Thalidomide *(BAN, USAN, rINN)*

E-217; K-17; NSC-66847; Talidomid; Talidomida; Talidomidi; Thalidomidum. 2-Phthalimidoglutarimide.

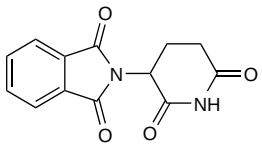
Талидомид

$C_{13}H_{10}N_2O_4$ = 258.2.

CAS — 50-35-1.

ATC — L04AX02.

ATC Vet — QL04AX02.



Pharmacopoeias. In *US.*

USP 31 (Thalidomide). A white to off-white powder. Sparingly soluble in water, in dehydrated alcohol, in acetone, in butyl acetate, in ethyl acetate, in glacial acetic acid, and in methyl alcohol; practically insoluble in chloroform, in ether, and in benzene; very soluble in dimethylformamide, in dioxan, and in pyridine. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Thalidomide was withdrawn from use as a hypnotic in the early 1960s after it was discovered that it produced teratogenic effects when given in early pregnancy. These effects, which could develop after a single dose, involved mainly malformations of the limbs and defects of the ears, eyes, and internal organs. Death at or shortly after birth was also common. Further abnormalities and problems, including effects on the CNS, developed in later life.

Thalidomide was reintroduced in 1998 for use as an immunomodulator but because of its severe teratogenic effects, it should not be used in women of child-bearing potential, or if such use is absolutely essential then stringent contraceptive measures must be used, including the simultaneous use of 2 reliable forms of contraception for at least 4 weeks before, during, and for 4 weeks after, thalidomide therapy. A pregnancy test must be carried out no longer than 24 hours before starting thalidomide treatment, and regular tests carried out during treatment. If pregnancy occurs during thalidomide therapy the drug must be stopped immediately and the patient given appropriate evaluation and counselling. As thalidomide is present in semen, male patients receiving thalidomide should use barrier methods of contraception even after successful vasectomy if their partner is of child-bearing potential. Patients should not donate blood or sperm during thalidomide therapy.

The other major adverse effect of thalidomide is peripheral neuropathy, which can be severe and irreversible.

Venous thromboembolism has been reported in a significant number of patients receiving thalidomide for multiple myeloma, particularly in those also receiving chemotherapeutic drugs, including dexamethasone.

Other common adverse effects include constipation, dizziness, and orthostatic hypotension. Drowsiness or somnolence occur frequently and, if affected, patients should not drive or operate machinery. Hypersensitivity reactions have occurred. An erythematous macular rash may develop, usually 2 to 10 days after initiation of therapy. Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported, and therefore thalidomide should be stopped if skin rash develops and only restarted after appropriate clinical evaluation. Thalidomide therapy should not be resumed if the rash is exfoliative, purpuric, or bullous, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected. Bradycardia, neutropenia, and an increase in the viral load in HIV-infected patients have also been reported; thalidomide therapy should not be started in neutropenic patients.

Although human data for breast feeding while taking thalidomide are lacking, licensed product information recommends that it should be avoided in view of the potential for serious adverse effects in the infant.

◊ Reviews.

1. Günzler V. Thalidomide in human immunodeficiency virus (HIV) patients: a review of safety considerations. *Drug Safety* 1992; **7:** 116–34.
2. Clark TE, *et al.* Thalomid (thalidomide) capsules: a review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing. *Drug Safety* 2001; **24:** 87–117.
3. Grover JK, *et al.* The adverse effects of thalidomide in relapsed and refractory patients of multiple myeloma. *Ann Oncol* 2002; **13:** 1636–40.
4. Ghobrial IM, Rajkumar SV. Management of thalidomide toxicity. *J Support Oncol* 2003; **1:** 194–205.
5. Dimopoulos MA, Eleutherakis-Papaiakovou V. Adverse effects of thalidomide administration in patients with neoplastic diseases. *Am J Med* 2004; **117:** 508–15.
6. Uhl K, *et al.* Thalidomide use in the US: experience with pregnancy testing in the S.T.E.P.S. programme. *Drug Safety* 2006; **29:** 321–9.

Effects on the blood. Thrombocytopenia has been reported in patients given thalidomide for multiple myeloma.[1,2]

1. Duyvendak M, *et al.* Thalidomide-associated thrombocytopenia. *Ann Pharmacother* 2005; **39:** 1936–9.
2. Prasad HK, *et al.* Isolated thrombocytopenia induced by thalidomide in a patient with multiple myeloma: case report and review of literature. *Am J Hematol* 2007; **82:** 855–7.

Effects on the cardiovascular system. Use of thalidomide in patients with malignant neoplastic disease has been associated with an increased risk of deep-vein thrombosis. There were 27 spontaneous reports of thromboembolic events in the first 18 months of thalidomide returning to the US market in July 1998; 26 of these were in patients with malignancies.[1] A review[2] of thromboembolic events associated with thalidomide identified 67 such reports from a total of 2075 adverse events reported to the FDA between October 1998 and June 2001; a further 29 cases were identified from clinical study data. Deep-vein thrombosis occurred in 48 of these patients, pulmonary embolism in 25, and 23 developed both. The most common primary diagnoses among these patients were multiple myeloma and renal cell carcinoma. However, it should be noted that patients with cancer are known to be at increased risk of venous thromboembolism and some chemotherapeutic regimens may further increase this risk. The contribution of thalidomide to the development of venous thromboembolism remains to be fully evaluated in controlled studies. Further reviews[3,4] of reports of venous thromboembolism associated with thalidomide concluded that the incidence of venous thromboembolism in patients with multiple myeloma is higher when thalidomide is given with chemotherapeutic drugs such as dexamethasone, melphalan, or doxorubicin.

Studies suggest that prophylactic use of a low-molecular-weight heparin (enoxaparin),[5] aspirin,[6] or warfarin[7] may reduce the incidence of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapeutic drugs.

Bradycardia has been associated with thalidomide therapy in some patients, although symptoms may be managed by a reduction in dose.[8,9] See also under Effects on the Endocrine System, below.

