

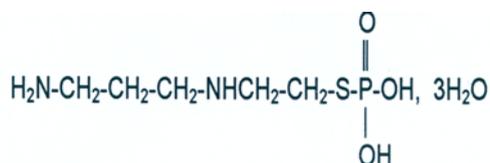
PRODUCT INFORMATION

ETHYOL[®] INJECTION

NAME OF THE MEDICINE

Amifostine

Chemical structure: $\text{NH}_2(\text{CH}_2)_3\text{NH}(\text{CH}_2)_2\text{SPO}_3\text{H}_2$



CAS number: CAS-20537-88-6

DESCRIPTION

Each vial of ETHYOL Lyophilised Powder for Injection contains 500 mg of amifostine (anhydrous). ETHYOL does not contain any preservative.

ETHYOL Powder for Injection is a sterile lyophilised powder. The 500 mg vial is reconstituted with 9.7 mL of sterile 0.9% sodium chloride solution (final reconstituted volume of 10 mL) before intravenous infusion.

PHARMACOLOGY

Amifostine (ethanethiol, 2-[(3-aminopropyl)amino]-dihydrogen phosphate (ester)) is an organic thiophosphate which, in animal models, selectively protects normal tissues but not tumours against cytotoxicity of ionising radiations, DNA-binding chemotherapeutic agents (classical alkylating agents such as cyclophosphamide and non-classical alkylating agents such as mitomycin-C and platinum-containing drugs).

Amifostine is a prodrug that is dephosphorylated to the active metabolite, WR-1065 (free thiol), by alkaline phosphatase and exits the bloodstream rapidly.

Pharmacokinetics

Clinical pharmacokinetic studies have shown that amifostine is rapidly cleared from the plasma with <10% remaining in the plasma 6 minutes after drug administration. Amifostine is rapidly metabolised into the active metabolite WR-1065 (free thiol). WR-33278 (disulfide) is the subsequent inactive metabolite. It is unknown if amifostine crosses the blood placenta barrier.

After a 15-minute infusion of a dose of 910 mg/m², the distribution half-life is <1 minute, the elimination half-life of amifostine is <10 minutes.

During a 15-minute infusion of 910 mg/m² the peak plasma concentration of amifostine is approximately 200 µmol/L, the V_{d_{ss}} (steady state) is 7 L and the clearance is 2 L/min. Peak plasma concentration of the active metabolite, WR-1065, during the 15-minute infusion is approximately 35 µmol/L. Measurement of WR-1065 in bone marrow cells 5-8 minutes after the infusion in three patients was 82, 121 and 227 µmol/kg. Less than 4% of amifostine and its metabolites are excreted in urine.

Clinical Trials

Chemotherapy

The indication is based on the results of a randomised controlled trial of six cycles of cyclophosphamide 1000 mg/m² and cisplatin 100 mg/m² with or without ETHYOL pre-treatment at 910 mg/m² which was conducted in two successive cohorts of 121 patients with advanced ovarian cancer. The results of this trial demonstrate that pre-treatment with ETHYOL can protect against both acute and cumulative haematologic and renal toxicity associated with cyclophosphamide and cisplatin (CP), which should allow better adherence to chemotherapy regimens. The protection of bone marrow and kidney was achieved with no reduction in the anti-tumour efficacy of the CP regimen. Results of the combined analysis of all 242 patients are displayed in Tables 1, 2 and 3.

Table 1. Effect of ETHYOL Pretreatment on the Toxicities Associated with the CP Regimen - Protection of Bone Marrow -

	ETHYOL + CP (N=122)	CP (N=120)	p-value 2-sided
Incidence of neutropenia with fever and/or infection requiring antibiotic therapy	8/122 (7%)	26/120 (22%)	0.001
Days in hospital	71	258	0.003
Days on antibiotics	78	304	0.002
Incidence of withdrawals for hematologic toxicity	1/122 (1%)	8/120 (7%)	0.016
Percent of patients with Grade 4 neutropenia following last cycle of chemotherapy	27/122 (22%)	51/120 (43%)	0.001
Percent of patients with Grade 4 neutropenia whose neutropenia count failed to recover to $\geq 1500/\text{mm}^3$ by day 22 ± 3 days	47/102 (46%)	64/99 (65%)	0.008

