancer treatment was reported in 1967. Marketing of teniposide in several countries began in 1976 (Imbert, 1998).

Teniposide is used in the treatment of adult and childhood leukaemia, typically at doses of 30–50 mg/m^2 per day for five days or three doses of about 200 mg/m^2 over seven days. The drug is also used in the treatment of brain tumours in adults and neuroblastoma in children. Teniposide is active against a number of other tumour types, including small-cell and non-small-cell lung cancer, lymphomas and bladder cancer. It is used much less commonly than the related drug etoposide (Giaccone, 1992; Giaccone *et al.*, 1992; Hirsch *et al.*, 1994; Muggia, 1994; Rivera *et al.*, 1994).

1.4 Occurrence

Teniposide is not known to occur as a natural product. No data on occupational exposure were available to the Working Group.

1.5 Regulations and guidelines

Teniposide is not listed in any international pharmacopoeias.

2. Studies of Cancer in Humans

This section summarizes only studies in which tepinoside was given without agents with known or suspected leukaemogenic properties. In studies in which patients were treated with both tepinoside and etoposide, the authors used various conversion factors to derive an ‘equivalent dose’ of etoposide from that of teniposide. The conversions were based, however, on the therapeutic effects rather than on metabolic considerations.

2.1 Cohort studies

Sixty-two children in Spain in whom acute lymphoblastic leukaemia was newly diagnosed between 1985 and 1988 were initially treated with teniposide (165 mg/m^2), cytarabine, vincristine, L-asparaginase and prednisone and subsequently with teniposide (165 mg/m^2), cytarabine, vincristine, cranial irradiation, mercaptopurine, methothrexate and prednisone (Verdeguer *et al.*, 1992). Of 60 patients in whom complete remission was achieved, 14 suffered a bone-marrow relapse. During treatment, acute myeloid

leukaemia developed in three of these patients (two cases of acute monoblastic leukaemia, one of acute myelomonocytic leukaemia). Thus, the frequency of conversion from acute lymphoblastic leukaemia to acute myeloid leukaemia was 3/60. The time from diagnosis to conversion was 17, 23 and 29 months. The authors noted that 45 children with non-T-cell acute lymphoblastic leukaemia were treated between 1981 and 1984 with a regimen that did not include teniposide and cytarabine, and no cases of acute myeloid leukaemia were observed at relapse. [The Working Group noted that it is difficult to establish the difference between lineage switch and mixed-lineage leukaemia. Tests for myeloid marker cells had not been performed at initial diagnosis in any of the three cases reported. No appropriate comparison of leukaemia risk between the two treatment groups was made.]

In the study of Pui *et al*. (1991), described in the monograph on etoposide, acute myeloid leukaemia developed in 20 out of 580 children treated with teniposide with or without etoposide for acute lymphoblastic leukaemia; one case was found in a patient treated with neither etoposide nor teniposide. The overall cumulative risk was 3.8% at six years. The median interval between the diagnoses of acute lymphoblastic leukaemia and acute myeloid leukaemia was 40 months. Six cases were acute myelomonocytic leukaemia, eight were acute monoblastic leukaemia, three were acute myeloblastic leukaemia, one was acute megakaryoblastic leukaemia, one was acute myeloid leukaemia and two were acute undifferentiated leukaemia. In four patients, acute myeloid leukaemia developed after relapse had occurred, and these were not included in the analysis. In the analysis of leukaemia risk, the doses of teniposide and etoposide were weighted equally since the potency of teniposide *in vitro*—10 times that of etoposide—is offset *in vitro* by extensive protein binding, resulting in 10 times less unbound active drug. The analyses indicated the importance of the schedule and frequency of epipodophyllotoxin treatment in determining the risk for acute myeloid leukaemia (see Table 1).

In a combined analysis of 12 trials in patients with various primary tumours who developed acute myeloid leukaemia after treatment with epipodophyllotoxins (Smith *et al*., 1999), described in the monograph on etoposide, the six-year actuarial risks for acute myeloid leukaemia or myelodysplastic syndrome were 3.3% (upper 95% confidence bound, 5.9%) with the low cumulative dose of epipodophyllotoxin, 0.7% (upper 95% confidence bound, 1.6%) with the moderate cumulative dose and 2.2% (upper 95% confidence bound, 4.6%) with the high cumulative dose. The *p* values for homogeneity of the risk for leukaemia across the cumulative dose strata were 0.012 (with a parametric test) and 0.011 (with a non-parametric test). In one of the trials, 251 patients with primary acute lymphoblastic leukaemia received only teniposide as three courses of 165 mg/m^2 for two days, for a cumulative dose of 990 mg/m^2, corresponding to a moderate cumulative dose of epipodophyllotoxin. No cases of leukaemia were observed. Thus, the data provide no support for an effect of the cumulative dose of epipodophyllotoxins on leukaemogenic activity, at least not within the cumulative dose range encompassed by the monitoring plan. [The Working Group noted that the

Table 1. Risks for secondary acute myeloid leukaemia (AML) in children with acute lymphoblastic leukaemia treated with epipodophyllotoxins, according to regimen

Regimen	Prognosis	Planned cumulative dose (mg/m^2)		Epipodophyllotoxin schedule	No. of patients treated	No. of patients with AML	Six-year cumulative risk % (95% CI)
		Teniposide	Etoposide				
X-LR1	Low risk	0	0	None	154	1	1.0 (0.6–6.3)
X-LR2	Low risk	1350	0	Every other week	155	1	1.1 (0.1–7.1)
X-HR	High risk	4620	0	Twice weekly	85	6	12 (5.7–25)
XI-LR1	Low risk	600	0	Induction only	39	0	0
XI-LR2	Low risk	5100	9000	Every other week	69	0	0
XI-HR2	High risk	5100	9000	Every other week	148	2	1.6 (0.4–6.1)
XI-HR3	High risk	5100	9000	Weekly	84	7	12 (6.1–24)

From Pui *et al.* (1991)
CI, confidence interval

three treatment strata were compared as if the cumulative dose of epipodophyllotoxin were the only difference between them; however, the strata also differed with respect to the primary tumour (stratum with solid tumours versus stratum with solid and lymphoid tumours) and treatment; one stratum with high-dose epipodophyllotoxin and high-dose cyclophosphamide versus a stratum with no cyclophosphamide and a moderate dose of epipodophyllotoxin and a stratum with high-dose cyclophosphamide given to part (one trial) of the stratum with low-dose epipodophyllotoxin. It is also not clear which patients received teniposide and which received etoposide.]