1. Clark TE, *et al.* Thalomid (thalidomide) capsules: a review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing. *Drug Safety* 2001; **24:** 87–117.
2. Bennett CL, *et al.* Thalidomide-associated deep vein thrombosis and pulmonary embolism. *Am J Med* 2002; **113:** 603–6.
3. Bennett CL, *et al.* Thalidomide- and lenalidomide-associated thromboembolism among patients with cancer. *JAMA* 2006; **296:** 2558–60.
4. Rajkumar SV. Thalidomide therapy and deep venous thrombosis in multiple myeloma. *Mayo Clin Proc* 2005; **80:** 1549–51.
5. Zangari M, *et al.* Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemotherapy: effects of prophylactic and therapeutic anticoagulation. *Br J Haematol* 2004; **126:** 715–21.
6. Baz R, *et al.* The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clin Proc* 2005; **80:** 1568–74.
7. Ikhlaque N, *et al.* Efficacy of prophylactic warfarin for prevention of thalidomide-related deep venous thrombosis. *Am J Hematol* 2006; **81:** 420–2.
8. Coutsouvelis J, Corallo CE. Thalidomide-induced bradycardia and its management. *Med J Aust* 2004; **180:** 366–7.
9. Fahdi IE, *et al.* Bradycardia during therapy for multiple myeloma with thalidomide. *Am J Cardiol* 2004; **93:**1052–5.

Effects on the endocrine system. Amenorrhoea has been reported[1,2] in women taking thalidomide for severe dermatological conditions; menses resumed 2 to 3 months after stopping thalidomide.[2]

Hypothyroidism has been associated with thalidomide use in patients with multiple myeloma,[3,4] and it was suggested[3] that some adverse effects of thalidomide, such as bradycardia and constipation, may be manifestations of hypothyroidism.

Severe hyperglycaemia has been reported[5] in a 70-year-old man 4 weeks after starting thalidomide for multiple myeloma. Plasma-glucose concentrations returned to normal after treatment with insulin and an oral antidiabetic and he continued with thalidomide therapy.

1. Passeron T, *et al.* Thalidomide-induced amenorrhoea: two cases. *Br J Dermatol* 2001; **144:** 1292–3.
2. Francès C, *et al.* Transient secondary amenorrhea in women treated by thalidomide. *Eur J Dermatol* 2002; **12:** 63–5.
3. Badros AZ, *et al.* Hypothyroidism in patients with multiple myeloma following treatment with thalidomide. *Am J Med* 2002; **112:** 412–13.
4. de Savary N, *et al.* Severe hypothyroidism after thalidomide treatment. *J R Soc Med* 2004; **97:** 443.
5. Pathak RD, *et al.* Thalidomide-associated hyperglycemia and diabetes: case report and review of literature. *Diabetes Care* 2003; **26:** 1322–3.

Effects on the gastrointestinal tract. Bowel perforation requiring surgery has been reported[1] in 3 patients taking thalidomide for malignant neoplasms. A fourth case of acute abdominal pain and suspected bowel perforation is also described but the patient died of a cardiac arrest before surgery.

1. McClay H, Cervi P. Thalidomide and bowel perforation: four cases in one hospital. *Br J Haematol* 2008; **140:** 360–1.

Effects on the liver. Hepatitis has been reported[1] in a 58-year-old woman taking thalidomide for end-stage plasma cell leukaemia. In another report of hepatotoxicity,[2] a 76-year-old woman with multiple myeloma being treated with thalidomide and dexamethasone developed jaundice and acute increases in liver enzymes, which returned to normal when thalidomide was stopped. Fatal fulminant hepatic failure with encephalopathy that appeared to be associated with thalidomide developed in a 64-year-old woman being treated for multiple myeloma.[3]

1. Fowler R, Imrie K. Thalidomide-associated hepatitis: a case report. *Am J Hematol* 2001; **66:** 300–2.
2. Hanje AJ, *et al.* Thalidomide-induced severe hepatotoxicity. *Pharmacotherapy* 2006; **26:** 1018–22.
3. Hamadani M, *et al.* Thalidomide-induced fulminant hepatic failure. *Mayo Clin Proc* 2007; **82:** 638.

Effects on the lungs. Interstitial pneumonitis has been reported in a patient taking thalidomide for multiple myeloma.[1] There have also been reports of dyspnoea in women taking thalidomide for ovarian cancer; resolution of symptoms occurred on drug withdrawal and some patients were able to continue therapy when reintroduced at a reduced dose.[2]

1. Onozawa M, *et al.* Thalidomide-induced interstitial pneumonitis. *J Clin Oncol* 2005; **23:** 2425–6.
2. Gordinier ME, Dizon DS. Dyspnea during thalidomide treatment for advanced ovarian cancer. *Ann Pharmacother* 2005; **39:** 962–5.

Effects on mental function. Symptoms of dementia appeared in a patient who had been taking thalidomide for about 2 months for the treatment of multiple myeloma.[1] Dementia later resolved completely within 48 hours of stopping thalidomide.

1. Morgan AE, *et al.* Reversible dementia due to thalidomide therapy for multiple myeloma. *N Engl J Med* 2003; **348:** 1821–2.

Effects on the nervous system. Peripheral neuropathy is a major adverse effect of thalidomide therapy, although the underlying mechanisms, risk factors, and optimum management are still not clear.[1] One prospective study[2] in patients with cutaneous or systemic lupus erythematosus concluded that the cumulative dose of thalidomide had no effect on the incidence of peripheral neuropathy, whereas results from a retrospective study[3] in patients with SLE or multiple myeloma showed that the risk of developing neurotoxicity as well as severity of symptoms did correlate with cumulative dose. However, the latter study[3] examined a range of doses and found that this correlation was most significant at cumulative doses over 20 g but either absent or equivocal at lower doses, which might explain the discrepancies in results between studies using different doses. Two further studies[4,5] in patients with multiple myeloma concluded that neurotoxicity was associated with duration of treatment of greater than 6 to 12 months rather than dose-intensity or total cumulative dose. Conversely, another study,[6] also in multiple myeloma patients, found electrophysiologic evidence of peripheral neuropathy in two-thirds of patients as early as 4 months from the start of treatment, and in all of them by 7 months; many patients also had clinical symptoms.

