8. Tejedor J, Rodríguez JM. Early retreatment of infantile esotropia: comparison of reoperation and botulinum toxin. *Br J Ophthalmol* 1999; **83:** 783–7.
9. Dawson EL, Lee JP. Does botulinum toxin have a role in the treatment of small-angle esotropia? *Strabismus* 2004; **12:** 257–60.
10. Dawson EL, *et al.* Does botulinum toxin have a role in the treatment of secondary strabismus? *Strabismus* 2005; **13:** 71–3.

Stuttering. Botulinum toxin may be of benefit in the treatment of stuttering (p.1001).[1,2]

1. Brin MF, *et al.* Laryngeal botulinum toxin injections for disabling stuttering in adults. *Neurology* 1994; **44:** 2262–6.
2. Cordivari C, *et al.* New therapeutic indications for botulinum toxins. *Mov Disord* 2004; **19** (suppl 8): S157–S161.

Tourette's syndrome. Improvement in tics was noted in patients with Tourette's syndrome (see Tics, p.954) treated with botulinum A toxin.[1,2]

1. Kwak CH, *et al.* Botulinum toxin in the treatment of tics. *Arch Neurol* 2000; **57:** 1190–3.
2. Marras C, *et al.* Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. *Neurology* 2001; **56:** 605–10.

Tremor. Local injection of botulinum A toxin[1-4] has been tried in patients with essential tremor (p.1231) that fails to respond to conventional treatment. Botulinum A toxin injection has also been successfully used to treat essential palatal tremor[5-7] and associated symptoms such as uncomfortable ear clicking.

1. Henderson JM, *et al.* Botulinum toxin A in non-dystonic tremors. *Eur Neurol* 1996; **36:** 29–35.
2. Jankovic J, *et al.* A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. *Mov Disord* 1996; **11:** 250–6.
3. Pacchetti C, *et al.* Botulinum toxin treatment for functional disability induced by essential tremor. *Neurol Sci* 2000; **21:** 349–53.
4. Brin MF, *et al.* A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. *Neurology* 2001; **56:** 1523–8.
5. Deuschl G, *et al.* Ear click in palatal tremor: its origin and treatment with botulinum toxin. *Neurology* 1991; **41:** 1677–9.
6. Jamieson DRS, *et al.* Ear clicks in palatal tremor caused by activity of the levator veli palatini. *Neurology* 1996; **46:** 1168–9.
7. Cho JW, *et al.* Case of essential palatal tremor: atypical features and remarkable benefit from botulinum toxin injection. *Mov Disord* 2001; **16:** 779–82.

Vaginismus. Report[1] of one patient who had relief of vaginismus (painful involuntary spasm of the vaginal or perianal muscles severe enough to prevent intercourse) for more than 24 months after injection of botulinum toxin into the vaginal wall muscles.

1. Brin MF, Vapnek JM. Treatment of vaginismus with botulinum toxin injections. *Lancet* 1997; **349:** 252–3.

Preparations

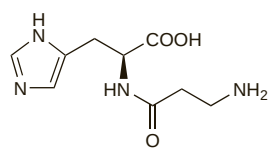
Ph. Eur.: Botulinum Toxin Type A for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Botox; Dysport; ***Austral.:*** Botox; Dysport; ***Austria:*** Botox; Dysport; NeuroBloc; ***Belg.:*** Botox; Dysport; ***Braz.:*** Botox; Dysport; Prosigne; ***Canad.:*** Botox; ***Chile:*** Dysl or; ***Cz.:*** Botox; Dysport; NeuroBloc; Vistabel; ***Denm.:*** Botox; Dysport; Vistabel; ***Fin.:*** Botox; Dysport; Vistabel; ***Fr.:*** Botox; Dysport; NeuroBloc; Vistabel; ***Ger.:*** Botox; Dysport; NeuroBloc†; Xeomin; ***Gr.:*** Botox; Dysport; Vistabel; ***Hong Kong:*** Botox; BTXA; Dysport; ***Hung.:*** Botox; Dysport; Vistabel; ***Indon.:*** Lanzox; ***Irl.:*** Botox; Dysport; NeuroBloc; ***Israel:*** Botox; Dysport; ***Ital.:*** Botox; Dysport; NeuroBloc; Vistabex; ***Jpn:*** Botox; ***Malaysia:*** Botox; Dysport; ***Mex.:*** Botox; ***Neth.:*** Botox; Dysport; NeuroBloc; ***Norw.:*** Botox; Dysport; Vistabel; ***NZ:*** Botox; Dysport; ***Philipp.:*** Botox; Dysport; ***Pol.:*** Botox; Dysport; ***Port.:*** Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***Rus.:*** Botox (Ботокс); Dysport (Диспорт); ***S.Afr.:*** Botox; ***Singapore:*** Botox; Dysport; ***Spain:*** Botox; Dysport; NeuroBloc; Vistabel; ***Swed.:*** Botox; Dysport; Vistabel; ***Switz.:*** Botox; Dysport; Vistabel; ***Thai.:*** Botox; Dysport; ***Turk.:*** Botox; Dysport; ***UK:*** Botox; Dysport; NeuroBloc; Vistabel; Xeomin; ***USA:*** Botox; Myobloc; ***Venez.:*** Botox; Dysport.

