

Anticonvulsants/antiepileptics

Control of epilepsy

Treatment should always be started with a single drug, but the choice of an anticonvulsant can only be made on an individual basis and will depend on the efficacy of the drug and the patient's tolerance of treatment. If a drug fails to control the seizures after it has been used in full therapeutic dosage for an adequate period, or if it is not tolerated, it should be gradually substituted with another with the first drug being withdrawn only when the new regimen is mainly established. If monotherapy is ineffective, two drugs should be given in combination and several regimens may need to be tried before the most appropriate is found.

Initial dose of the drug of choice should be determined on the basis of the degree of urgency, the size and age of the patient. It should be increased gradually until an effective response is obtained. All antiepileptics commonly produce neurological adverse effects at too high a dose, and patients should be monitored closely for adverse effects to help in accurate dose titration. Except for phenytoin, it is rarely useful to measure plasma-drug concentrations as an aid to dose adjustment. Non-compliance because of inappropriate dosing and overdosing is a major impediment to effective antiepileptic treatment. Patients should ideally remain under supervision throughout treatment.

WITHDRAWAL

Treatment is normally continued for a minimum of two years after the last seizure. Withdrawal should be extended over a period of several months because abrupt withdrawal can lead to complications such as status epilepticus. In patients receiving several antiepileptic drugs, only one drug should be withdrawn at a time. Many adult patients relapse once treatment is withdrawn and it may be justified to continue treatment indefinitely, particularly when the patient's livelihood or lifestyle can be endangered by recurrence of a seizure.

PREGNANCY AND BREASTFEEDING

Untreated epilepsy during pregnancy may cause harm to the fetus; there is therefore no justification for abrupt withdrawal of treatment although withdrawal of therapy may be an option if the patient has been seizure-free for at least 2 years; resumption of treatment may be considered after the first trimester. If antiepileptics are continued in pregnancy, monotherapy with the lowest effective dose is preferred, with adjustment made to take account of changes in plasma levels associated with pregnancy. There is an increased risk of birth defects with the use of anticonvulsants, particularly **carbamazepine**, **valproate** and **phenytoin**. However, if there is good seizure control, there is probably no advantage in changing pregnant patients' antiepileptic drugs. In view of the risks of neural tube and other defects, patients who may become pregnant should be informed of the risks and referred for advice, and pregnant patients should be offered counselling and antenatal screening. To counteract the risk of neural tube defects, adequate **folate** supplements are advised for women before and during pregnancy. In view of the risk of neonatal bleeding associated with **carbamazepine**, **phenobarbital** and **phenytoin**, prophylactic **phytomenadione**

(vitamin K₁) is recommended for the neonate and the mother before delivery. Antiepileptic drugs can be continued during breastfeeding (see also Appendix 3).

DRIVING

Regulations are in place in many countries which may, for example, restrict driving by patients with epilepsy to those whose seizures are controlled. Further, antiepileptic drugs may cause CNS depression, particularly in the early stages of treatment and patients affected by adverse effects such as drowsiness or dizziness should not operate machinery or drive.

Choice of antiepileptic in management of convulsive disorders

GENERALIZED TONIC-CLONIC, SIMPLE PARTIAL AND COMPLEX PARTIAL SEIZURES

Carbamazepine, **phenobarbital**, **phenytoin**, and **valproate** are widely used in the treatment of these conditions. However, each of these drugs is associated with dose-related and idiosyncratic adverse effects and monitoring of haematological and hepatic function is often advised, particularly for carbamazepine and valproate.

ABSENCE SEIZURES

Both **ethosuximide** and **valproate** are widely used in the treatment of absence seizures (petit mal) and are usually well tolerated. However, ethosuximide can, rarely, cause lupus erythematosus and psychoses which call for immediate, but cautious, discontinuation. Absence seizures are commonly associated with tonic-clonic seizures and valproate is preferred since it is effective in both disorders.

TONIC SEIZURES, ATONIC SEIZURES AND ATYPICAL ABSENCE SEIZURES

Phenobarbital or **phenytoin** is widely used for tonic seizures, **valproate** or **clonazepam** for atonic seizures, and **clonazepam** for atypical absence seizures.