Central neurotoxicity has also been reported[7] in a patient who developed encephalopathy after receiving thalidomide monotherapy for multiple myeloma over 21 months.

1. Apfel SC, Zochodne DW. Thalidomide neuropathy: too much or too long? *Neurology* 2004; **62:** 2158–9.
2. Briani C, *et al.* Thalidomide neurotoxicity: prospective study in patients with lupus erythematosus. *Neurology* 2004; **62:** 2288–90.
3. Cavaletti G, *et al.* Thalidomide sensory neurotoxicity: a clinical and neurophysiologic study. *Neurology* 2004; **62:** 2291–3.
4. Tosi P, *et al.* Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. *Eur J Haematol* 2005; **74:** 212–16.
5. Mileshkin L, *et al.* Development of neuropathy in patients with myeloma treated with thalidomide: patterns of occurrence and the role of electrophysiologic monitoring. *J Clin Oncol* 2006; **24:** 4507–14.
6. Plasmati R, *et al.* Neuropathy in multiple myeloma treated with thalidomide: a prospective study. *Neurology* 2007; **69:** 573–81.
7. Sohlbach K, *et al.* Encephalopathy in a patient after long-term treatment with thalidomide. *J Clin Oncol* 2006; **24:** 4942–4.

Effects on sexual function. Dose-related sexual dysfunction, including loss of libido, loss of penile rigidity, and premature ejaculation, was associated with thalidomide use in 2 male patients.[1] Erectile dysfunction has been reported[2] in 6 patients within 4 weeks of starting thalidomide therapy.

1. Pouaha J, *et al.* Thalidomide and sexual dysfunction in men. *Br J Dermatol* 2002; **146:** 1112–13.
2. Murphy PT, O'Donnell JR. Thalidomide induced impotence in male hematology patients: a common but ignored complication? *Haematologica* 2007; **92:** 1440.

Effects on the skin. Toxic epidermal necrolysis has been reported[1] in a 62-year-old woman about 5 weeks after starting thalidomide for the treatment of a glioblastoma. Although she was taking several other drugs, including dexamethasone, thalidomide was considered responsible since its use had the closest temporal relationship to the adverse effect. Toxic epidermal necrolysis has also been reported[2] in a 64-year-old patient 24 days after starting thalidomide and dexamethasone for myeloma. It was suggested that there might be an adverse interaction between thalidomide and dexamethasone. Thalidomide had previously been studied[3] for the *treatment* of toxic epidermal necrolysis, but the study was prematurely terminated because of significantly higher mortality in the thalidomide group; the causes of death were those usually attributed to the disease itself. Thalidomide had been chosen as an investigative drug because it is a potent inhibitor of TNF-α, which has been implicated in the pathogenesis of this condition. However, the authors noted that

there was a tendency for plasma concentrations of TNF-α to increase after treatment with thalidomide compared with the placebo group, and postulated that thalidomide might paradoxically enhance TNF-α production in these patients.

Exacerbation of psoriasis by thalidomide, reported, in 2 patients might also have been due to an increase in TNF-α production.[4,5]

In an open-label study in 87 patients with multiple myeloma[6] comparing thalidomide given as monotherapy or given with dexamethasone, minor to moderate skin eruptions were noted in about 45% of patients in each group, and included morbilliform, seborrhoeic, maculopapular, and non-specific dermatitis. Three patients receiving thalidomide and dexamethasone developed severe skin reactions (exfoliative erythroderma, erythema multiforme, or toxic epidermal necrolysis) that required treatment to be stopped.

1. Horowitz SB, Stirling AL. Thalidomide-induced toxic epidermal necrolysis. *Pharmacotherapy* 1999; **19:** 1177–80.
2. Rajkumar SV, *et al.* Life-threatening toxic epidermal necrolysis with thalidomide therapy for myeloma. *N Engl J Med* 2000; **343:** 972–3.
3. Wolkenstein P, *et al.* Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998; **352:** 1586–9.
4. Dobson CM, Parslew RA. Exacerbation of psoriasis by thalidomide in Behçet's syndrome. *Br J Dermatol* 2003; **149:** 432–3.
5. Varma K, Finlay AY. Exacerbation of psoriasis by thalidomide in a patient with erythema multiforme. *Br J Dermatol* 2006; **154:** 789–90.
6. Hall VC, *et al.* Dermatologic side effects of thalidomide in patients with multiple myeloma. *J Am Acad Dermatol* 2003; **48:** 548–52.

Migraine. Migraine attacks were associated with thalidomide use in a 36-year-old man.[1]

1. García-Albea E, *et al.* Jaqueca típica y talidomida. *Med Clin (Barc)* 1993; **100:** 557.

Mutagenicity. Reports of the birth of 3 malformed infants to parents who had themselves been exposed to thalidomide *in utero*[1,2] provoked fears that thalidomide may be a mutagen. However, the limb malformations seen in the infants were not typical of mutagenesis[3] and the teratogenic effect of thalidomide was likely to be associated with interference with angiogenesis in the fetus rather than mutation.[4] Review[5] of the evidence up to 1998 concluded that there was no scientific basis for the hypothesis that thalidomide is a mutagen and birth defects appeared to be no more common in children born to thalidomide-affected parents than in the population as a whole. Further support for the counter-argument came in 2002 from a Swedish retrospective study in which malformations or functional anomalies consistent with thalidomide embryopathy were not found in 64 children born to 34 parents with thalidomide embryopathy.[6]

1. McBride WG. Thalidomide may be a mutagen. *BMJ* 1994; **308:** 1635–6.
2. Tenconi R, *et al.* Amniotic band sequence in child of thalidomide victim. *BMJ* 1994; **309:** 1442.
3. Read AP. Thalidomide may be a mutagen. *BMJ* 1994; **308:** 1636.
4. D'Amato RJ, *et al.* Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci U S A* 1994; **91:** 4082–5.
5. Smithells D. Does thalidomide cause second generation birth defects? *Drug Safety* 1998; **19:** 339–41.
6. Strömland K, *et al.* Offspring of male and female parents with thalidomide embryopathy: birth defects and functional anomalies. *Teratology* 2002; **66:** 115–21.