Table 2. Renal Protection

	ETHYOL + CP (N=122)	CP (N=120)	p-value 2-sided
Protracted elevation in serum creatinine levels >1.5 mg/dL at day 22	(3%)	(17%)	0.004
Proportion of patients with $\geq 40\%$ reduction from baseline in creatinine clearance	(10%)	(32%)	<0.001
Incidence of Grade 2 or worse hypomagnesaemia	(2%)	(11%)	0.001

Table 3. Lack of Protection by ETHYOL on the Antitumour Efficacy of the CP Regimen - Pathologic Tumour Response Rate -

Patient Cohort / Response Rate	ETHYOL + CP	CP
Intent-to-Treat Analysis	(N=122)	(N=120)
Pathologic complete response rate	26 (21.3%)	19 (15.8%)
Pathologic complete + partial response rate	45 (36.9%)	34 (28.3%)
Analysis of Patients Who Underwent Second-Look Surgery	(N=60)	(N=52)
Pathologic complete response rate	26 (43.3%)	19 (36.5%)
Pathologic complete + partial response rate	45 (75.0%)	34 (65.4%)
Overall Survival for All Patients (months) (Median Follow-up = 41 Months)	(N=122)	(N=120)
Median	31.3	31.8
Mean	33.7	34.3

Radiotherapy

The pivotal randomised, parallel group study evaluated the incidence and severity of radiation induced toxicities in patients with head and neck cancer treated with standard fractionated radiation therapy (1.8-2.0 Gy/day, 5 days/week for 5-7 weeks) with or without pretreatment with ETHYOL 200 mg/m². The intent-to-treat analyses involved 150 patients randomised to radiation + ETHYOL and 153 patients randomised to radiation alone.

Pretreatment with ETHYOL reduced the incidences of acute grade 2 xerostomia from 78% to 50% (p<0.0001) and late effect grade 2/3 xerostomia from 62% to 31% (p=0.001). There was no significant difference in the incidence of acute grade 3/4 mucositis in the total population, being 35% for the ETHYOL plus radiotherapy arm versus 39% for radiotherapy alone (p=0.438). However, a sub-group analysis demonstrated a significant reduction in the overall severity of mucositis (p=0.002) and the incidence of grade 3/4 mucositis (p=0.048) when small, but not large, mucosal volumes were included in the radiation field. (Other randomised studies have shown ETHYOL 300 mg/m² to be safe and effective in reducing severe mucositis.) A Patient Benefit Questionnaire demonstrated a significant benefit in the amifostine group at 12 months (p=0.002), principally due to a reduction in dryness of mouth.

Pre-treatment with amifostine did not affect the anti-tumour efficacy of radiation with a locoregional control rate at 1 year of 63% in the radiation + ETHYOL arm and 64% in the radiation alone arm. Similarly, the disease free and overall survival curves were comparable, with hazard ratios and 95% confidence limits of 1.139 (0.729 to 1.780) and 1.413 (0.769 to 2.597) for disease free and overall survival respectively.

INDICATIONS

ETHYOL is indicated to decrease the incidence of neutropenia-related fever and infection induced by DNA-binding chemotherapeutic agents (classical alkylating agents such as cyclophosphamide and non-classical alkylating agents such as mitomycin-C and platinum-containing drugs); decrease the incidence of acute and cumulative nephrotoxicity associated with platinum-based therapy; and provide better adherence to these types of chemotherapy regimens.

ETHYOL is also indicated to protect against acute and late xerostomia associated with standard fractionated radiation therapy in patients with head and neck cancer.

CONTRAINDICATIONS

Known sensitivity to aminothiols compounds. Patients who are hypotensive or in a state of dehydration should not receive ETHYOL.

As ETHYOL is to be administered in conjunction with drugs that are known teratogens and mutagens, therapy should not be administered to pregnant or lactating women.

Due to lack of experience in patients with renal or hepatic impairment, children or patients older than 70 years of age, ETHYOL is contraindicated in these groups.