Carisoprodol *(BAN, rINN)*

Carisoprodolum; Isopropylmeprobamate; Karisoprodol; Karisoprodoli; Karizoprodol; Karizoprodolis. 2-Methyl-2-propyltrimethylene carbamate isopropylcarbamate.

Каризопродол
$C_{12}H_{24}N_2O_4$ = 260.3.
CAS — 78-44-4.
ATC — M03BA02.
ATC Vet — QM03BA02.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Carisoprodol). A white or almost white fine powder. M.p. 92° to 95°. Very slightly soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane.
USP 31 (Carisoprodol). A white crystalline powder having a mild characteristic odour. M.p. 91° to 94°. Soluble 1 in 2083 of water, 1 in 2.5 of alcohol and of acetone, and 1 in 2.3 of chloroform. Store in airtight containers.

Dependence and Withdrawal, Adverse Effects, Treatment, and Precautions

As for Meprobamate, p.1006.

The most common adverse effects reported with carisoprodol are drowsiness, dizziness, and headache. Sedation may affect the performance of skilled tasks and affected patients should not drive or operate machinery. Poor metabolisers, deficient in the cytochrome P450 isoenzyme CYP2C19, may be at greater risk of drowsiness.

Idiosyncratic reactions may occur within minutes of a dose in patients who have not previously received carisoprodol. Such reactions have been reported rarely and include anaphylactic shock, syncope, tachycardia, confusion, transient quadriplegia, and bronchospasm. Cross-reactivity can occur with its metabolite meprobamate.

Overdosage may result in seizures, stupor, coma, shock, respiratory depression, and rarely death.

Carisoprodol should be used with caution in patients with impaired hepatic or renal function.

Cases of dependence and abuse have been reported with the prolonged use of carisoprodol, particularly in patients with a history of addiction; withdrawal reactions have also occurred when treatment is suddenly stopped after prolonged use or the use of high doses. The increased risk of abuse and addiction with carisoprodol, as well as the risk of altered mental state and psychomotor impairment, has led the EMEA and some other authorities to recommend that it is suspended from the market; in the USA, however, it is recommended that use is limited to 2 to 3 weeks.

Abuse. Analysis[1] of data from the Norwegian Prescription Database found that carisoprodol was used in higher doses than recommended indicating its potential as a drug of abuse. Subsequently, the Norwegian Medicines Agency and the EMEA have recommended for suspension (see above).

1. Bramness JG, *et al.* Carisoprodol use and abuse in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol* 2007; **64:** 210–18.

Breast feeding. Carisoprodol is distributed into breast milk, achieving concentrations 2 to 4 times those in maternal plasma; UK licensed product information and the *BNF* recommend that it is best avoided in women who are breast feeding although US licensed product information states to use with caution.

Dependence. There are reports of carisoprodol dependence, probably due to its metabolism to meprobamate.[1,2] In one case the patient had symptoms of meprobamate withdrawal that resolved with a dose-reducing schedule of meprobamate.

Dependence may occur more often when carisoprodol is given in high doses and for prolonged periods, especially in patients with a history of alcohol or drug dependence or in those with marked personality disorders. One group[2] found that patients with a history of substance abuse were twice as likely to use carisoprodol in larger doses to those prescribed than those with no such history.

The risk of dependence with carisoprodol has led the EMEA and some other authorities to recommend its suspension from the market (see above).

1. Luehr JG, *et al.* Mail-order (veterinary) drug dependence. *JAMA* 1990; **263:** 657.
2. Reeves RR, *et al.* Carisoprodol (Soma): abuse potential and physician unawareness. *J Addict Dis* 1999; **18:** 51–6.

Porphyria. Carisoprodol has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The CNS effects of carisoprodol may be potentiated by alcohol or other CNS depressants. Carisoprodol may cause hepatic enzyme induction and it may therefore affect the metabolism of a number of drugs. The metabolism of carisoprodol is mediated by the cytochrome P450 isoenzyme CYP2C19; use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of carisoprodol, however, there is a lack of data.