MYOCLONIC SEIZURES

Valproate is widely used and most effective for juvenile myoclonic seizures. However, both valproate and this type of seizure are associated with a high relapse rate and it is often necessary to continue therapy indefinitely. Other myoclonic seizures are often resistant to treatment and some do not have an epileptic basis. **Valproate** or **clonazepam** can be of value in this case and other antiepileptic drugs may be useful in intractable cases. Both drugs are generally well accepted, although tolerance to clonazepam has been reported.

INFANTILE SPASM (INFANTILE MYOCLONIC EPILEPSY)

Infantile spasms, which are often associated with severe brain damage, can be resistant to antiepileptic drugs. **Clonazepam** is sometimes of value in resistant cases.

FEBRILE CONVULSIONS

Brief febrile convulsions usually respond to sponging with tepid water and by giving an antipyretic such as paracetamol (section 2.1.2). Recurrent febrile convulsions or prolonged convulsions (those lasting 15 minutes or longer) are treated with **diazepam**, either rectally in solution or by intravenous injection, to prevent possible brain damage.

Intermittent prophylaxis, with diazepam administered at the onset of fever, may prevent recurrence of febrile convulsions, but only in a small proportion of children. Use of antiepileptics for *continuous prophylaxis* is controversial; it is probably indicated in only a small proportion of children including those whose first seizure occurred during the first 14 months of life, or who already have evident neurological abnormalities, or who have had previous prolonged or focal convulsions.

Phenobarbital may be used for this purpose but careful clinical monitoring and dosage adjustment are necessary in order to minimize the risk of adverse effects.

Valproate, although effective, is not recommended because of the greater risk of hepatotoxicity in young children.

Status epilepticus.

Status epilepticus is a medical emergency which carries a high mortality rate. Initial management includes positioning the patient to avoid injury, supporting respiration including provision of oxygen, maintaining blood pressure, and the correction of any hypoglycaemia; maintenance of the airway and assisted ventilation are crucial even when the seizures are controlled, because the drugs used in its management may also depress respiration.

Intravenous **diazepam** or **clonazepam** are often effective in status epilepticus. Diazepam, which acts rapidly, should be administered first and should be followed immediately by a loading dose of **phenytoin** which has a longer-acting effect. When cannulation is impossible, diazepam may be administered rectally as a solution (absorption from suppositories is too slow for treatment of status epilepticus). Intravenous **phenobarbital** is also effective but is more likely to cause respiratory depression; it is used in refractory cases but should be avoided in patients who have recently received oral phenobarbital. Rectal paraldehyde may also be used; it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

If seizures continue despite treatment, general anaesthesia may be required. The underlying cause must be identified and remedied in all cases.

Carbamazepine

Tablets, carbamazepine 100 mg, 200 mg

Uses:

generalized tonic-clonic and partial seizures; trigeminal neuralgia; bipolar disorder (section 24.2.2)

Contraindications:

atrioventricular conduction abnormalities; history of bone-marrow depression; porphyria

Precautions:

hepatic impairment (Appendix 5); renal impairment (Appendix 4); cardiac disease (see also Contraindications); skin reactions (see Adverse effects); history of blood disorders (blood counts before and during treatment); glaucoma; pregnancy (**important** see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); avoid sudden withdrawal; **interactions:** Appendix 1

BLOOD, HEPATIC OR SKIN DISORDERS. Patients or their carers should be told how to recognize signs of blood, liver or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising or bleeding develop. Leukopenia which is severe, progressive and associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative)

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above

Dosage:

Generalized tonic-clonic seizures, partial seizures, *by mouth* , **ADULT** initially 100 mg twice daily, increased gradually according to response to usual maintenance dose of 0.8–1.2 g daily in divided doses; **ELDERLY** reduce initial dose; **CHILD** 10–20 mg/kg daily in divided doses

Trigeminal neuralgia, *by mouth* , **ADULT** initially 100 mg 1–2 times daily increased gradually according to response; usual dose 200 mg 3–4 times daily with up to 1.6 g daily in some patients