WARNINGS

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

PRECAUTIONS

Patients should be adequately hydrated prior to ETHYOL infusion and kept in a supine position during the infusion of the reconstituted ETHYOL solution. If hypotension occurs, patients should be placed in the Trendelenburg position and be given an infusion of normal saline. Hypotension may occur during or shortly after ETHYOL infusion despite adequate hydration and positioning of the patient. In rare cases, sometimes during or after hypotension, the following have been reported: tachycardia, bradycardia, dyspnea, apnea, hypoxia, chest pain, myocardial ischaemia, renal failure, myocardial infarction, convulsions, unconsciousness, respiratory arrest and cardiac arrest.

Serious cutaneous reactions requiring hospitalization and discontinuation of treatment have been reported rarely with the use of ETHYOL. These cutaneous reactions, which were sometimes fatal, include cases of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, toxoderma, and bullous toxicity. Most cases occurred in patients receiving ETHYOL as a radioprotectant, and occurred after 10 or more days of exposure to ETHYOL. Cutaneous evaluation of the patient prior to each ETHYOL administration should be performed with particular attention paid to the development of the following:

- Any rash involving the lips or involving mucosa not known to be due to another etiology (e.g. radiation mucositis, herpes simplex, etc.)
- Erythematous, edematous, or bullous lesions on the palms of the hands or soles of the feet and/or other cutaneous reactions on the trunk (front, back, abdomen).
- Cutaneous reactions with associated fever or other constitutional symptoms.

Cutaneous reactions must be clearly differentiated from radiation-induced dermatitis and from cutaneous reactions related to an alternate etiology.

For cutaneous reactions that appear outside the injection site or outside the radiation port without a known etiology, ETHYOL should be withheld and dermatologic consultation and biopsy should be considered to classify the reaction. The cutaneous reaction should be treated symptomatically. Re-initiation of ETHYOL administration should be at the clinician's discretion based on medical evaluation and appropriate dermatologic consultation.

ETHYOL should be permanently discontinued for any cutaneous reactions that are considered to be erythema multiforme, toxic epidermal necrolysis, Stevens Johnson Syndrome, or exfoliative dermatitis, and for any cutaneous reaction associated with fever or any other constitutional symptoms not known to be due to any other etiology.

During the use of ETHYOL, special attention should be paid to the renal function in patients with known risk factors of renal insufficiency such as vomiting, dehydration, severe hypotension, nephrotoxic chemotherapy or age over 60 years.

Prior to chemotherapy, it is important that the infusion of the recommended dose (740 - 910 mg/m²) be given over 15 minutes. The administration of ETHYOL as a longer infusion is associated with a higher incidence of side effects. Guidelines for interrupting and re-starting ETHYOL in case of decrease in systolic blood pressure are given under Dosage and Administration.

Data concerning the consecutive use of ETHYOL on regimens including chemotherapy by cisplatin or alkylating agents (ETHYOL dosage: 910 mg/m²) and radiotherapy (ETHYOL dosage: 200 mg/m²) are limited.

Prior to radiation therapy, ETHYOL should be administered at the recommended dose (200 mg/m²) over 3 minutes.

Where mucosal tissue or salivary glands are not in the field of radiation, limited information regarding protection of radiation induced toxicities is available.

It is recommended that antiemetic medication including dexamethasone 20 mg i.v. and a 5-HT₃ antagonist be administered prior to and in conjunction with ETHYOL at doses relevant for chemotherapy (740-910 mg/m²) especially when used with strongly emetogenic chemotherapy such as cisplatin.

At doses relevant for radiotherapy (200 mg/m²), prophylactic antiemetics are recommended. In the pivotal clinical trial of ETHYOL in radiotherapy, prophylactic antiemetics were used in the majority of patients who received the drug. However, no clear benefit of antiemetic use was demonstrated.

When ETHYOL is administered with highly emetogenic chemotherapy, the fluid balance of the patient should be monitored carefully.

Prior to chemotherapy, antihypertensive therapy should be interrupted 24 hours prior to the administration of ETHYOL and these patients should be monitored carefully during treatment. Patients receiving treatment with ETHYOL and radiotherapy and concurrent anti-hypertensive medication should be monitored carefully during treatment.