Interactions

The sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine has been reported to be enhanced by thalidomide. Use with other drugs that have the potential to cause peripheral neuropathy should be undertaken cautiously.

Antineoplastics. There may be an increased risk of deep-vein thrombosis from the use of thalidomide with *doxorubicin* (see p.714). See also Effects on the Cardiovascular System, above.

For the effect of thalidomide on the metabolism of *irinotecan*, see under Interactions of Irinotecan, p.738.

Corticosteroids. For reference to a possible interaction between thalidomide and *dexamethasone*, see under Effects on the Skin, above.

Hormonal contraceptives. Thalidomide does *not* alter the metabolism of ethinylestradiol and norethisterone,[1,2] and so the efficacy of oral contraceptives should not be affected by thalidomide therapy. Nevertheless, 2 reliable forms of contraception should always be used simultaneously when taking thalidomide (see Adverse Effects and Precautions, above), bearing in mind that the reliability of hormonal contraceptives may be compromised by drugs other than thalidomide (see p.2067).

1. Trapnell CB, *et al.* Thalidomide does not alter the pharmacokinetics of ethinyl estradiol and norethindrone. *Clin Pharmacol Ther* 1998; **64:** 597–602.
2. Scheffler MR, *et al.* Thalidomide does not alter estrogen-progesterone hormone single-dose pharmacokinetics. *Clin Pharmacol Ther* 1999; **65:** 483–90.

Interferons. Neurological toxicity was reported[1] in 4 of 13 patients in a phase II study of thalidomide and interferon alfa-2a used together in the treatment of renal cell carcinoma. It was suggested that the membrane-destabilising properties of both drugs could have produced such serious toxicity since it exceeded that expected from either drug alone. A fifth patient experienced a Stevens-Johnson reaction that was also attributed to the combination. The study was halted as a result of these serious adverse effects.

Severe bone marrow depression has been reported[2] in a patient given thalidomide with peginterferon alfa-2b that was also attributed to the combined effect of the 2 drugs.

1. Nathan PD, *et al.* Unexpected toxicity of combination thalidomide and interferon alfa-2a treatment in metastatic renal cell carcinoma. *J Clin Oncol* 2002; **20:** 1429–30.
2. Gómez-Rangel JD, *et al.* Pegylated-interferon induced severe bone marrow hypoplasia in a patient with multiple myeloma receiving thalidomide. *Am J Hematol* 2003; **74:** 290–1.

Pharmacokinetics

Thalidomide is slowly absorbed from the gastrointestinal tract; peak plasma concentrations are reached within about 3 to 6 hours of an oral dose. It crosses the placenta and is distributed into the semen. The exact metabolic route and fate of thalidomide is unknown, although it appears to undergo non-enzymatic hydrolysis in plasma. The elimination half-life is about 5 to 7 hours.

◊ References.

1. Aweeka F, *et al.* Pharmacokinetics and pharmacodynamics of thalidomide in HIV patients treated for oral aphthous ulcers: ACTG protocol 251. *J Clin Pharmacol* 2001; **41:** 1091–7.
2. Wohl DA, *et al.* Safety, tolerability, and pharmacokinetic effects of thalidomide in patients infected with human immunodeficiency virus: AIDS Clinical Trials Group 267. *J Infect Dis* 2002; **185:** 1359–63.
3. Teo SK, *et al.* Clinical pharmacokinetics of thalidomide. *Clin Pharmacokinet* 2004; **43:** 311–27.
4. Kamikawa R, *et al.* The pharmacokinetics of low-dose thalidomide in Japanese patients with refractory multiple myeloma. *Biol Pharm Bull* 2006; **29:** 2331–4.

Uses and Administration

Thalidomide has immunomodulating activity. It should always be given under appropriately supervised and controlled conditions because of the teratogenic risks and other potential adverse effects (see Adverse Effects and Precautions, above).

Thalidomide is used for the treatment of acute cutaneous manifestations of moderate to severe type 2 (erythema nodosum leprosum) lepra reactions (see Leprosy, p.176), but should not be given as monotherapy if moderate to severe neuritis is present; in such cases, corticosteroid therapy should also be given and continued until neuritis improves. Thalidomide may also be used for maintenance therapy for prevention and suppression of the cutaneous manifestations of recurrent type 2 lepra reactions. It is of no value in type 1 lepra reactions. It may be given orally in usual initial doses of 100 to 300 mg once daily. In severe cases up to 400 mg daily may be given. The dose should be reduced gradually by 50 mg every 2 to 4 weeks once a satisfactory response has been achieved. An alternative regimen is to start treatment with 100 mg once daily, and if symptoms are not controlled, increase the dose by increments of 100 mg at weekly intervals up to a maximum of 400 mg once daily.

Thalidomide is also used in the treatment of multiple myeloma (p.658) refractory to standard therapies. It is given orally in an initial dose of 200 mg once daily and, according to patient tolerance, the dose may be increased by 100 mg at weekly intervals up to a maximum dose of 800 mg daily. Thalidomide may be used with melphalan (p.742) and prednisone (p.1542) in patients with newly diagnosed multiple myeloma who are over 65 years of age or in those ineligible for high dose chemotherapy; thalidomide is given in a dose of 200 mg daily for a maximum of 12 cycles of 6 weeks each. Thalidomide may also be used with dexamethasone (p.1526) in the treatment of patients with newly diagnosed multiple myeloma: thalidomide 200 mg is given once daily; dexamethasone 40 mg is given orally on days 1 to 4, 9 to 12, and 17 to 20 in 28-day cycles.

Thalidomide should preferably be given at bedtime and at least 1 hour after the evening meal.

Thalidomide has been used in several other conditions whose aetiology may involve the immune system, such as treatment and prevention of graft-versus-host disease, treatment and prevention of recurrent aphthous stomatitis in severely and terminally immunocompromised patients, treatment of the clinical manifestations of both tuberculous and non-tuberculous mycobacterial infection, treatment of myelodysplastic syndrome and treatment of HIV-associated wasting syndrome, Kaposi's sarcoma, and Crohn's disease. It has also been used in the treatment of primary brain malignancies. Thalidomide is being investigated in some other malignancies.