Negligible risks for acute myeloid leukaemia were reported in two large series of children with acute lymphoblastic leukaemia who received treatments without epipodophyllotoxins (Neglia *et al*., 1991; Kreissman *et al*., 1992). The patients in these series received treatments similar to those in the study by Pui *et al*. (1991): most received cranial irradiation, all received methotrexate, 6-mercaptopurine, prednisone, vincristine and L-asparaginase, and a substantial proportion received cyclophosphamide and doxorubicin. Neglia *et al*. (1991) reported only two cases of acute myeloid leukaemia among 9720 children treated according to protocols of the US Children's Cancer Study Group between 1972 and 1988. The median follow-up was 4.7 years. Kreissman *et al*. (1992) reported two cases of acute myeloid leukaemia in 779 children treated for acute lymphoblastic leukaemia at the Dana Farber Cancer Institute, Boston, USA. The median follow-up time was 4.4 years. The estimated overall risk for secondary acute myeloid leukaemia was 0.61 per 1000 patient–years of follow-up, which was significantly lower (p = 0.0008) than the reported risk of 5.8 per 1000 patient–years for patients with acute lymphoblastic leukaemia in the study of Pui *et al.* (1989) who were treated with epipodophyllotoxins.

2.2 Case–control studies

Hawkins *et al*. (1992) reported the results of a case–control study of secondary leukaemia nested in a cohort of 16 422 children aged < 15 years who had survived at least one year after a diagnosis of a childhood neoplasm in the United Kingdom between 1962 and 1983. The mean follow-up period beyond one year of survival for the entire cohort was 7.7 years. Twenty-six cases of secondary leukaemia occurring after diagnosis of the initial childhood neoplasm between 1940 and 1983 were each matched with up to four controls for sex, histological type of first cancer and age at first diagnosis. In addition, the controls had to have survived free of any second primary neoplasm for at least as long as the interval between the first primary neoplasm and secondary leukaemia in the corresponding case. Ninety-six controls were selected. Of those patients receiving chemotherapy (69% of cases, 55% of controls), 77% had received alkylating agents, 51% antibiotics, 54% antimetabolites, 97% vinca alkaloids and 30% epipodophyllotoxins. Ten patients with leukaemia had received epipodophyllotoxins during their treatment: nine had received teniposide and one had received etoposide. Two methods were used to categorize the doses of epipodophyllotoxins and

the other groups of agents: first, a ranking method based on the assumption that all drugs within an etiological group have equal leukaemogenic potency within the corresponding third of their respective dose distributions; secondly, an approach based on the simple assumption that all agents in a particular group have equal leukaemogenic potency for a specified amount of drug given per unit of surface area. Multivariate analysis of the relative risk for leukaemia (adjusted for active bone marrow radiation dose and exposure to alkylating agents) according to the total dose of epipodophyllotoxins estimated by either method showed evidence of a trend ($p = 0.012$ and $p = 0.006$) in the relative risk with dose of epipodophyllotoxins (see Table 2). [The Working Group noted that, even though multivariate analysis was conducted to adjust for confounding by leukaemogenic agents, interaction between epipodophyllotoxins and these agents could not be ruled out.]

Detailed information from the medical records of a cohort of 1939 patients treated for Hodgkin disease between 1966 and 1986 in the Netherlands (van Leeuwen *et al*., 1994) was obtained for 32 cases of acute myeloid leukaemia, 12 cases of myelodysplastic syndrome and 124 matched controls in whom leukaemia had not developed. The controls had to have survived without a second cancer for at least as long as the interval between the diagnosis of Hodgkin disease and leukaemia in the case patient. Controls were matched to the case patient on cancer centre, sex, date of birth and date of diagnosis of Hodgkin disease. In multivariate analyses, all of the relative risks were adjusted for mechlorethamine dose, lomustine, dacarbazine, cyclophosphamide given in combinations, teniposide, interaction between cyclophosphamide and teniposide, splenectomy and number of episodes of chemotherapy. In these analyses, treatment with teniposide (median dose, 300 mg; seven cases, six controls) did not increase the risk for leukaemia (relative risk, 0.9; 95% confidence interval, 0.12–7.0) over that of patients never treated with teniposide. Since only one case patient and two controls received teniposide without cyclophosphamide, however, the independent effect of teniposide on the risk for leukaemia could not be assessed reliably. Treatment with cyclophosphamide alone was not significantly associated with an increased risk for leukaemia. The combination of cyclophosphamide and teniposide, which had been used in six patients who developed leukaemia and four controls, was associated with a strongly increased relative risk (125 000; $p = 0.03$). Most of the patients who received this combination were treated alternately with procarbazine, vincristine, prednisone and nitrogen mustard (MOPP) (see IARC, 1987), cyclophosphamide, doxorubicin, teniposide and prednisone. [The Working Group noted that the increased relative risk was based on very small numbers.]

3. Studies of Cancer in Experimental Animals

No data were available to the Working Group.