Although reports of clinically relevant hypocalcaemia are rare, serum calcium levels should be monitored in patients at risk of hypocalcaemia, such as those with nephrotic syndrome or patients receiving multiple doses of ETHYOL. If necessary, calcium supplements should be administered as needed. Caution should be exercised during treatment of patients receiving hypocalcaemic agents. With administration of ETHYOL, convulsions have also been reported rarely.

Since convulsions have been reported rarely with administration of ETHYOL, caution should be exercised during treatment of patients receiving other drugs with a potential to cause convulsions.

There are no available data to support a long term beneficial effect from amifostine with respect to secondary cancer, late fibrosis or late skin toxicity.

ETHYOL should be used with care in patients with pre-existing cardiovascular or cerebrovascular conditions. During the use of ETHYOL, special attention should be paid to renal function in patients with known risk factors of renal insufficiency such as vomiting, dehydration, severe hypotension, nephrotoxic chemotherapy or age over 60 years.

ETHYOL has only been evaluated with chemotherapy doses that are intensive, but within the range of accepted clinical practice. It is not known whether ETHYOL could protect against the toxicities of chemotherapeutic agents dosed outside the range of accepted clinical practice.

Use in Pregnancy (Category B3)

There are no studies in pregnant women. Amifostine was not teratogenic or fetotoxic at i.v. doses up to 60 mg/kg/day in rats. Fetotoxicity was seen at 50 mg/kg/day i.v. in rabbits but this dose also caused frank toxicity in pregnant females. Amifostine was not teratogenic at the maximum i.v. dose of 75 mg/kg/day tested in rabbits. The effects of amifostine on peri- and post-natal development have not been investigated in animals. Amifostine and/or its metabolites crossed the placenta and entered the foetus in rats. As this drug is used in conjunction with known teratogenic and mutagenic agents, pregnant women or women of child bearing potential should not be treated with ETHYOL.

Use in Lactation

It is not known if amifostine or its metabolites are excreted into human breast milk. Therefore, it is recommended that breast feeding be discontinued prior to the initiation of ETHYOL therapy.

Carcinogenicity, Mutagenicity and Impairment of Fertility

No long-term animal studies have been performed to evaluate the carcinogenic potential of amifostine. Amifostine was negative in the Ames test and in the mouse micronucleus test. The free thiol metabolite, however, was positive in the Ames test with S9 microsomal fraction in the TA1535 *Salmonella typhimurium* strain and at the TK locus in the mouse L5178Y cell assay. The metabolite was negative in the mouse micronucleus test and negative for clastogenicity in human lymphocytes.

In a 90-day rat study a dose level of 25 mg/kg/day IV was determined to be the minimal effect dose. At this dose level, clinical signs of abnormality were limited to presence of urogenital wetness and brown matted fur around the mouth associated with excessive salivation. These changes were all minimal and judged to be of little clinical significance. At this dose there was no evidence of changes to the male reproductive system. At the 50 mg/kg/day dose level (300 mg/m²/day) amifostine showed toxicity in the male reproductive system in rats. These changes included testicular atrophy, interstitial hyperplasia and bilateral degeneration of the germinal epithelium of the testis, decreased seminal secretions and bilateral hypospermia in the epididymides. The severity of toxicity did not decrease after treatment was ceased. These changes were not observed at the 25 mg/kg/day dose level.

Interactions with other medicines

Limited experience from interaction studies is available. Pretreatment with dexamethasone and metoclopramide has no effect on amifostine pharmacokinetics. The rapid clearance of amifostine from the plasma minimises the risk of direct interactions between amifostine and other drugs.

Special consideration should be given with respect to the concurrent administration of ETHYOL with antihypertensive medication or other drugs that could potentiate hypotension.

No specific drug interaction studies have been carried out in patients receiving ETHYOL with radiotherapy.

ADVERSE EFFECTS

Hypotension, as manifested by a transient reduction in systolic blood pressure and less frequently by a decrease in diastolic blood pressure, has been reported. In the randomised study for patients with ovarian cancer, where ETHYOL was administered at 910 mg/m² prior to chemotherapy, the median time to onset of hypotension was 13 minutes into the 15-minute period of ETHYOL infusion and the median duration was 5 minutes. In some cases, the infusion had to be terminated prematurely due to a more pronounced drop in systolic blood pressure. In most cases, the blood pressure returned to normal within 5-15 minutes. If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic, the infusion may be restarted, so that the full dose of ETHYOL can be administered (see Dosage and Administration).