NOTE. Plasma concentration for optimum response 4–12 mg/litre (17–50 micromol/litre)

Adverse effects:

dizziness, drowsiness, headache, ataxia, blurred vision, diplopia (may be associated with high plasma levels); gastrointestinal intolerance including nausea and vomiting, anorexia, abdominal pain, dry mouth, diarrhoea or constipation; commonly, mild transient generalized erythematous rash (withdraw if worsens or is accompanied by other symptoms); leukopenia and other blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia); cholestatic jaundice, hepatitis, acute renal failure, Stevens-Johnson syndrome (erythema multiforme), toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, arrhythmias, heart block and heart failure, dyskinesias, paraesthesia, depression, impotence, male infertility, gynaecomastia, galactorrhoea, aggression, activation of psychosis, photosensitivity, pulmonary hypersensitivity, hyponatraemia, oedema, disturbances of bone metabolism with osteomalacia also reported; confusion and agitation in elderly

Clonazepam

Drug subject to international control under the Convention on Psychotropic Substances (1971)

Clonazepam is a representative benzodiazepine anticonvulsant. Various drugs can serve as alternatives

Clonazepam is a complementary drug

Tablets , clonazepam 500 micrograms

Uses:

atonic seizures; myoclonic seizures; atypical absence seizures; absence seizures resistant to ethosuximide or valproate; infantile spasms

Contraindications:

respiratory depression; acute pulmonary insufficiency; myasthenia gravis

Precautions:

respiratory disease; hepatic impairment (Appendix 5); renal impairment (Appendix 4); elderly and debilitated; pregnancy (see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); avoid sudden withdrawal; porphyria; **interactions:** Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving; effects of alcohol enhanced; see also notes above

Dosage:

Epilepsy (see Uses above), *by mouth* , **ADULT** initially 1 mg at night for 4 nights, increased gradually over 2–4 weeks to a usual maintenance dose of 4–8 mg daily in divided doses; **ELDERLY** (or debilitated patients) initial dose 500 micrograms increased as above; **CHILD** up to 1 year initially 250 micrograms increased as above to 0.5–1 mg daily in divided doses; 1–5 years initially 250 micrograms increased to 1–3 mg daily in divided doses; 5–12 years initially 500 micrograms increased to 3–6 mg daily in divided doses

Adverse effects:

drowsiness, lethargy, ataxia, paradoxical aggression, irritability and mental changes; rarely blood disorders, abnormal hepatic function tests, excessive salivation

Diazepam

Drug subject to international control under the Convention on Psychotropic Substances (1971)

Diazepam is a representative benzodiazepine anticonvulsant. Various drugs can serve as alternatives

Injection (Solution for injection), diazepam 5 mg/ml, 2-ml ampoule

Rectal solution, diazepam 2 mg/ml, 1.25- and 2.5-ml tube; 4 mg/ml, 2.5-ml tube [not included on WHO Model List]

Uses:

status epilepticus; emergency management of recurrent seizures; febrile convulsions; seizures associated with poisoning and drug withdrawal; adjunct in acute alcohol withdrawal; premedication (section 1.3); anxiety disorders (section 24.3)

Contraindications:

respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; myasthenia gravis; avoid injections containing benzyl alcohol in neonates

Precautions:

respiratory disease, muscle weakness, history of alcohol or drug abuse, marked personality disorder; pregnancy (see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); reduce dose in elderly or debilitated and in hepatic impairment (avoid if severe, Appendix 5), renal impairment (Appendix 4); avoid prolonged use and abrupt withdrawal; when given intravenously facilities for reversing respiratory depression with mechanical ventilation must be at hand (see below); porphyria; **interactions:** Appendix 1

PRECAUTIONS FOR INTRAVENOUS INFUSION. Intravenous infusion of diazepam is potentially hazardous (especially if prolonged) calling for close and constant observation and best carried out in a specialist centre with intensive care facilities. Prolonged intravenous infusion may lead to accumulation and delay recovery

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above

Dosage:

Status epilepticus or emergency management of recurrent epileptic seizures, *by slow intravenous injection* (at rate of 5 mg/minute), **ADULT** 10–20 mg, repeated if necessary after 30–60 minutes; may be followed *by intravenous infusion* to maximum 3 mg/kg over 24 hours; *by slow intravenous injection*, **CHILD** 200 to 300 micrograms/kg (*or* 1 mg per year of age); *by rectum* as solution, **ADULT** and

CHILD over 10 kg, 500 micrograms/kg, **ELDERLY** 250 micrograms/kg; repeated if necessary every 12 hours; if convulsions not controlled, other measures should be instituted

Febrile convulsions (preferred treatment), *by rectum* as solution [injection solution may be used], **CHILD** over 10 kg, 500 micrograms/kg (maximum 10 mg), with dose repeated if necessary

Febrile convulsions (alternative treatment), *by slow intravenous injection*, **CHILD** 200–300 micrograms/kg (*or* 1 mg per year of age)

Drug or alcohol withdrawal, *by slow intravenous injection* (at rate of 5 mg/minute), **ADULT** 10 mg; higher doses may be required depending on severity of symptoms

Seizures associated with poisoning, *by slow intravenous injection* (at rate of 5 mg/minute), **ADULT** 10–20 mg

Adverse effects:

drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression; muscle weakness; occasionally headache, vertigo, salivation changes, gastrointestinal disturbances, skin reactions, visual disturbances, dysarthria, tremor, changes in libido, incontinence, urinary retention; blood disorders and jaundice; hypotension and apnoea, pain and thrombophlebitis (with injection)

Ethosuximide

Ethosuximide is a complementary antiepileptic drug

Capsules, ethosuximide 250 mg

Syrup, ethosuximide 250 mg/5 ml

Uses:

absence seizures

Precautions:

hepatic or renal impairment; blood counts and hepatic and renal function tests recommended; pregnancy (see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); avoid sudden withdrawal; porphyria; **interactions:** Appendix 1

BLOOD DISORDERS. Patients or their carers should be told how to recognize signs of blood disorders, and advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising or bleeding develop

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above

Dosage:

Absence seizures, *by mouth* , **ADULT** and **CHILD** over 6 years initially 500 mg daily, increased by 250 mg at intervals of 4–7 days to a usual dose of 1–1.5 g daily (occasionally, up to maximum of 2 g daily); **CHILD** under 6 years initially 250 mg daily, increased gradually to usual dose of 20 mg/kg daily

Patient Advice. Daily doses of 1 g and above should be taken as 2 or more divided doses

NOTE. Plasma concentration for optimum response 40–100 mg/litre (300–700 micromol/litre)

Adverse effects:

gastrointestinal disturbances including anorexia, hiccups, nausea and vomiting, epigastric pain (particularly during initial treatment); weight loss, drowsiness, dizziness, ataxia, headache, depression, mild euphoria; rarely, rash including Stevens-Johnson syndrome (erythema multiforme), systemic lupus erythematosus, disturbances of liver and renal function (see Precautions), haematological disorders including leukopenia, agranulocytosis, aplastic anaemia, thrombocytopenia, pancytopenia; gum hyperplasia, swelling of tongue, irritability, hyperactivity, sleep disturbances, night terrors, aggressiveness, psychosis, increased libido, myopia, vaginal bleeding, also reported

Phenobarbital

Drug subject to international control under the Convention on Psychotropic Substances (1971)

Tablets, phenobarbital 15 mg, 30 mg, 60 mg, 100 mg

Elixir (Oral solution), phenobarbital 15 mg/5 ml

Injection (Concentrate for solution for injection), phenobarbital sodium 200 mg/ml [not included on WHO Model List]

Uses:

generalized tonic-clonic seizures; partial seizures; neonatal seizures; febrile convulsions; status epilepticus (see notes above)

Contraindications:

porphyria; absence seizures

Precautions:

elderly, debilitated, children (may cause behavioural changes); impaired renal function (Appendix 4) or hepatic function (Appendix 5), respiratory depression (avoid if severe); pregnancy (see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); avoid sudden withdrawal; **interactions:** Appendix 1

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving; see also notes above

Dosage:

Generalized tonic-clonic seizures, partial seizures, *by mouth* , **ADULT** 60–180 mg at night; **CHILD** up to 8 mg/kg daily

Febrile convulsions, *by mouth* , **CHILD** up to 8 mg/kg daily

Neonatal seizures, *by intravenous injection* (dilute injection 1 in 10 with water for injections), **neonate** 5–10 mg/kg every 20–30 minutes up to plasma concentration of 40 mg/litre

Status epilepticus, *by intravenous injection* (dilute injection 1 in 10 with water for injections), **ADULT** 10 mg/kg at a rate of not more than 100 mg/minute (up to maximum total dose of 1 g); **CHILD** 5–10 mg/kg at a rate of not more than 30 mg/minute

NOTE. For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect.

Plasma concentration for optimum response 15–40 mg/litre (65–170 micromol/litre)

Adverse effects:

sedation, mental depression, ataxia, nystagmus; allergic skin reactions including rarely, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema multiforme); paradoxical excitement, restlessness and confusion in the elderly; irritability and hyperactivity in children; megaloblastic anaemia (may be treated with folic acid); osteomalacia; status epilepticus (on treatment withdrawal); hypotension, shock, laryngospasm and apnoea (with intravenous injection)

Phenytoin sodium

Tablets , phenytoin sodium 25 mg, 50 mg, 100 mg

Capsules , phenytoin sodium 25 mg, 50 mg, 100 mg

Injection (Solution for injection), phenytoin sodium 50 mg/ml, 5-ml ampoule

Uses:

generalized tonic-clonic seizures; partial seizures; status epilepticus

Contraindications:

porphyria; avoid parenteral use in sinus bradycardia, sino-atrial block, second- and third-degree heart block, Stokes-Adams syndrome

Precautions:

hepatic impairment (reduce dose; Appendix 5); pregnancy (**important**, see notes above; Appendix 2); breastfeeding (see notes above; Appendix 3); diabetes mellitus; monitor blood counts; hypotension and heart failure (caution with parenteral use); intravenous administration—resuscitation facilities must be available; injection solution alkaline (irritant to tissues); **interactions:** Appendix 1

BLOOD OR SKIN DISORDERS. Patients or their carers should be told how to recognize signs of blood or skin disorders and advised to seek immediate medical attention if symptoms such as sore throat, rash, mouth ulcers, bruising or bleeding develop. Leukopenia which is severe, progressive or associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative)

SKILLED TASKS. May impair ability to perform skilled tasks, for example operating machinery, driving; see notes above

Dosage:

Generalized tonic-clonic seizures, partial seizures, *by mouth*, **ADULT** initially 3–4 mg/kg daily (as a single dose *or* in 2 divided doses), increased gradually at intervals of 2 weeks as necessary (with plasma-phenytoin concentration monitoring); usual dose 200–500 mg daily; **CHILD** initially 5 mg/kg daily in 2 divided doses; usual dose range 4–8 mg/kg daily (maximum 300 mg)

NOTE. Plasma concentration for optimum response 10–20 mg/litre (40–80 micromol/litre)

Patient Advice. Preferably taken with or after food

Status epilepticus, *by slow intravenous injection or by intravenous infusion* (with blood pressure and ECG monitoring), **ADULT** 15 mg/kg at a rate of not more than 50 mg/minute, as a loading dose; maintenance doses of about 100 mg *by mouth* or *by slow intravenous injection* should be given thereafter at intervals of 6–8 hours, monitored by measurement of plasma concentrations; rates and dose reduced according to weight; **CHILD** 15 mg/kg as a loading dose at rate of 1 mg/kg/minute (not exceeding 50 mg/minute); **neonate** 15–20 mg/kg as a loading dose at rate of 1–3 mg/kg/minute