Table 2. Risks for acute myeloid leukaemia in children treated for primary neoplasms with epipodophyllotoxins, in relation to dose

Dose of epipodophyllotoxin	No. of leukaemia cases	No. of controls[a]	Adjusted relative risk[b]
Total dose by third of distribution			
0	16	85	1
First	2	5	2.9
Second	4	4	8.4
Third	4	2	24
Total equivalent (mg/m^2)			$p = 0.012$
0	16	85	1
1–750	2	5	2.6
751–1200	3	4	6.6
≥ 1201	5	2	17
Total	26	96	$p = 0.006$

From Hawkins *et al*. (1992)
[a] Patients with childhood malignancies who did not develop leukaemia
[b] Adjusted for radiation dose to the active bone marrow and exposure to alkylating agents

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The pharmacokinetics of teniposide in humans has been summarized (Clark & Slevin, 1987). After intravenous administration of 50–200 mg/m^2, the disposition of the drug typically fitted a two-compartment model, with terminal elimination half-times of 6–10 h (Rossi *et al*., 1984; D'Incalci *et al*., 1985; Gigante *et al*., 1995). Tri-exponential decay has also been reported, with terminal half-times of 26 h after administration of [^{3}H]teniposide (Creaven & Allen, 1975), 20 h after a low intravenous dose of 30 mg/m^2 (Canal *et al*., 1985) and 48 h after doses of ≤ 1000 mg/m^2 (Holthuis *et al*., 1987). The distribution volume of teniposide in these studies was 8–30 L/m^2, indicating that the drug is distributed mainly in the extracellular fluid compartment, with a total plasma clearance rate of 7–17 mL/min per m^2 and a low renal clearance rate of 0.8–2.2 mL/min per m^2 (Clark & Slevin, 1987). The pharmacokinetics of teniposide was linear up to 1000 mg/m^2, the highest dose tested (Holthuis *et al*., 1987).

The pharmacokinetics of teniposide in children is similar to that in adults, with elimination half-times of 9–10.3 h and a total plasma clearance rate of 5–15 mL/min per m^2, but possibly with a smaller distribution volume of 3–10 L/m^2 (Evans *et al*., 1983; Sinkule *et al*., 1984; Rodman *et al*., 1987; Petros *et al*., 1991).

After intravenous infusion of 150 mg/m^2 over 24 h in adults, the peak plasma concentrations were 4–12 μg/mL (D'Incalci *et al*., 1985). In children receiving 450 mg/m^2 over 72 h, 10 of 11 values were between 4 and 13 μg/mL, and the remaining value was 30 μg/mL (Rodman *et al*., 1987).

Considerable variation in the pharmacokinetics of teniposide between patients has been described, which may explain some of the variation in the pharmacodynamics of the drug. Rodman *et al*. (1987) reported a lower plasma clearance rate (12 versus 21 mL/min per m^2) and a longer elimination half-time (12 versus 6.6 h) in responding than in non-responding cancer patients receiving a 72-h teniposide infusion. This resulted in a > 50% increase in systemic exposure, as measured by the steady-state plasma concentration (15.2 versus 6.2 mg/L).

Few studies have investigated the metabolism of teniposide in cancer patients. In children given teniposide, the main metabolite in serum and urine was reported to be the hydroxy acid, formed by opening of the lactone ring; the *cis*-isomer, which may be a degradation product formed during storage, was also detected. The aglycone, formed by loss of the glucopyranoside moiety, was not detected (Evans *et al*., 1982). The hydroxy acid has not been found in plasma or urine in other studies with high doses of teniposide, and no changes in the measured concentration of teniposide in these samples was found after incubation with glucuronidase, indicating formation of little or none of the proposed glucuronide metabolites (Holthuis *et al*., 1987). In another study, however, 6% of the administered dose of teniposide was excreted in the urine as parent drug over 24 h, and a further 8% as a proposed aglycone glucuronide, which was not formally identified (Rossi *et al*., 1984).

In patients given [^{3}H]teniposide, urinary excretion accounted for about 45% of the administered radiolabel and biliary excretion for < 10% (Creaven & Allen, 1975). With high-performance liquid chromatography assays specific for teniposide, urinary excretion accounted for only 4–14% of the dose up to 24 h (Rossi *et al*., 1984; D'Incalci *et al*., 1985; Holthuis *et al*., 1987). The fate of most of an administered dose of teniposide therefore remains unknown.

Teniposide was detected in one patient who died three days after a cumulative intravenous dose of 576 mg, the highest concentrations occurring in the spleen, prostate, heart, large bowel, liver and pancreas. Teniposide was not detected in any tissue from four patients who died 5–52 days (median, eight days) after their last treatment with teniposide, for a cumulative dose of 234–1577 mg, indicating a relatively short tissue half-time (Stewart *et al*., 1993). Teniposide was detected in intracerebral tumours at concentrations of 0.05–1.12 μg/g tissue in 11 patients given 100–150 mg/m^2 teniposide 1.5–3 h before tumour resection. The concentrations in adjacent normal brain tissue

were low (< 0.9 μg/g tissue) in three patients and undetectable (< 0.05 μg/g tissue) in the others (Zucchetti *et al.*, 1991).

After intravenous administration of teniposide, the integrated area under the curve of concentration–time (AUC) in malignant ascites fluid was 12–90% of that measured in plasma (Canal *et al.*, 1985). In one patient in whom serial cerebrospinal fluid and plasma samples were collected after administration of teniposide at doses up to 1000 mg/m^2, the concentrations of the drug in eight samples of cerebrospinal fluid were only 0.03–0.55% of the simultaneous plasma concentrations (mean, 0.17%) (Holthuis *et al.*, 1987). Teniposide was not detected in samples of cerebrospinal fluid collected 97–740 min after dosing of patients with 100–150 mg/m^2 intravenously (Zucchetti *et al.*, 1991). The concentrations in serial saliva samples from two patients were only 0.37% (n = 22) and 0.42% (n = 29) of the corresponding plasma concentrations (Holthuis *et al.*, 1987). These results are in line with the reported protein binding of teniposide of 99% or higher (Allen & Creaven, 1975; Evans *et al.*, 1992). The binding of the drug to protein decreased with decreasing serum albumin concentration and increasing bilirubin concentration, with a resultant increase in free drug, from 0.44 to 1.25% in newly diagnosed and relapsed patients. The percentage decrease in leukocyte count correlated with the AUC for free teniposide rather than with that for total teniposide (Evans *et al.*, 1992).