Clinical symptoms of hypotension are usually quickly reversed by fluid infusion and postural management of the patient. In rare cases, sometimes during or after hypotension, the following have been reported: tachycardia, bradycardia, dyspnea, apnea, hypoxia, chest pain, myocardial ischaemia, renal failure, myocardial infarction, convulsions, unconsciousness, respiratory arrest and cardiac arrest.

Rare cases of arrhythmias such as atrial fibrillation/flutter and supraventricular tachycardia have been reported. In some instances, these are associated with hypotension or allergic reactions.

Transient hypertension and exacerbation of preexisting hypertension has been observed rarely after ETHYOL administration.

In the randomised study for patients with head and neck cancer where ETHYOL was administered at lower doses prior to radiotherapy (200 mg/m²), hypotension was reported less frequently. With administration of ETHYOL prior to radiotherapy, the blood pressure should be measured prior to and following the infusion of ETHYOL (see Precautions).

Nausea and/or vomiting are frequently reported. ETHYOL increased the incidence of mild to moderate nausea/vomiting on Day 1 of chemotherapy. However, ETHYOL does not increase the incidence of delayed nausea and vomiting induced by cisplatin-based chemotherapy. Nausea and vomiting are amenable to treatment with standard antiemetics.

Severe allergic reactions have been reported with the use of ETHYOL. The majority of cases presented with non-specific symptoms including fever, chills, rigors, chest pain and skin rashes. There have been rare reports of anaphylactoid reactions, including dyspnea, hypoxia, laryngeal edema, hypotension, chest tightness and urticaria. During an anaphylactoid reaction cardiac arrest may occur. Very rare, cases of chest tightness, toxicoderma and bullous and exfoliative dermatitis have been reported

Serious, sometimes fatal skin reactions including erythema multiforme, and in rare cases Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been reported. In the limited number of patients in clinical trials, the reported rate is 4 of 379 patients receiving radiotherapy [105.5 cases per 10 000 patients] and 1 out of 1356 patients receiving chemotherapy [7.4 cases per 10 000 patients]. The reported incidence of serious skin reactions with ETHYOL in the postmarketing setting is estimated at 6.0 to 9.0 cases per 10 000 patients receiving radiotherapy and 0.8 to 1.0 cases per 10 000 receiving chemotherapy (see Warnings and Precautions).

Other effects which have been described during or following ETHYOL infusion are flushing/feeling of warmth, chills/feeling of coldness, dizziness, somnolence, hiccups and sneezing. Convulsions have also been reported rarely. Rare cases of fever have been reported during the infusion of ETHYOL or within a few hours.

Decrease in serum calcium concentrations is a known pharmacological effect of ETHYOL. The mechanism of hypocalcemia may be due to induction of hypoparathyroidism. At the recommended doses, clinically significant hypocalcemia has occurred rarely (see Precautions).

DOSAGE AND ADMINISTRATION

ETHYOL should only be used under the supervision of physicians experienced in cancer chemotherapy or radiotherapy.

Chemotherapy

In adults, the recommended starting dose of ETHYOL is 740-910 mg/m² administered once daily as a 15-minute intravenous infusion starting within 30 minutes prior to chemotherapy with agents given by short infusion (see Reconstitution for Intravenous Administration).

If the predominant toxicities to be ameliorated are those associated with cisplatin, then the starting dose of ETHYOL should be correlated with the dose and schedule of cisplatin. For cisplatin doses of 100-120 mg/m², the recommended starting dose of ETHYOL is 910 mg/m² administered as a 15-minute infusion starting within 30 minutes prior to chemotherapy.

If the dose of cisplatin is less than 100 mg/m², the recommended starting dose of ETHYOL is 740 mg/m² administered as a 15-minute infusion starting within 30 minutes prior to chemotherapy.

The 15-minute infusion for the 740-910 mg/m² dose is reportedly better tolerated than more extended infusion durations. Further reduced infusion times have not been systematically explored with chemotherapy regimens.

During the infusion of ETHYOL, arterial blood pressure should be monitored.