◊ Guidelines on the clinical use of thalidomide.

1. Powell RJ, Gardner-Medwin JMM. Guideline for the clinical use and dispensing of thalidomide. *Postgrad Med J* 1994; **70:** 901–4.
2. Lary JM, *et al.* The return of thalidomide: can birth defects be prevented? *Drug Safety* 1999; **21:** 161–9.
3. Zeldis JB, *et al.* S.T.E.P.S.: a comprehensive program for controlling and monitoring access to thalidomide. *Clin Ther* 1999; **21:** 319–30. Further information available at: http://www.thalomid.com/steps_program.aspx (accessed 27/05/08)
4. Chave TA, *et al.* All-Wales Dermatology Audit Committee. Thalidomide usage in Wales: the need to follow guidelines. *Br J Dermatol* 2001; **144:** 310–15.

Action. The mechanism of action of thalidomide is not completely understood, although investigations have shown that it has anti-inflammatory and immunomodulating effects, including inhibition of the synthesis of tumour necrosis factor (TNF)-α. However, this inhibition is incomplete and selective, and increased plasma-TNF-α concentrations have been seen in some patient groups. Other immunomodulatory and anti-inflammatory properties include inhibition of leucocyte chemotaxis into the site of inflammation and reduction of phagocytosis by polymorphonuclear leucocytes. Thalidomide also appears to modulate interleukins, although results of investigations into its effect on specific interleukins and interferon gamma have so far been equivocal. Effects on CD4+ cells and variable effects on other mediators of intercellular reactions have also been implicated. Thalidomide also inhibits angiogenesis, which may have implications in solid tumours and other diseases.

General references to the mechanism of action and uses of thalidomide.[1-8]

1. Schuler U, Ehninger G. Thalidomide: rationale for renewed use in immunological disorders. *Drug Safety* 1995; **12:** 364–9.
2. Calabrese L, Fleischer AB. Thalidomide: current and potential clinical applications. *Am J Med* 2000; **108:** 487–95.
3. Peuckmann V, *et al.* Potential novel uses of thalidomide: focus on palliative care. *Drugs* 2000; **60:** 273–92.
4. Franks ME, *et al.* Thalidomide. *Lancet* 2004; **363:** 1802–11.
5. Rajkumar SV. Thalidomide: tragic past and promising future. *Mayo Clin Proc* 2004; **79:** 899–903.
6. Joglekar S, Levin M. The promise of thalidomide: evolving indications. *Drugs Today* 2004; **40:** 197–204.
7. Bessmertny O, Pham T. Thalidomide use in pediatric patients. *Ann Pharmacother* 2002; **36:** 521–5.
8. Teo SK. Properties of thalidomide and its analogues: implications for anticancer therapy. *AAPS J* 2005; **7:** E14–E19.

Behçet's syndrome. Thalidomide was effective for the treatment of oral and genital ulceration and follicular lesions in a randomised, double-blind, placebo-controlled study[1] in 96 male patients with Behçet's syndrome (p.1499). It was also noted that the development of new oral and genital ulcers was prevented, although relapses may occur on cessation of therapy. Thalidomide has also been reported[2,3] to be of benefit for severe oral and genital ulceration in children with Behçet's syndrome unresponsive to other treatments. Thalidomide also improved symptoms in a woman with Behçet's syndrome who had recurrent perforating intestinal ulcers.[4]

1. Hamuryudan V, *et al.* Thalidomide in the treatment of the mucocutaneous lesions of the Behçet syndrome: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998; **128:** 443–50.
2. Shek LP-C, *et al.* Thalidomide responsiveness in an infant with Behçet's syndrome. *Pediatrics* 1999; **103:** 1295–7.
3. Kari JA, *et al.* Behçet's disease in UK children: clinical features and treatment including thalidomide. *Rheumatology (Oxford)* 2001; **40:** 933–8.
4. Sayarlioglu M, *et al.* Treatment of recurrent perforating intestinal ulcers with thalidomide in Behçet's disease. *Ann Pharmacother* 2004; **38:** 808–11.

Cachexia. For the use of thalidomide in HIV-associated wasting, see HIV-associated Complications, below, and in cancer-related cachexia, see Malignant Neoplasms, below.

Graft-versus-host disease. A review[1] of studies investigating the use of thalidomide in chronic graft-versus-host disease (see Haematopoietic Stem Cell Transplantation, p.1811) concluded that although thalidomide appeared to be of benefit in some patients unresponsive to other treatments, doses greater than 200 mg daily are poorly tolerated in most patients. Giving thalidomide as prophylaxis led to poor survival, possibly through interfering with development of tolerance. Thalidomide was not of benefit when given as treatment for newly diagnosed disease.

1. Flowers MED, Martin PJ. Evaluation of thalidomide for treatment or prevention of chronic graft-versus-host disease. *Leuk Lymphoma* 2003; **44:** 1141–6.

HIV-associated complications. It has been proposed that thalidomide's inhibitory activity against TNF-α may explain its anti-HIV effect. However, there are conflicting reports as both decreased and increased TNF-α levels, as well as unchanged levels, have been seen in HIV-patients.[1] Nevertheless, thalidomide has shown some promise as a therapeutic agent for some AIDS-related diseases. It is an effective treatment for severe ulceration of the mouth (p.1700), oropharynx, and oesophagus in patients with HIV-infection.[2-5] Thalidomide has also been tried with some success in HIV-infected patients with prurigo nodularis,[6] alopecia areata[7] (p.1577), and hypertrophic genital herpes[8] (p.854). It has also proved to be of benefit in HIV-associated wasting[9] (p.858), and has shown promise in high doses for the treatment of AIDS-related Kaposi's sarcoma[10] (p.675). However, of concern is the finding that modest increases in plasma HIV RNA levels have been seen in some patients, which correlated with increases in TNF-α levels.[2,4]

