4. Morelli A, *et al.* Effects of terlipressin on systemic and regional haemodynamics in catecholamine-treated hyperkinetic septic shock. *Intensive Care Med* 2004; **30:** 597–604.
5. Leone M, *et al.* Terlipressin in catecholamine-resistant septic shock patients. *Shock* 2004; **22:** 314–19.
6. Jolley DH, *et al.* Terlipressin infusion in catecholamine-resistant shock. *Anaesth Intensive Care* 2003; **31:** 560–4.
7. Rodríguez-Núñez A, *et al.* Terlipressin for catecholamine-resistant septic shock in children. *Intensive Care Med* 2004; **30:** 477–80.

Variceal haemorrhage. Systematic review has indicated[1] that terlipressin is effective in the management of acute oesophageal variceal haemorrhage (see under Monoethanolamine, p.2346), and reduces the relative risk of mortality by about one-third. Differences in effectiveness from other therapies could not be conclusively shown. Comparison of a regimen of terlipressin given by intravenous bolus injection, plus glyceryl trinitrate given sublingually, with balloon tamponade in variceal bleeding has suggested similar efficacy.[2] However, tamponade was successful in all patients that were previously unresponsive to terlipressin plus glyceryl trinitrate whereas this drug combination failed in all patients previously unresponsive to tamponade. A comparison of terlipressin and endoscopic injection sclerotherapy found them to be equally effective for the control of acute variceal bleeding.[3]

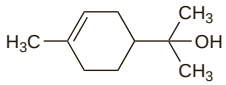
1. Ioannou G, *et al.* Terlipressin for acute esophageal variceal hemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/09/05).
2. Fort E, *et al.* A randomized trial of terlipressin plus nitroglycerin vs balloon tamponade in the control of acute variceal hemorrhage. *Hepatology* 1990; **11:** 678–81.
3. Escorsell À, *et al.* Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. *Hepatology* 2000; **32:** 471–6.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Glycylpressin; ***Austria:*** Glycylpressin; Haemopressin; ***Belg.:*** Glypressin; ***Braz.:*** Glypressin†; ***Cz.:*** Glypressin; Remestyp; ***Denm.:*** Glypressin; ***Fin.:*** Glypressin; ***Fr.:*** Glypressine; ***Ger.:*** Glycylpressin; Haemopressin; ***Gr.:*** Glypressin; ***Hong Kong:*** Glypressin; ***Hung.:*** Glypressin; ***Irl.:*** Glypressin; ***Ital.:*** Glipressina; ***Malaysia:*** Glypressin; ***Mex.:*** Glyverase; ***Neth.:*** Glypressin; ***Pol.:*** Remestyp; ***Rus.:*** Remestyp (Реместил)†; ***Singapore:*** Glypressin; ***Spain:*** Glypressin; ***Switz.:*** Glypressine; ***Thai.:*** Glypressin; ***Turk.:*** Glypressin; ***UK:*** Glypressin.

Terpineol

$C_{10}H_{18}O$ = 154.2.
CAS — 8000-41-7 (terpineol); 98-55-5 (α-terpineol).



Pharmacopoeias. In *Br.*
BP 2008 (Terpineol). A mixture of structural isomers in which α-terpineol predominates. It is a colourless, slightly viscous liquid which may deposit crystals; it has a pleasant characteristic odour. Very slightly soluble in water; freely soluble in alcohol (70%); soluble in ether.

Profile
Terpineol has disinfectant and solvent properties. It is used with other volatile agents in preparations for respiratory-tract disorders.

Preparations
BP 2008: Chloroxylenol Solution.

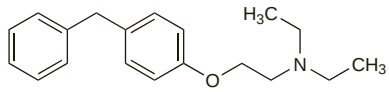
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Arg.:*** Aseptobron; Aseptobron Ampicilina†; Atomo Desinflamante; Atomo Desinflamante Familiar; Atomo Desinflamante G; Bronco Etersan; Di-Neumobron; ***Austral.:*** Karvol†; Tixylix Chest Rub†; ***Braz.:*** Bromil; Eucaliptan†; Mentalol†; Penetro; Tabletes Valda†; Valda†; ***Cz.:*** Coldastop; ***Fr.:*** Nazinette du Docteur Gilbert; Pectoderme†; Valda; ***Hong Kong:*** Valda†; ***India:*** Dettol Obstetric; Easi Breathe; Fairgenol†; Karvol Plus; Sinarest Vapocaps; ***Irl.:*** Karvol; Valda†; ***Israel:*** Gargol; Karvol; Rexitol; ***Ital.:*** Calyptol; Rikospray; Skab 2; ***NZ:*** Tixylix Chest Rub; ***Port.:*** Valda†; ***S.Afr.:*** AF; Karvol; ***Singapore:*** Karvol; ***Spain:*** Caltoson Balsamico; Eupnol; Pastillas Juanola†; ***Switz.:*** Perskindol Classic; Sedotussin†; ***UK:*** Chymol; Jacksons Mentholated Balm; Karvol; Nowax; Waxwane†.