The infusion of ETHYOL should be interrupted if the systolic blood pressure decreases significantly from the baseline value as listed in the following guideline:

Guideline for Interrupting ETHYOL Infusion Due to Decrease in Systolic Blood Pressure

	Baseline Systolic Blood Pressure (mmHg)				
	<100	100-119	120-139	140-179	≥180
Decrease in systolic blood pressure during infusion of ETHYOL (mmHg)	20	25	30	40	50

If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic, the infusion may be restarted so that the full dose of ETHYOL may be administered. If the full dose of ETHYOL cannot be administered, the dose of ETHYOL for subsequent chemotherapy cycles should be reduced by 20%. For example, the 910 mg/m² dose would be reduced to 728 mg/m².

With chemotherapy, it is recommended that antiemetic medication including dexamethasone 20 mg i.v. and a 5-HT₃ antagonist be administered prior to and in conjunction with ETHYOL especially when used with strongly emetogenic chemotherapy such as cisplatin.

Radiotherapy

The recommended dose of ETHYOL is 200 mg/m² administered daily as a slow i.v. push over 3 minutes starting within 15-30 minutes prior to standard fractionated radiation therapy.

Blood pressure should be measured prior to and following the infusion (see Precautions).

Prophylactic antiemetics are recommended. In the pivotal clinical trial of ETHYOL in radiotherapy, prophylactic antiemetics were used in the majority of patients who received the drug. However, no clear benefit of antiemetic use was demonstrated.

Reconstitution for Intravenous Administration

The 500 mg vial is reconstituted with 9.7 mL of sterile normal saline (0.9% sodium chloride) solution resulting in 10 mL of amifostine 50 mg/mL solution. Agitate the vial gently to dissolve the powder completely.

For use prior to radiotherapy, the reconstituted solution does not have to be diluted further.

For use prior to chemotherapy, the reconstituted solution is further diluted in sterile normal saline for i.v. infusion to achieve amifostine concentrations ranging from 5 mg/mL to 40 mg/mL. The volume of the i.v. solution for use prior to chemotherapy is typically 100 mL to 250 mL.

The reconstituted solution is clear and colourless. As for all parenteral drug products, the reconstituted material should be inspected visually for discoloration and particulate matter prior to administration. Do not use if cloudiness or precipitate is observed.

Stability of Reconstituted Solution

When reconstituted in 9.7 mL of sterile 0.9% sodium chloride solution, the reconstituted ETHYOL solution may be kept 6 hours at room temperature (below 25°C) or 24 hours under refrigeration (2° to 8°C). For microbiological reasons the reconstituted solution should be used immediately after preparation. As the reconstituted solution contains no preservative, use only once and discard any residue.

Compatibility with Other Drugs

The compatibility of ETHYOL with solutions other than 0.9% Sodium Chloride for Injection or sodium chloride solutions with other additives has not been examined. The use of other solutions is not recommended. No other drug should be mixed or co-administered with the reconstituted ETHYOL solution. The intravenous line should be flushed with normal saline prior to administration of other agents.

OVERDOSAGE

In phase I trials, the maximum single dose of ETHYOL administered was 1300 mg/m². No information is available on single doses higher than this in adults. In the setting of a clinical trial, children have received single doses of ETHYOL up to 2.7 g/m². At the higher doses, anxiety and reversible urinary retention occurred. Likely symptoms of overdosage may include nausea, vomiting, hypotension and hypocalcemia which should be managed by supportive measures as clinically indicated.

PRESENTATION AND STORAGE CONDITIONS

ETHYOL Lyophilised Powder for Injection is in a 10 mL clear glass vial fitted with a grey rubber stopper sealed with an aluminium seal and a plastic flip-off cap.
Pack size: 500 mg - 3 vials; 375 mg – 1 vial*.

Store below 25°C.

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2-8 °C for not more than 24 hours.

* pack size not marketed

POISONS SCHEDULES OF THE MEDICINE

S4. Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
54-68 Ferndell Street,
South Granville, NSW 2142
Australia

Merck Sharp & Dohme (New Zealand) Ltd
P O Box 99 851
Newmarket
Auckland 1149
New Zealand

This product information was approved by the Therapeutic Goods Administration on 9 May 2001.
Date of most recent amendment: 19 July 2011