Concurrent administration of ciclosporin at 5 mg/kg bw over 2 h, followed by 30 mg/kg bw over 48 h intravenously, increased the AUC for teniposide by 50%, due to a reduction in clearance (Toffoli *et al.*, 1997). Conversely, concurrent administration of phenytoin increased the clearance rate of teniposide to 32 mL/min per m^2 from 13 mL/min per m^2 for control patients (Baker *et al.*, 1992).

The oral bioavailability of teniposide was around 40% at doses of 60 and 120 mg/m^2, and 29% at a dose of 250 mg/m^2, with marked differences among patients (Splinter *et al.*, 1992).

4.1.2 *Experimental systems*

The pharmacokinetics of teniposide and etoposide differed in tumour-bearing mice, teniposide having a lower clearance rate (12 versus 17 mL/kg per min), a longer terminal elimination half-time (77 versus 33 min) and a larger volume of distribution (1400 versus 820 mL/kg) (Broggini *et al.*, 1983; Colombo *et al.*, 1986). A similar, rapid distribution half-time of about 2 min was observed for both drugs.

Studies of cellular uptake suggested that the passage of teniposide into leukaemic cells in culture was linear up to 5 min and reached a steady state by 20 min, the intracellular concentrations being about 20 times higher than the extracellular concentrations. When the drug was removed, an exponential efflux was observed (Allen, 1978). Other authors have reported greater cellular accumulation of teniposide than etoposide at the same extracellular concentration of the two drugs in Lewis lung carcinoma cells *in vitro*, with intracellular concentrations of 1.6 nmol/8×10^6 cells and

0.1 nmol/8 × 10^6 cells, respectively, for teniposide and etoposide after a 30-min incubation at 17 μmol/L (Colombo *et al*., 1986).

The ratios of the AUC for tissue to that for plasma in mice suggest that teniposide concentrates in a number of tissues, and particularly in the liver (AUC ratio, 4.8), intestine (AUC ratio, 5.7) and kidney (AUC ratio, 3.8) (Colombo *et al*., 1986).

Although few published data are available on the metabolism of teniposide in experimental systems, it appears to be similar to that of etoposide (see section 4.1 of the monograph on etoposide). In isolated human liver preparations, cytochrome P450 mixed-function isozymes catalysed metabolism of the (pendant) E-ring to *O*-demethylated and catechol metabolites (Relling *et al*., 1992). This metabolism was subsequently attributed primarily to CYP3A4 activity and to a lesser degree to CYP3A5 (Relling *et al*., 1994). Peroxidase-mediated *O*-demethylation of teniposide has also been reported (Haim *et al*., 1986).

4.2 Toxic effects

4.2.1 *Humans*

The toxic effects in 1069 patients entered into 25 early phase I and II studies with teniposide as a single agent have been summarized (Macbeth, 1982). With the more commonly used five-day regime (30–60 mg/m^2 per day), bone-marrow suppression was the dose-limiting toxic effect, with leukopenia reported in 28–38% of patients and thrombocytopenia in 7–30%. The lowest blood counts typically occurred around day 10, with recovery by day 21. Nausea and vomiting were reported as mild, occurring in up to 20% of patients, with occasional reports of diarrhoea. Less common toxic effects in this group included increased liver enzyme activity (11 patients), acute hypotension (10 patients), fever (six patients) and anaphylaxis (five patients).

More recent studies of patients given 50–80 mg/m^2 per day for five days confirmed these findings, haematological effects occurring most commonly. Severe neutropenia or leukopenia occurred in 30–50% of patients (Cox *et al*., 1988; Boas *et al*., 1990; Oishi *et al*., 1990; Sørensen *et al*., 1991; Berenberg *et al*., 1993; Grozea *et al*., 1997). Episodes of nausea, vomiting and diarrhoea occurred occasionally but were generally mild, and some degree of alopecia was observed in most patients. Less common effects in these studies included transient increases in liver enzyme activity, anaphylaxis, hypotension and hypertension, which in one study was attributed to the vegetable oil base used in the formulation (Oishi *et al*., 1990). Single doses of 100 mg/m^2 given once weekly are generally less toxic (Tirelli *et al*., 1984; Sorio *et al*., 1990).

Because of the reports of hypotension and anaphylaxis in the early studies, reports of 82 hypersensitivity reactions in 2250 patients (3.6% incidence) were reviewed (O'Dwyer *et al*., 1986). Of these reactions, 45% occurred in patients with neuroblastoma or brain tumour, a much higher incidence than in patients with other tumour types. These reactions are manifest as respiratory difficulty, changes in blood pressure, urticaria and flushing.

When teniposide was given at a high total dose of 300–1000 mg/m^2 over three days, haematological toxic effects were dose-limiting, with leukocyte counts of < 0.5–10^9/L in all three patients at 1000 mg/m^2. These patients also developed an intensely pruritic erythematous rash with purpura four to seven days after the start of chemotherapy, which involved the upper part of the chest and the upper part of the legs. In two of these patients, ulceration was also seen. The rash cleared spontaneously within one week and, in two patients who were treated again at 500 mg/m^2, no rash occurred. In the one patient who received a second dose of 1000 mg/m^2, paraesthesia and an abnormal electromyography were seen (de Vries *et al*., 1986).

In one study, the intravenous formulation was tested orally after dilution in 100 mL of syrup or orange juice (Smit *et al*., 1992). Several patients retched during administration, 12 received antiemetics, and vomiting persisted in five patients. The dose-limiting toxic effect was myelosuppression, and gastrointestinal toxicity was also common.

4.2.2 *Experimental systems*

In cell lines, teniposide was 6–10 times more toxic than etoposide, but in a murine model *in vivo*, it was only three times more toxic, with LD_{10} values of 9.4 mg/kg bw for etoposide and 3.4 mg/kg bw for teniposide. At equitoxic doses, the two drugs had equivalent anti-tumour activity in a murine tumour model *in vivo* (Jensen *et al*., 1990).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

A woman in whom Burkitt lymphoma was diagnosed in the 22nd week of pregnancy was treated with a number of anticancer agents, including teniposide given intravenously at 75–100 mg every 2.5–3 weeks until delivery in the 37th week (a total of six courses of treatment). The infant was fully developed and normal in all respects, the examinations including electrocardiography and blood counts. The mother died seven weeks after delivery (Lowenthal *et al*., 1982).