1. Ravot E, *et al.* New uses for old drugs in HIV infection: the role of hydroxyurea, cyclosporin and thalidomide. *Drugs* 1999; **58:** 953–63.
2. Jacobson JM, *et al.* Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. *N Engl J Med* 1997; **336:** 1487–93.
3. Ramirez-Amador VA, *et al.* Thalidomide as therapy for human immunodeficiency virus-related oral ulcers: a double-blind placebo-controlled clinical trial. *Clin Infect Dis* 1999; **28:** 892–4.
4. Jacobson JM, *et al.* Thalidomide for the treatment of esophageal aphthous ulcers in patients with human immunodeficiency virus infection. *J Infect Dis* 1999; **180:** 61–7.
5. Shetty K. Thalidomide in the management of recurrent aphthous ulcerations in patients who are HIV-positive: a review and case reports. *Spec Care Dentist* 2005; **25:** 236–41.
6. Maurer T, *et al.* Thalidomide treatment for prurigo nodularis in human immunodeficiency virus-infected subjects: efficacy and risk of neuropathy. *Arch Dermatol* 2004; **140:** 845–9.

7. Baranda L, *et al.* Severe and unresponsive HIV-associated alopecia areata successfully treated with thalidomide. *Acta Derm Venereol* 2005; **85:** 277–8.
8. Holmes A, *et al.* Thalidomide therapy for the treatment of hypertrophic herpes simplex virus-related genitalis in HIV-infected individuals. *Clin Infect Dis* 2007; **44:** e96–e99. Available at: http://www.journals.uchicago.edu/doi/abs/10.1086/517513 (accessed 18/01/08)
9. Reyes-Terán G, *et al.* Effects of thalidomide on HIV-associated wasting syndrome: a randomized, double-blind, placebo-controlled trial. *AIDS* 1996; **10:** 1501–7.
10. Little RF, *et al.* Activity of thalidomide in AIDS-related Kaposi's sarcoma. *J Clin Oncol* 2000; **18:** 2593–2602.

Inflammatory bowel disease. Small open-label studies[1-3] have shown efficacy of thalidomide in patients with refractory Crohn's disease (see under Inflammatory Bowel Disease, p.1697). In many of those patients already receiving corticosteroids the dosage could be reduced and in some corticosteroids could be stopped completely. Reduction of TNF-α and interleukin-12 by thalidomide may be responsible for its clinical effects in Crohn's disease.[4] Thalidomide has also been reported[5] to be of benefit in children and young adults with intractable inflammatory bowel disease (both Crohn's disease and ulcerative colitis).

1. Ehrenpreis ED, *et al.* Thalidomide therapy for patients with refractory Crohn's disease: an open-label trial. *Gastroenterology* 1999; **117:** 1271–7.
2. Vasiliauskas EA, *et al.* An open-label pilot study of low-dose thalidomide in chronically active, steroid-dependent Crohn's disease. *Gastroenterology* 1999; **117:** 1278–87.
3. Bariol C, *et al.* Early studies on the safety and efficacy of thalidomide for symptomatic inflammatory bowel disease. *J Gastroenterol Hepatol* 2002; **17:** 135–9.
4. Bauditz J, *et al.* Thalidomide reduces tumour necrosis factor α and interleukin 12 production in patients with chronic active Crohn's disease. *Gut* 2002; **50:** 196–200.
5. Lazzerini M, *et al.* Efficacy and safety of thalidomide in children and young adults with intractable inflammatory bowel disease: long-term results. *Aliment Pharmacol Ther* 2007; **25:** 419–27.

Kaposi's sarcoma. See under HIV-associated complications, above and under Malignant Neoplasms, below.

Lupus erythematosus. Thalidomide has been found to be of benefit in lupus erythematosus, including chronic discoid lupus erythematosus,[1,2] lupus erythematosus profundus,[3,4] SLE[5] (p.1513), and cutaneous lupus erythematosus.[6-11] The beneficial effect of thalidomide on cutaneous lupus erythematosus may be partly mediated through protection against UV-induced inflammation.[11]

1. Knop J, *et al.* Thalidomide in the treatment of sixty cases of chronic discoid lupus erythematosus. *Br J Dermatol* 1983; **108:** 461–6.
2. Brocard A, *et al.* Lupus érythémateux chronique: traitement par thalidomide. *Ann Dermatol Venereol* 2005; **132:** 853–6.
3. Burrows NP, *et al.* Lupus erythematosus profundus with partial C4 deficiency responding to thalidomide. *Br J Dermatol* 1991; **125:** 62–7.
4. Wienert S, *et al.* Facetten des Lupus erythematodes: Pannikulitis mit gutem Ansprechen auf Thalidomid. *J Dtsch Dermatol Ges* 2008; **6** 214–16.
5. Bessis D, *et al.* Thalidomide for systemic lupus erythematosus. *Lancet* 1992; **339:** 549–50.
6. Atra E, Sato EI. Treatment of the cutaneous lesions of systemic lupus erythematosus with thalidomide. *Clin Exp Rheumatol* 1993; **11:** 487–93.
7. Stevens RJ, *et al.* Thalidomide in the treatment of the cutaneous manifestations of lupus erythematosus: experience in sixteen consecutive patients. *Br J Rheumatol* 1997; **36:** 353–9.
8. Duong DJ, *et al.* American experience with low-dose thalidomide therapy for severe cutaneous lupus erythematosus. *Arch Dermatol* 1999; **135:** 1079–87.
9. Pelle MT, Werth VP. Thalidomide in cutaneous lupus erythematosus. *Am J Clin Dermatol* 2003; **4:** 379–87.
10. Cuadrado MJ, *et al.* Thalidomide for the treatment of resistant cutaneous lupus: efficacy and safety of different therapeutic regimens. *Am J Med* 2005; **118:** 246–50.
11. Cummins DL, Gaspari AA. Photoprotection by thalidomide in patients with chronic cutaneous and systemic lupus erythematosus: discordant effects on minimal erythema dose and sunburn cell formation. *Br J Dermatol* 2004; **151:** 458–64.