Pharmacokinetics

Carisoprodol is absorbed from the gastrointestinal tract and peak plasma concentrations are reached after 1.5 to 2 hours. It is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP2C19, which shows genetic polymorphism, and excreted in urine as metabolites, including meprobamate. The terminal elimination half-life of carisoprodol is about 2 hours. It is distributed in substantial amounts into breast milk.

◊ References.

1. Olsen H, *et al.* Carisoprodol elimination in humans. *Ther Drug Monit* 1994; **16:** 337–40.

Uses and Administration

Carisoprodol is a centrally acting skeletal muscle relaxant whose mechanism of action is not completely understood but may be related to its sedative actions. After oral doses its effects begin within about 30 minutes and last for 4 to 6 hours. It is used as an adjunct in the short-term symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. A usual oral dose is 250 to 350 mg given three or four times daily for up to 2 to 3 weeks. Half the usual dose or less is recommended in elderly patients. It is also given with analgesics in compound preparations.

The EMEA and some other authorities have recommended for carisoprodol to be suspended from the market due to the increased risk of abuse and addiction, as well as the risk of altered mental state and psychomotor impairment.

Preparations

USP 31: Carisoprodol and Aspirin Tablets; Carisoprodol Tablets; Carisoprodol, Aspirin, and Codeine Phosphate Tablets.

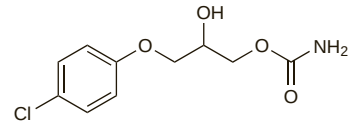
Proprietary Preparations (details are given in Part 3)
Arg.: Listaflex; ***Canad.:*** Soma†; ***Denm.:*** Somadril†; ***India:*** Carisoma; ***Mex.:*** Somacid; ***Norw.:*** Somadril†; ***Spain:*** Mio Relax†; ***Swed.:*** Somadril†; ***Thai.:*** Myolax†; ***UK:*** Carisoma†; ***USA:*** Soma.

Multi-ingredient: ***Arg.:*** Algiseda; Flexicamin; Flexicamin A; Flexicamin B12; Flogiatrin; Flogiatrin B12; Ketazon Flex†; Mefenix Relax†; Naprontag Flex; Rumisedan Fuerte†; Solocalm Plus; Solocalm-Flex; ***Braz.:*** Algi-Butazolon†; Algi-Tanderil†; Beserol; Cedrilax†; Diclofetamol; Dorilax; Flexalgin; Mio-Citalgan; Mioflex; Mioflex A; Mionevrix; Paceflex†; Sanilax; Sedilax; Tandene; Tanderalgin; Tandriflan; Tandrilax; Torsilax; Trilax†; ***Cz.:*** Scutamil C†; ***Fin.:*** Somadril Comp†; ***Gr.:*** Relacton-C†; ***Hung.:*** Scutamil C†; ***India:*** Carisoma Compound; Somaflam; ***Indon.:*** New Skelan; Somadril Compound; ***Ital.:*** Soma Complex†; ***Mex.:*** Blocacid; Contraxen; Dolaren; Dorsal; Duoflex; Empatil; Naxodol; Profenlax; Somalgesic; ***Spain:*** Flexagil†; Relaxibys†; ***Swed.:*** Somadril Comp†; ***Thai.:*** Alaxan; Asialax; Cariso-Co†; Carisoma Compound†; Caritasone; Cenpadol; Muscelax; Myophen; Polixan; ***USA:*** Sodol Compound; Soma Compound with Codeine†; Soma Compound†; ***Venez.:*** Cotar†; Flexidone†; Praxona.

Chlorphenesin Carbamate *(BANM, USAN, pINNM)*

Carbamato de clorfenesina; Chlorphénésine, Carbamate de; Chlorphenesini Carbamatum; U-19646. 3-(4-Chlorophenoxy)propane-1,2-diol 1-carbamate.

Хлорфенезина Карбамат
$C_{10}H_{12}ClNO_4$ = 245.7.
CAS — 104-29-0 (chlorphenesin); 886-74-8 (chlorphenesin carbamate).



Pharmacopoeias. In *Jpn*.

Adverse Effects and Precautions

Chlorphenesin carbamate produces drowsiness and dizziness. There may also be nausea, headache, weakness, confusion, agitation, and insomnia. Hypersensitivity reactions have been reported. There are rare reports of blood disorders.

It should be used with caution in patients with hepatic impairment. Patients affected by drowsiness should not drive or operate machinery.

Interactions

The CNS effects of chlorphenesin carbamate may be potentiated by alcohol or other CNS depressants.

Pharmacokinetics

Chlorphenesin carbamate is readily and completely absorbed from the gastrointestinal tract and partly metabolised in the liver. It is excreted in the urine, mainly as the glucuronide metabolite.