4.3.2 *Experimental systems*

Groups of 3–14 pregnant Swiss albino mice were given a single dose of teniposide at 0.5, 0.75 or 1.0 mg/kg bw intraperitoneally on day 6, 7 or 8 of gestation (vaginal plug, day 0), and the fetuses were removed and examined on day 17. No effect on maternal body-weight gain was seen in any group. In animals injected on day 6, no embryotoxicity was seen with 0.5 mg/kg bw, but 0.75 mg/kg bw reduced fetal weights, and 1.0 mg/kg bw increased the frequencies of intrauterine death and fetal malformations and reduced fetal body weight. Injection on day 7 caused embryolethality only at the high dose, and increased the frequency of fetal malformations and reduced

fetal weights at the intermediate and high doses. Injection on day 8 caused no embryotoxicity or effect on fetal body weight at the low and intermediate doses, but the frequencies of embryolethality and fetal malformations were increased at 1.0 mg/kg bw. Teniposide was considerably more embryotoxic and teratogenic than etoposide, which was also included in this investigation (see the monograph on etoposide). The commonest malformations observed at the highest dose were dextrocardia, seen in 9.4% and 10% of fetuses of dams injected on days 6 and 7, respectively, and exencephaly in 5.7% and 14% of fetuses after injection on days 7 and 8, respectively (Sieber *et al.* 1978).

4.4 Genetic and related effects

4.4.1 *Humans*

Teniposide has been associated with leukaemias that show translocations similar to those seen with etoposide. In a case report, Secker-Walker *et al.* (1985) suggested that acute lymphoblastic leukaemia with translocation t(4;11) was a complication of treatment of neuroblastoma with a regimen that included teniposide. A second case of treatment-related acute lymphoblastic leukaemia with t(4;11) was reported after primary treatment for acute lymphoblastic leukaemia with a teniposide-containing regimen (Brizard *et al.*, 1991). Weh *et al.* (1986) described a case of acute monoblastic leukaemia with translocation t(9;11)(p21;q23) that arose subsequent to treatment of neuroblastoma with a teniposide-containing regimen. Teniposide has been used most often in the treatment of childhood acute lymphoblastic leukaemia, sometimes in combination with etoposide; the observations of specific leukaemia-associated chromosomal translocations in this situation, most of which involve chromosome band 11q23, are described in the monograph on etoposide (see also Pui *et al.*, 1991). In patients receiving another primary treatment regimen for acute lymphoblastic leukaemia that included teniposide as the only DNA topoisomerase II inhibitor, Verdeguer *et al.* (1992) observed three cases of treatment-related acute monoblastic leukaemia; the karyotype was normal in one case, revealed +8, t(3;17)(p11;q25), t(4;11)(q21;q23) in the second case and +8, -15, del(11)(q23)+der(15)t(15;7)(p11;7) in the third, again showing consistent involvement of chromosome band 11q23.

Hawkins *et al.* (1992) reported 10 cases of leukaemia after treatment with epipodophyllotoxin (see section 2); teniposide was used in nine cases and etoposide in one. Cytogenetic studies were performed in six cases, and translocations of chromosome band 11q23 were observed in two of these. In one case, the treatment-related leukaemia was acute lymphoblastic leukaemia with t(4;11)(q21;q23). In the other case, the translocation partner was at band 16p13. The karyotype was normal in the other four cases.

Hunger *et al.* (1992) used Southern blot analysis to examine 10 cases of leukaemia that arose after combination chemotherapy that included teniposide in eight cases and

doxorubicin in two. Rearrangements of the *MLL* gene at chromosome band 11q23 were identified in seven cases with known karyotypic abnormalities and in two cases in which the karyotyping was unsuccessful. The break-points were localized in the cluster region between exons 5 and 11 of the *MLL* gene. Partner genes involved in translocations with *MLL* at the karyotypic level were located at bands 9p22, 16p13 and 19p13. In one case, the karyotype of the leukaemic cells was shown to be t(3;13)(q26;q12), and *MLL* was not rearranged.

To investigate the translocation mechanism, Atlas *et al*. (1998) examined the genomic break-point sequences in four cases of DNA topoisomerase II inhibitor-related leukaemia with translocation t(9;11)(p22;q23), which fuses *MLL* to *AF-9*. Two patients had received teniposide as the only DNA topoisomerase II inhibitor, and the karyotype showed t(9;11)(p22;q23). In one patient who received teniposide and etoposide, the karyotype showed t(9;11)(p22;q23), +der(9)t(9;11)(p22q23). The *MLL* break-points were at positions 3173, 6230 and 6784, indicating heterogeneity in the break-point distribution in the 3′ and 5′ cluster region. These break-points were proximal to regions of homology to a putative DNA topoisomerase II binding site identified *in vitro*, suggesting that DNA topoisomerase II may have played a mechanistic role in the translocation process. Evidence that such regions of homology may not accurately predict functional sites of cleavage by DNA topoisomerase II *in vivo* (Felix *et al*., 1995) has also been presented. In one case of leukaemia, there was homology to seven of eight bases of a χ-like sequence element. Another case showed homology to VDJ recombinase signal sequences and to TRANSLIN binding sequences near the break-points in both *MLL* and *AF-9*. In addition, one of the break-points fell within an *Alu* sequence. The presence of these sequences near the translocation break-points may facilitate recombination.

In an assay for DNA topoisomerase II cleavage *in vitro*, Felix *et al*. (1995) showed that multiple cleavage sites within the *MLL* break-point cluster region are enhanced by teniposide.