Malignant neoplasms. Thalidomide has shown benefit in the treatment of patients with relapsed advanced multiple myeloma[1-4] (p.658) and also in patients with newly diagnosed disease;[4-8] the response improves when given with dexamethasone. Thalidomide also improved response when added to the regimen of pegylated liposomal doxorubicin, vincristine, and decreased frequency dexamethasone in patients with relapsed-refractory or newly diagnosed multiple myeloma,[9] and when added to melphalan and prednisone in newly-diagnosed elderly patients.[10,11] Thalidomide has also been investigated as maintenance treatment after intensive chemotherapy supported with haematopoietic stem-cell transplantation in patients with newly diagnosed disease;[12,13] thalidomide improved the response rate and event-free survival in both studies, although no improvement in overall survival was seen in one.[12] Thalidomide has also been tried in the treatment of several non-plasma cell malignancies with variable results.[14] It has shown promise in patients with recurrent high-grade gliomas[15] (p.660) and is under investigation for non-AIDS-related Kaposi's sarcoma[16,17] (p.675), metastatic melanoma[18] (p.673), myelofibrosis with myeloid metaplasia,[19-21] and androgen-independent prostate cancer[22,23] (p.671). Thalidomide has shown some benefit in the treatment of cancer-related cachexia (p.2115) in patients with pancreatic cancer.[24]

1. Singhal S, *et al.* Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999; **341:** 1565–71.
2. Rajkumar SV, *et al.* Thalidomide in the treatment of relapsed multiple myeloma. *Mayo Clin Proc* 2000; **75:** 897–901.
3. Kumar S, *et al.* Response rate, durability of response, and survival after thalidomide therapy for relapsed multiple myeloma. *Mayo Clin Proc* 2003; **78:** 34–9.
4. Palumbo A, *et al.* Thalidomide for treatment of multiple myeloma: 10 years later. *Blood* 2008; **111:** 3968–77.
5. Rajkumar SV, *et al.* Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol* 2002; **20:** 4319–23.
6. Weber D, *et al.* Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *J Clin Oncol* 2003; **21:** 16–19.
7. Rajkumar SV, *et al.* Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2006; **24:** 431–6.
8. Rajkumar SV, *et al.* Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. *J Clin Oncol* 2008; **26:** 2171–7.
9. Hussein MA, *et al.* Phase 2 study of pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide in newly diagnosed and relapsed-refractory multiple myeloma. *Mayo Clin Proc* 2006; **81:** 889–95.
10. Palumbo A, *et al.* Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet* 2006; **367:** 825–31.
11. Facon T, *et al.* Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet* 2007; **370:** 1209–18.
12. Barlogie B, *et al.* Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* 2006; **354:** 1021–30.
13. Attal M, *et al.* Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006; **108:** 3289–94.
14. Kumar S, *et al.* Thalidomid: current role in the treatment of non-plasma cell malignancies. *J Clin Oncol* 2004; **22:** 2477–88. Correction. *ibid.*; 2973. [title]
15. Fine HA, *et al.* Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high-grade gliomas. *J Clin Oncol* 2000; **18:** 708–15.
16. Ben M'barek L, *et al.* A retrospective analysis of thalidomide therapy in non-HIV-related Kaposi's sarcoma. *Dermatology* 2007; **215:** 202–5.
17. Rubegni P, *et al.* Thalidomide in the treatment of Kaposi's sarcoma. *Dermatology* 2007; **215:** 240–4.
18. Danson S, *et al.* Randomized phase II study of temozolomide given every 8 hours or daily with either interferon alfa-2b or thalidomide in metastatic malignant melanoma. *J Clin Oncol* 2003; **21:** 2551–7.
19. Mesa RA, *et al.* Durable responses to thalidomide-based drug therapy for myelofibrosis with myeloid metaplasia. *Mayo Clin Proc* 2004; **79:** 883–9.
20. Marchetti M, *et al.* Low-dose thalidomide ameliorates cytopenias and splenomegaly in myelofibrosis with myeloid metaplasia: a phase II trial. *J Clin Oncol* 2004; **22:** 424–31.
21. Thomas DA, *et al.* Thalidomide therapy for myelofibrosis with myeloid metaplasia. *Cancer* 2006; **106:** 1974–84.
22. Figg WD. The 2005 Leon I. Goldberg Young Investigator Award Lecture: Development of thalidomide as an angiogenesis inhibitor for the treatment of androgen-independent prostate cancer. *Clin Pharmacol Ther* 2006; **79:** 1–8.
23. Cox MC, *et al.* The use of thalidomide in androgen-independent prostate cancer. *Urol Oncol* 2006; **24:** 246–9.
24. Gordon JN,*et al*. Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut* 2005; **54:** 540–5.

Mouth ulceration. See under Behçet's syndrome, above and under HIV-associated complications, above.

Oesophageal ulceration. Thalidomide has been shown to be of benefit in the treatment of idiopathic oesophageal ulcers in patients with AIDS (see under HIV-associated complications, above). Thalidomide has also been reported to have healed an oesophageal ulcer refractory to other treatments in an immunocompetent patient,[1] and in an immunocompromised patient after liver transplant.[2]

1. Ollivier S, *et al.* Idiopathic giant oesophageal ulcer in an immunocompetent patient: the efficacy of thalidomide treatment. *Gut* 1999; **45:** 463–4.
2. Atiq M, *et al.* Successful treatment with thalidomide in a liver transplant recipient with giant esophageal ulcers. *Liver Transpl* 2006; **12:** 987–8.

Rheumatic disorders. Beneficial responses to thalidomide have been reported in the treatment of refractory rheumatoid arthritis[1] and adult-onset Still's disease.[2] Thalidomide also improved symptoms in 2 children with systemic onset juvenile rheumatoid arthritis, in whom other therapy, including etanercept, had been ineffective.[3] Efficacy was also shown in a further 11 children with refractory disease who were able to reduce their use of prednisone.[4]

1. Gutiérrez-Rodríguez O, *et al.* Treatment of refractory rheumatoid arthritis—the thalidomide experience. *J Rheumatol* 1989; **16:** 158–63.
2. Stambe C, Wicks IP. TNFα and response of treatment-resistant adult-onset Still's disease to thalidomide. *Lancet* 1998; **352:** 544–5.
3. Lehman TJA, *et al.* Thalidomide therapy for recalcitrant systemic onset juvenile rheumatoid arthritis. *J Pediatr* 2002; **140:** 125–7.
4. Lehman TJ, *et al.* Thalidomide for severe systemic onset juvenile rheumatoid arthritis: a multicenter study. *J Pediatr* 2004; **145:** 856–7.