DILUTION AND ADMINISTRATION. According to manufacturer's directions

Adverse effects:

gastric intolerance, headache, sleeplessness, agitation (during initial phase); sedation, confusion, blurred vision, ataxia, nystagmus, diplopia, slurred speech, cerebellar-vestibular symptoms, behavioural disorders, hallucinations, hyperglycaemia (may be signs of overdose); gingival hyperplasia, acne, coarse facies, hirsutism, fever, hepatitis, neurological changes (peripheral neuropathy, choreiform movements,

impaired cognition, increased seizure frequency); osteomalacia, rickets (associated with reduced plasma calcium levels); lymph-node enlargement; rashes (discontinue; if mild re-introduce cautiously, but discontinue if recurrence); very rarely, Stevens-Johnson syndrome (erythema multiforme), systemic lupus erythematosus, toxic epidermal necrolysis; rarely blood disorders including megaloblastic anaemia (may be treated with folic acid), leukopenia, thrombocytopenia, agranulocytosis with or without bone marrow depression; intravenous administration—cardiovascular and CNS depression (particularly if administered too rapidly) with arrhythmias, hypotension and cardiovascular collapse, alterations in respiratory function (including respiratory collapse)

Sodium valproate

Gastro-resistant tablets (Enteric-coated tablets), sodium valproate 200 mg, 500 mg

Uses:

generalized tonic-clonic seizures; partial seizures; atonic seizures; absence seizures; myoclonic seizures; acute mania (section 24.2.2)

Contraindications:

active liver disease, family history of severe hepatic dysfunction; pancreatitis; porphyria

Precautions:

monitor liver function before and during first 6 months of therapy (Appendix 5), especially in patients at most risk (children under 3 years of age, those with metabolic disorders, degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation, or multiple antiepileptic therapy); ensure no undue potential for bleeding before starting and before major surgery or anticoagulant therapy; renal impairment (Appendix 4); pregnancy (**important** see notes above; Appendix 2 (neural tube screening)); breastfeeding (see notes above; Appendix 3); systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal; **interactions:** Appendix 1

BLOOD OR HEPATIC DISORDERS. Patients or their carers should be told how to recognize signs of blood or liver disorders, and advised to seek immediate medical attention if symptoms including loss of seizure control, malaise, weakness, anorexia, lethargy, oedema, vomiting, abdominal pain, drowsiness, jaundice, or spontaneous bruising or bleeding develop

PANCREATITIS. Patients or their carers should be told how to recognize signs of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea and vomiting develop; discontinue sodium valproate if pancreatitis diagnosed

Dosage:

Generalized tonic-clonic seizures, partial seizures, absence seizures, atonic seizures; myoclonic seizures, *by mouth* , **ADULT** initially 600 mg daily in 2 divided doses, preferably after food, increased by 200 mg daily at 3-day intervals to maximum of 2.5

g daily in divided doses; usual maintenance dose 1–2 g daily (20–30 mg/kg daily); **CHILD** up to 20 kg, initially 20 mg/kg daily in divided doses, may be increased provided plasma concentrations monitored (above 40 mg/kg daily also monitor clinical chemistry and haematological parameters); **CHILD** over 20 kg, initially 400 mg daily in divided doses, increased until control (usually in range of 20–30 mg/kg daily); maximum 35 mg/kg daily

NOTE. Plasma concentrations in therapeutic range of 40–100 mg/litre (280 to 700 micromol/litre); not generally considered useful in assessing control, but higher levels associated with increased incidence of adverse effects; indicator of compliance, dose change or co-medication

Adverse effects:

gastrointestinal irritation, nausea, increased appetite and weight gain, hyperammonaemia; ataxia, tremor; transient hair loss (regrowth may be curly); oedema, thrombocytopenia, inhibition of platelet aggregation; impaired hepatic function and rarely fatal hepatic failure (see Precautions—withdraw treatment immediately if malaise, weakness, lethargy, oedema, abdominal pain, vomiting, anorexia, jaundice, drowsiness or loss of seizure control); sedation reported and also increased alertness; behavioural disturbances; rarely pancreatitis (measure plasma amylase if acute abdominal pain), extrapyramidal symptoms, leukopenia, pancytopenia, red cell hypoplasia, fibrinogen reduction; irregular periods, amenorrhoea, gynaecomastia, hearing loss, Fanconi syndrome, dementia, toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema multiforme), vasculitis, hirsutism and acne reported