4.4.2 *Experimental systems*

General reviews on the mutagenicity of inhibitors of DNA topoisomerase II enzymes, including teniposide, have been published (Anderson & Berger, 1994; Ferguson & Baguley, 1994, 1996; Baguley & Ferguson, 1998: Ferguson, 1998). The results are summarized in Table 3.

Teniposide gave mainly negative responses in a range of assays in prokaryotes and lower eukaryotes. Thus, in most studies, it did not induce significant increases in reverse mutation frequency as measured in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100, *Escherichia coli* WP2 *uvr*A, and in other *E. coli* assays, in the presence or absence of exogenous metabolic activation. It also gave negative results in the SOS chromotest with *E. coli* TK104. Teniposide caused about a twofold increase in the frequency of revertant colonies in *S. typhimurium* strain

Table 3. Genetic and related effects of teniposide

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Prophage induction, *Escherichia coli*	–	NT	50	DeMarini & Lawrence (1992)
Escherichia coli, TK104, SOS chromotest	–	NT	8	Albertini *et al*. (1995)
Bacillus subtilis rec strains, differential toxicity	+	+	10 µg/disc	Nakanomyo *et al*. (1986)
T4 bacteriophage, reverse mutation	–	NT	660	DeMarini & Lawrence (1988)
Salmonella typhimurium TA102, reverse mutation	(+)	NT	100 µg/plate	Gupta *et al*. (1987)
Salmonella typhimurium TA102, reverse mutation	+	NT	250 µg/plate	Albertini *et al*. (1995)
Salmonella typhimurium TA1535, reverse mutation	–	–	400 µg/plate	Nakanomyo *et al*. (1986)
Salmonella typhimurium TA1537, reverse mutation	(+)	–	50 µg/plate	Nakanomyo *et al*. (1986)
Salmonella typhimurium TA1538 and TA98, reverse mutation	(+)	(+)	100 µg/plate	Nakanomyo *et al*. (1986)
Salmonella typhimurium TA100, reverse mutation	–	(+)	200 µg/plate	Nakanomyo *et al*. (1986)
Escherichia coli WP2 *uvr*A, reverse mutation	–	–	400 µg/plate	Nakanomyo *et al*. (1986)
Neurospora crassa, forward mutation, *ad-3A* frameshift strain	–	NT	100	Gupta (1990)
Neurospora crassa, reverse mutation, *ad-3A* frameshift strain	–	NT	525 µg/plate	Gupta (1990)
Drosophila melanogaster, somatic mutation and recombination	+		50 in feed	Frei & Würgler (1996)
DNA double-strand breaks in mouse L1210 cells *in vitro*	+	NT	0.66	Ross *et al*. (1984)
DNA single-strand breaks in mouse L1210 cells *in vitro*	+	NT	0.66	Kerrigan *et al*. (1987)
DNA–protein cross-links in mouse L1210 cells *in vitro*	+	NT	0.66	Kerrigan *et al*. (1987)
Mutation, Chinese hamster ovary cells, *Hprt* locus *in vitro*	+	NT	0.04	Singh & Gupta (1983)
Mutation, Chinese hamster ovary cells, *Ak* locus *in vitro*	(+)	NT	0.04	Singh & Gupta (1983)
Mutation, Chinese hamster ovary CHO-D422 cells, *Aprt* locus *in vitro*	+	NT	0.02	Han *et al*. (1993)
Mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	+	NT	0.0005	DeMarini *et al*. (1987)
Mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	+	NT	0.005	Albertini *et al*. (1995)

Table 3 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Mutation, mouse lymphoma L5178Y cells, *Hprt* locus *in vitro*	–	NT	0.02	Albertini *et al*. (1995)
Mutation, mouse L cells, *Hprt* locus *in vitro*	+	NT	0.05	Gupta *et al*. (1987)
Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	NT	0.66	Lim *et al*. (1986)
Micronucleus formation, Chinese hamster ovary CHO-K5 cells *in vitro*	+	NT	0.015	Albertini *et al*. (1995)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	NT	0.005	Charron & Hancock (1991)
Chromosomal aberrations, Chinese hamster Don cells *in vitro*	+	NT	0.05	Fernández *et al*. (1995)
Chromosomal aberrations, mouse lymphoma L5178Y cells *in vitro*	+	NT	0.0005	DeMarini *et al*. (1987)
Aneuploidy[c], Chinese hamster ovary cells *in vitro*	+	NT	0.05	Charron & Hancock (1991)
Polyploidy, murine erythroleukaemic (T3CL2) cells *in vitro*	+	NT	1	Zucker *et al*. (1991)
DNA single-strand breaks, human lung carcinoma A459 cells *in vitro*	+	NT	0.066	Long *et al*. (1984)
DNA single- and double-strand breaks, human lung carcinoma A459 cells *in vitro*	+	NT	0.066	Long *et al*. (1985)
DNA double-strand breaks, Raji (Burkitt's lymphoma) cells *in vitro*	+	NT	1.32	Johnson & Beerman (1994)
DNA single-strand breaks in human colon carcinoma HT-29 and human embryonic VA-13 cells *in vitro*	+	NT	0.66	Kerrigan *et al*. (1987)
DNA–protein cross-links in human colon carcinoma HT-29 and human embryonic VA-13 cells *in vitro*	+	NT	0.66	Kerrigan *et al*. (1987)
DNA single- and double-strand breaks, human breast cancer MCF-7 cells *in vitro*	+	NT	0.66	Gewirtz *et al*. (1993)
DNA double-strand breaks, human leukaemia HL60 cells *in vitro*	+	NT	0.05	Binaschi *et al*. (1997)

Table 3 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus formation, bone-marrow cells of mice *in vivo*	+		0.5 ip × 2	Nakanomyo *et al*. (1986)
Chromosomal aberrations, bone marrow of pregnant Swiss mice and cells of their embryos *in vivo*	+		1 ip × 3	Sieber *et al*. (1978)
Chromosomal aberration, spermatogonial cells from *Xenopus laevis*, spermatocytes and spermatid stages to nuclear elongation stages observed	+	NT	3.3	Morse-Gaudio & Risley (1994)

[a] +, positive; (+), weak positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw per day; ip, intraperitoneally
[c] Formation of quadriradial chromosomes due to defective segregation

TA102 and caused differential toxicity in *Bacillus subtilis* H17 *rec*$^+$ and M45 *rec*$^-$. In several of these bacterial tests, toxicity but not mutagenicity occurred at a dose of 250 μg/plate, which is higher than those studied in mammalian cells.