Sarcoidosis. Case reports[1-5] of thalidomide in the treatment of sarcoidosis suggest that it might be of benefit.

1. Carlesimo M, *et al.* Treatment of cutaneous and pulmonary sarcoidosis with thalidomide. *J Am Acad Dermatol* 1995; **32:** 866–9.
2. Baughman RP, *et al.* Thalidomide for chronic sarcoidosis. *Chest* 2002; **122:** 227–32.
3. Walter MC, *et al.* Successful treatment of muscle sarcoidosis with thalidomide. *Acta Myol* 2003; **22:** 22–5.
4. Nguyen YT, *et al.* Treatment of cutaneous sarcoidosis with thalidomide. *J Am Acad Dermatol* 2004; **50:** 235–41.
5. Hammond ER, *et al.* Thalidomide for acute treatment of neurosarcoidosis. *Spinal Cord* 2007; **45:** 802–3.

Skin disorders. Thalidomide has shown efficacy in several severe dermatological disorders refractory to conventional therapies.[1,2] A review[3] of studies of thalidomide in the treatment of severe type 2 (erythema nodosum leprosum) lepra reactions concluded that it is an effective alternative to corticosteroid therapy. It has also been investigated in other severe skin disorders and beneficial responses have been reported in erythema multiforme[4,5] (p.1580), pruritus associated with uraemia,[6] Langerhans-cell histiocytosis[7] (p.650), epidermolysis bullosa and its variants,[8-10] prurigo nodularis,[11,12] pyoderma gangrenosum[13,14] (p.1583), and Schnitzler's syndrome.[15]

1. Wu JJ, *et al.* Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol* 2005; **153:** 254–73.
2. Faver IR, *et al.* Thalidomide for dermatology: a review of clinical uses and adverse effects. *Int J Dermatol* 2005; **44:** 61–7.
3. Walker SL, *et al.* The role of thalidomide in the management of erythema nodosum leprosum. *Lepr Rev* 2007; **78:** 197–215.
4. Bahmer FA, *et al.* Thalidomide treatment of recurrent erythema multiforme. *Acta Derm Venereol (Stockh)* 1982; **62:** 449–50.
5. Moisson YF, *et al.* Thalidomide for recurrent erythema multiforme. *Br J Dermatol* 1992; **126:** 92–3.
6. Silva SRB, *et al.* Thalidomide for the treatment of uremic pruritus: a crossover randomized double-blind trial. *Nephron* 1994; **67:** 270–3.
7. McClain KL, Kozinetz CA. A phase II trial using thalidomide for Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2007; **48:** 44–9.
8. Goulden V, *et al.* Linear prurigo simulating dermatitis artefacta in dominant dystrophic epidermolysis bullosa. *Br J Dermatol* 1993; **129:** 443–6.
9. Ozanic Bulic S, *et al.* Thalidomide in the management of epidermolysis bullosa pruriginosa. *Br J Dermatol* 2005; **152:** 1332–4.
10. Strauss RM, *et al.* A child with laryngo-onychocutaneous syndrome partially responsive to treatment with thalidomide. *Br J Dermatol* 2006; **155:** 1283–6.
11. Ferrándiz C, *et al.* Sequential combined therapy with thalidomide and narrow-band (TL01) UVB in the treatment of prurigo nodularis. *Dermatology* 1997; **195:** 359–61.
12. Lan C-CE, *et al.* Treatment of idiopathic prurigo nodularis in Taiwanese patients with low-dose thalidomide. *J Dermatol* 2007; **34:** 237–42.
13. Federman GL, Federman DG. Recalcitrant pyoderma gangrenosum treated with thalidomide. *Mayo Clin Proc* 2000; **75:** 842–4.
14. Koca E, *et al.* Successful treatment of myelodysplastic syndrome-induced pyoderma gangrenosum. *Neth J Med* 2006; **64:** 422–4.
15. Worm M, Kolde G. Schnitzler's syndrome: successful treatment of two patients using thalidomide. *Br J Dermatol* 2003; **148:** 601–2.

Preparations

USP 31: Thalidomide Capsules.

Proprietary Preparations (details are given in Part 3)
India: Thalix; ***Mex.:*** Inmunoprin; Talizer; ***USA:*** Thalomid.

Thallium Acetate

Talio, acetato de; Thallous Acetate.

$C_2H_3O_2Tl$ = 263.4.

CAS — 7440-28-0 (thallium); 563-68-8 (thallium acetate); 7446-18-6 (thallium sulfate).

Adverse Effects

Thallium salts are toxic when inhaled, ingested, or absorbed through the skin. Symptoms of poisoning may appear within 12 to 24 hours of a single toxic dose and include severe abdominal pain, nausea and vomiting, diarrhoea, gastrointestinal haemorrhage, salivation, metallic taste, paralytic ileus, pancreatic damage, and in severe cases cardiovascular collapse, tremors, delirium, convulsions, paralysis, and coma, leading to death in 1 to 2 days. However, the acute reaction may subside, to be followed within about 10 days by the development of neurological effects including paraesthesia, myalgia, myopathy, motor neuropathy, and visual disturbances due to optic neuropathy, psychosis, delirium, convulsions, and other signs of encephalopathy, tachycardia, hypertension, skin eruptions, and hepatorenal injury. Recovery from neurological damage is slow and may be incomplete. Alopecia occurs within 15 to 20 days; stomatitis may also develop. Death may result from respiratory failure; patients are also predisposed for several weeks to cardiac arrhythmias and sudden death. Fatalities have occurred after ingestion of 1 g or less in adults, although the UK Poisons Information Service consider the usual lethal dose by ingestion to be in the range 3 to 10 g in adults.

Smaller repeated doses are also toxic, with symptoms appearing over several weeks. Constipation is a common feature of less severe poisoning.