Tesmilifene Hydrochloride *(USAN, rINNM)*

BMS-217380-01; BMY-33419; DPPE; Hidrocloruro de tesmilifeno; Tesmilifène, Chlorhydrate de; Tesmilifeni Hydrochloridum. 2-[(α-Phenyl-*p*-tolyl)oxy]triethylamine hydrochloride; *N,N*-Diethyl-2-[4-(phenylmethyl)phenoxy]-ethanamine hydrochloride.

Тезмилифена Гидрохлорид

$C_{19}H_{25}NO,HCl$ = 319.9.
CAS — 98774-23-3 (tesmilifene); 92981-78-7 (tesmilifene hydrochloride).



(tesmilifene)

Profile
Tesmilifene hydrochloride is an intracellular histamine antagonist that appears to augment the antineoplastic activity of drugs such as the anthracyclines and taxanes. It is under investigation for the treatment of various cancers, including hormone-refractory cancer of the prostate and gastric and hepatic cancers.

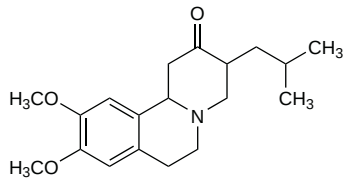
◊ References.
1. Reyno L, *et al.* Phase III study of N,N-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine (BMS-217380-01) combined with doxorubicin versus doxorubicin alone in metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA19. *J Clin Oncol* 2004; **22:** 269–76.
2. Raghavan D, *et al.* Phase II trial of tesmilifene plus mitoxantrone and prednisone for hormone refractory prostate cancer: high subjective and objective response in patients with symptomatic metastases. *J Urol (Baltimore)* 2005; **174:** 1808–13.

Tetrabenazine *(BAN, rINN)*

Ro-1-9569; Tetrabenatsiini; Tetrabenazin; Tetrabenazina; Tétrabénazine; Tetrabenazinum. 1,3,4,6,7,11b-Hexahydro-3-isobutyl-9,10-dimethoxybenzo-[*a*]quinolizin-2-one.

Тетрабеназин

$C_{19}H_{27}NO_3$ = 317.4.
CAS — 58-46-8.
ATC — N07XX06.
ATC Vet — QN07XX06.



Adverse Effects
Drowsiness is the most frequent adverse effect of tetrabenazine. Orthostatic hypotension, symptoms of extrapyramidal dysfunction, gastrointestinal disturbances, and depression may also occur. Neuroleptic malignant syndrome and parkinsonism have been reported rarely. Overdosage has produced sedation, sweating, hypotension, and hypothermia.

Effects on mental function. Depression is well documented as an adverse effect of tetrabenazine, and occurs in about 15% of patients; it has been reported to respond to reboxetine.[1] Florid psychiatric symptoms such as panic attacks and obsessive-compulsive symptoms may be precipitated or exacerbated by tetrabenazine.[2]

1. Schreiber W, *et al.* Reversal of tetrabenazine induced depression by selective noradrenaline (norepinephrine) reuptake inhibition. *J Neurol Neurosurg Psychiatry* 1999; **67:** 550.
2. Bruneau MA, *et al.* Catastrophic reactions induced by tetrabenazine. *Can J Psychiatry* 2002; **47:** 683.

Extrapyramidal disorders. Dysphagia and choking were associated with tetrabenazine in the treatment of Huntington's chorea.[1] Fatal pneumonia, probably as a consequence of aspiration, had also been reported.

1. Snaith RP, Warren H de B. Treatment of Huntington's chorea with tetrabenazine. *Lancet* 1974; **i:** 413–14.

Overdosage. A patient who swallowed about 1 g (40 tablets) of tetrabenazine became drowsy 2 hours later and marked sweating occurred.[1] Her state of consciousness improved after 24 hours and she talked rationally and gained full control of micturition after 72 hours.

1. Kidd DW, McLellan DL. Self-poisoning with tetrabenazine. *Br J Clin Pract* 1972; **26:** 179–80.

Precautions
Tetrabenazine may exacerbate the symptoms of parkinsonism. It may cause drowsiness; affected patients should not drive or operate machinery.