Teniposide did not induce prophage in *E. coli* or revert a frameshift mutant of T4 bacteriophage. The drug induced neither forward nor reverse mutations in *Neurospora crassa.*

Teniposide induced DNA breakage in mammalian cells both *in vitro* and *in vivo*. It caused protein-masked DNA double-strand breaks, DNA–protein cross-links and a small proportion of DNA single-strand breaks in various animal cells and in human cell lines. The damage induced by teniposide was found in genomic DNA in preference to episomal (Epstein-Barr virus) DNA in the Raji Burkitt lymphoma cell line. Teniposide has been suggested to inactivate DNA synthesis by inhibiting replicon cluster initiation (Suciu, 1990). Gewirtz *et al*. (1993) showed that teniposide reduced the expression of the c-*myc* oncogene in a MCF-7 human breast cancer cell line.

Teniposide caused chromosomal aberrations in cultured Chinese hamster cells and in mouse lymphoma cell lines, and micronuclei in Chinese hamster ovary (CHO-K5) cells. Teniposide induced the formation of quadriradial chromosomes and affected accurate chromosomal segregation in Chinese hamster ovary cells. Fluorescence in-situ hybridization techniques revealed that about 40% of the rearrangement sites in teniposide-induced quadriradial and triradial chromosomal configurations in Chinese hamster Don cells involved a telomere-like block of base sequences (Fernández *et al*., 1995). Teniposide induced micronuclei and chromosomal aberrations in the bone marrow of mice.

The drug induced sister chromatid exchange in V79 Chinese hamster cells and mutation and somatic recombination in *Drosophila melanogaster* in the wing spot test. It did not induce mutations at the *Hprt* locus in mouse lymphoma L5178Y cells, although it had weak effects at the same locus in Chinese hamster ovary cells. It induced primarily small colony mutants at the *Tk* locus in L5178Y cells; these mutants are usually caused by chromosomal mutations, and teniposide induced a series of deletions and duplications in the *Aprt* gene of Chinese hamster ovary cells.

Cytogenetic changes were measured in bone marrow and embryonic tissue from pregnant mice given a single intraperitoneal injection of 1.0 mg/kg bw teniposide on day 6, 7 or 8 of gestation and killed 48 h later. Treatment on day 7 or 8 increased the frequency of embryonic cells with structural aberrations, one-fourth or more of which were stable, consisting of chromosomes with metacentric or submetacentric markers. Teniposide increased the percentage of embryonic cells with numerical aberrations, but this was statistically significant only on day 8. Most of the aberrations were hypoploidy (usually monosomy) and hyperploidy (usually trisomy) (Sieber *et al*., 1978).

Whether cellular damage results in mutation or apoptosis depends on a number of factors (Ferguson & Baguley, 1994). Teniposide-induced apoptosis has been demonstrated in various cell types including unstimulated mouse splenic lymphocytes (Roy *et al*., 1992), human Hl-60 and MOLT-4 cells (Gorczyca *et al*., 1993) and human

HT-29 and HL-60 cells (Bertrand *et al*., 1991). Teniposide can cause a widespread DNA degradative process in nuclear DNA, but mitochondrial DNA appears to be resistant (Tepper & Studzinski, 1992). Aratani *et al*. (1996) used gene transfer assays to assess whether teniposide affects non-homologous (illegitimate) recombination and found that it stimulated integration of closed circular or linearized plasmids carrying the wild-type *Aprt* gene into *Aprt*-deficient Chinese hamster cells by non-homologous (illegitimate) recombination. Treatment of simian virus 40 (SV40)-infected monkey BSC-1 cells with teniposide resulted in DNA of high relative molecular mass, which Bodley *et al*. (1993) showed to consist of recombinant SV40 DNA sequences covalently joined with cellular DNA. Their results suggest a direct role for DNA topoisomerase II in viral integration. Polyploidy induced by teniposide was demonstrated by flow cytometry techniques in Chinese hamster ovary cells (Zucker *et al*., 1991). Teniposide induced differentiation of human HL-60 leukaemia cells (Gieseler *et al*., 1993). It caused hypomethylation of DNA at CpG dinucleotides, resulting in altered patterns of distribution of 5-methylcytosine residues at these sites, thereby potentially modifying gene expression (Nyce, 1989; Wachsman, 1997).

In general, the effects of teniposide in mammalian cells *in vitro* occurred in the absence of exogenous metabolic activation. Various metabolic species of teniposide have been identified, but their mutagenic properties have not been studied.

Teniposide affects not only somatic cells but also germ cells. Incubation of isolated spermatogonial cells from *Xenopus laevis* with this drug led to dose-dependent induction of DNA breaks in all spermatocytes and spermatid stages to nuclear elongation stages. Spermatogonia B, meiotic divisions and pachytene spermatocytes appeared to be particularly sensitive to teniposide-induced DNA damage and production of morphological abnormalities (Morse-Gaudio & Risley, 1994).

4.5 Mechanistic considerations

Teniposide has two properties that are likely to lead to mutation.

1. It is an inhibitor of DNA topoisomerase II enzymes: Teniposide is a DNA topoisomerase II poison that has been shown to promote DNA cleavage, with a strong preference for a C or T at position –1 (Pommier *et al*., 1991). Most of the mutational events reported in mammalian cells, including point mutations, chromosomal deletions and exchanges and aneuploidy, can be explained by this activity. Teniposide does not inhibit bacterial topoisomerases and may not mutate bacterial cells by the same mechanism as mammalian cells. Unlike many other DNA topoisomerase II poisons, teniposide does not bind to DNA, either covalently or by intercalation. Instead, it appears to interact directly with the DNA topoisomerase II enzyme (Burden & Osheroff, 1998).