Interactions
Tetrabenazine has been reported to block the action of reserpine. It may also diminish the effects of levodopa and exacerbate the symptoms of parkinsonism. Use of tetrabenazine immediately after a course of an MAOI may lead to confusion, restlessness, and disorientation; tetrabenazine should not be given with, or within 14 days of stopping, such therapy.

Pharmacokinetics
Absorption of tetrabenazine is poor and erratic after oral doses. It appears to be extensively metabolised by first-pass metabolism. Its major metabolite, hydroxytetrabenazine, which is formed by reduction, is reported to be as active as the parent compound. It is excreted in the urine mainly in the form of metabolites.

Uses and Administration
Tetrabenazine is used in the management of movement disorders including chorea (p.953), ballism (p.953), dystonias (p.809), tardive dyskinesia (see under Extrapyramidal Disorders, p.971), and similar symptoms of CNS dysfunction.

For the treatment of chorea, ballism, and other organic CNS movement disorders, a starting oral dose of 25 mg three times daily has been recommended; the *BNF* considers a dose of 12.5 mg twice daily (or 12.5 mg daily in the elderly) more appropriate initially, which is less likely to cause excessive sedation. The dose may be gradually increased by 25 mg daily every 3 or 4 days according to response up to a maximum of 200 mg daily. If the patient does not respond within 7 days of receiving the maximum dose further treatment with tetrabenazine is unlikely to be of benefit.

For moderate to severe tardive dyskinesia, a dose of 12.5 mg daily is recommended initially, subsequently titrated according to response.

Extrapyramidal disorders. In a long-term study[1] of the use of tetrabenazine in 400 patients with movement disorders, the best responses seemed to be in tardive dyskinesia, tardive dystonia, and Huntington's disease but benefit was also obtained in some patients with idiopathic dystonia, segmental myoclonus, and Tourette's syndrome. Others have commented that in severe dystonia unresponsive to other drugs a combination of tetrabenazine with trihexyphenidyl and pimozide is sometimes effective.[2] Tetrabenazine significantly reduced chorea in ambulatory patients with Huntington's disease in a small 12-week randomised placebo-controlled study.[3] It was well tolerated, although there was a significant increase in reports of drowsiness and insomnia, which generally resolved with adjustment of doses.

1. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. *Neurology* 1997; **48:** 358–62.
2. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.
3. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. *Neurology* 2006; **66:** 366–72.

Preparations
Proprietary Preparations (details are given in Part 3)
Canad.: Nitoman; ***Denm.:*** Nitoman; ***Fr.:*** Xenazine; ***India:*** Revocon; ***Irl.:*** Nitoman; ***Israel:*** Xenazine; ***NZ:*** Xenazine; ***Port.:*** Nitoman; Revocon; ***UK:*** Xenazine.

Tetrachlorodecaoxide

TCDO; Tetrachlorodecaoxygen Anion Complex; Tetraclorodecaóxido; WF-10.

Cl_4O_{10} = 301.8.
CAS — 92047-76-2.

Profile
Tetrachlorodecaoxide is a water-soluble anion complex containing oxygen in a chlorite matrix. Active oxygen is only released in the presence of biological material. It has been applied as a solution for the stimulation of wound healing.

Wounds. Tetrachlorodecaoxide was reported to promote wound healing compared with saline in a double-blind study of 271 patients,[1] but a smaller study failed to show any benefit over glycerol.[2]

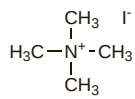
1. Hinz J, *et al.* Rationale for and results from a randomised, double-blind trial of tetrachlorodecaoxygen anion complex in wound healing. *Lancet* 1986; **i:** 825–8.
2. Hughes LE, *et al.* Failure of tetrachlorodecaoxygen anion complex to assist wound healing. *Lancet* 1989; **ii:** 1271.

Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Oxilium; ***Indon.:*** Oxoferin; ***Port.:*** Oxoferin; ***Switz.:*** Oxilium†; ***Thai.:*** Immunokine; Oxoferin; ***Venez.:*** Oxoferin.

Tetramethylammonium Iodide

Tetrametilamonio, ioduro de.

$C_4H_{12}IN$ = 201.0.
CAS — 75-58-1.



Profile
Tetramethylammonium iodide is a quaternary ammonium compound that has been used for the emergency disinfection of drinking water. It has also been employed for its ganglion-blocking properties.

Thalidomide *(BAN, USAN, rINN)*

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

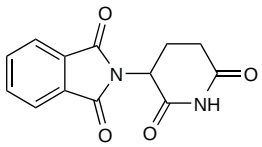
Талидомид

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