2. It possesses readily oxidizable functions: Teniposide formed phenoxy radical intermediates in the presence of horseradish peroxidase or prostaglandin synthase (Haim *et al*., 1986), but none of the mutations induced by teniposide is of the type usually associated with reactive oxygen species.

Regimens containing teniposide and other DNA topoisomerase II inhibitors are associated with leukaemias with chromosomal translocations. The role of DNA topoisomerase II inhibitors in translocations associated with leukaemia is unknown. Two possibilities are plausible. The first is that teniposide itself causes the translocations, perhaps through a cytotoxic action. The planar ring structures of epipodophyllotoxins confer an ability to form stable, stacked complexes with DNA and DNA topoisomerase II. It has been proposed that DNA cleavage induced directly by DNA topoisomerase II or by the drug-induced apoptotic cellular response is responsible for the nonrandom chromosomal translocations that lead to leukaemogenesis (Dassonneville & Bailly, 1998). In one model in which the drug causes the translocations, the process involves drug-induced DNA topoisomerase II-mediated chromosomal breakage and formation of the translocations by further processing and resolution of the breakage through cellular mechanisms of DNA repair (Felix *et al.*, 1998).

The second possibility for the role of teniposide in causing translocations is that it selects for cells that already have translocations. Indeed, *MLL* tandem duplications, a form of translocation, have been identified in peripheral blood and bone marrow of healthy adults (Schnittger *et al*., 1998). Chemotherapy has profound effects on the kinetics of the marrow: it causes cell death, forcing many marrow stem cells to divide, which might select for the rare stem cells with a translocation (Knudson, 1992).

In favour of the first possibility is the specificity of the association between DNA topoisomerase II inhibitors, but not other forms of chemotherapy that cause cell death in the marrow (such as alkylating agents), and leukaemias characterized by translocations.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Teniposide is a semi-synthetic podophyllotoxin derivative that has been used in cancer treatment since the late 1970s. This DNA topoisomerase II inhibitor has been used in combination with other chemotherapeutic agents in the treatment of adult and childhood leukaemia, brain tumours in adults and neuroblastoma in children and, to a lesser extent, a number of other cancers.

5.2 Human carcinogenicity data

One large, well-conducted cohort study of acute lymphoblastic leukaemia in the USA and one case–control study of childhood cancer in United Kingdom found strong positive associations between the incidence of acute myeloid leukaemia and treatment with teniposide. A dose–response relationship was found in the case–control study. In both studies, teniposide was administered with other cytotoxic drugs. Although some of the other agents may have contributed to the positive association seen in the cohort

study, use of these agents has not been associated with acute myeloid leukaemia in other large studies of childhood cancer. In the case–control study, the use of other potentially leukaemogenic agents was adjusted for in the analysis; however, the possibility cannot be excluded that interaction occurred between teniposide and those agents. It is unlikely that the large excess risk for acute myeloid leukaemia can be explained fully by misclassification or phenotypic change of the initial haematological malignancy.

Other cohort studies have also reported strongly increased risks for acute myeloid leukaemia after treatment of various primary malignancies with teniposide-containing regimens that also included alkylating agents or teniposide-containing regimens in combination with etoposide. In these studies, the possibility cannot be excluded that the excess risk for leukaemia was partly or wholly due to the other agents.

5.3 Animal carcinogenicity data

No data were available to the Working Group.

5.4 Other relevant data

In humans, teniposide is eliminated biphasically, with a terminal half-time of 6–10 h in adults and children. The pharmacokinetics of teniposide is linear at doses up to 1000 mg/m^2. The oral bioavailability is about 40%. About 45% of a radiolabelled dose of teniposide was excreted in the urine, 4–14% occurring as the parent drug. There are few data on the metabolism of teniposide in humans. Teniposide is highly protein-bound in plasma (99%).

In mice, the pharmacokinetics of teniposide differs from that of etoposide, a closely related drug, with lower clearance, a larger volume of distribution and a longer terminal elimination half-time. The accumulation of teniposide in leukaemic cells *in vitro* was some 15 times higher than that of etoposide applied at the same concentration. Metabolism to the catechol and quinone metabolites *in vitro* has been described.

The major dose-limiting toxic effect of teniposide in clinical trials is myelosuppression, manifest mainly as leukopenia. Less severe effects, including nausea and vomiting, diarrhoea and alopecia, are common; less common effects include transient increases in liver enzyme activity, hypertension and hypersensitivity reactions. Embryotoxicity and teratogenicity, especially in the heart and central nervous system, have been observed in mice.

Teniposide is orders of magnitude more toxic in mammalian than in microbial cells and is mutagenic in mammalian cells. The effects in mammals arise primarily because teniposide is a poison of DNA topoisomerase II enzymes. Teniposide causes accumulation of protein-masked double-stranded DNA breaks in cells and, with time, a variety of chromosomal aberrations. It is also an effective recombinogen. The predominant mutagenic effects in mammalian cells appear to involve deletion and/or interchange of

large DNA segments. Teniposide also induces aneuploidy and polyploidy. It may affect gene expression through hypomethylation of DNA.

Teniposide-containing regimens are strongly related to leukaemia in which the cells contain chromosomal translocations similar to those induced by etoposide and other DNA topoisomerase II inhibitors. The translocations are key events in leukaemogenesis.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of teniposide.

There is *inadequate evidence* in experimental animals for the carcinogenicity of teniposide.

Overall evaluation

Teniposide is *probably carcinogenic to humans (Group 2A)*.

In reaching this conclusion, the Working Group noted that teniposide causes distinctive cytogenetic lesions in leukaemic cells that can be readily distinguished from those induced by alkylating agents. The short latency of these leukaemias contrasts with that of leukaemia induced by alkylating agents. Potent protein-masked DNA breakage and clastogenic effects occur in human cells *in vitro* and animal cells *in vivo*.

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