Uses and Administration

Chlorphenesin carbamate is a centrally acting skeletal muscle relaxant related to mephenesin (p.1897). Its mode of action may be related to general depressant effects on the CNS. It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. The usual initial oral dose is 250 mg three times daily, adjusted according to response. It has been recommended that chlorphenesin carbamate should not be given for longer than 8 weeks.

Chlorphenesin base (p.529) is used as an antifungal.

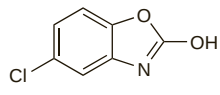
Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Rinlaxer; ***USA:*** Maolate†.

Chlorzoxazone *(BAN, rINN)*

Chlorobenzoxazolinone; Chlorzoxazonum; Clorzoxazona; Klooritsoksatsoni; Klorzoksazon; Klorzoxazon. 5-Chlorobenzoxazol-2(3*H*)-one.

Хлорзоксазон
$C_7H_4ClNO_2$ = 169.6.
CAS — 95-25-0.
ATC — M03BB03.
ATC Vet — QM03BB03.



Pharmacopoeias. In *US*.
USP 31 (Chlorzoxazone). A white or practically white, practically odourless, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol, in isopropyl alcohol, and in methyl alcohol; soluble in solutions of alkali hydroxides and ammonia. Store in airtight containers.

Adverse Effects and Treatment

The most common adverse effects of chlorzoxazone are drowsiness and dizziness. There may occasionally also be gastrointestinal irritation and gastrointestinal bleeding has been reported rarely. Other effects that have occurred are headache, overstimulation, and rarely sensitivity reactions including skin rashes, petechiae, ecchymoses, urticaria and pruritus; very rarely, angioedema or anaphylactoid reactions may occur. Some patients taking chlorzoxazone have developed jaundice and liver damage suspected to be caused by the drug.

After overdosage there may be gastrointestinal disturbances, drowsiness, dizziness, headache, malaise, and sluggishness followed by marked loss of muscle tone, hypotension, and respiratory depression. Emptying the stomach by lavage should be considered, followed by activated charcoal and supportive therapy.

Effects on the liver. Hepatotoxicity, sometimes fatal, has been associated with chlorzoxazone treatment.[1]

1. Powers BJ, *et al.* Chlorzoxazone hepatotoxic reactions: an analysis of 21 identified or presumed cases. *Arch Intern Med* 1986; **146:** 1183–6.

Overdosage. Overdosage and coma occurred on 2 occasions in a patient taking chlorzoxazone; on the second occasion, the patient responded to intravenous flumazenil.[1]

1. Roberge RJ, *et al.* Two chlorzoxazone (Parafon forte) overdoses and coma in one patient: reversal with flumazenil. *Am J Emerg Med* 1998; **16:** 393–5.

Torticollis. There has been a report of a patient with a spasmodic torticollis-like syndrome, consisting of tonic deviation of the head to the right, clenching of the teeth, and dysarthria, which developed repeatedly within 2 hours of ingesting chlorzoxazone for low back pain.[1] Intravenous injection of benzatropine mesilate 1 mg gave rapid relief of symptoms.

1. Rosin MA. Chlorzoxazone-induced spasmodic torticollis. *JAMA* 1981; **246:** 2575.

Precautions

Chlorzoxazone should not be given to patients with impaired liver function and should be stopped if signs of liver toxicity appear. Patients should be advised to report to their doctor any signs or symptoms of possible liver toxicity such as fever, rash, jaundice, dark urine, anorexia, nausea, vomiting, or right upper quadrant pain. Chlorzoxazone may cause drowsiness; patients affected should not drive or operate machinery.

The urine of patients taking chlorzoxazone may be coloured orange or reddish-purple by a phenolic metabolite.

Porphyria. Chlorzoxazone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

The CNS effects of chlorzoxazone may be enhanced by alcohol and other CNS depressants.

Disulfiram. A study[1] of the efficacy of disulfiram as an inhibitor of the cytochrome P450 isoenzyme CYP2E1 (an enzyme involved in the metabolism of chlorzoxazone) found that a single 500-mg dose of disulfiram reduced plasma clearance of chlorzoxazone by 85%, resulting in a doubling of the latter's peak plasma concentrations and prolongation of its elimination half-life from a mean of 0.92 to 5.1 hours.

1. Kharasch ED, *et al.* Single-dose disulfiram inhibition of chlorzoxazone metabolism: a clinical probe for P450 2E1. *Clin Pharmacol Ther* 1993; **53:** 643–50.

Isoniazid. Isoniazid inhibited the clearance of chlorzoxazone by 56% when given to 10 slow acetylator subjects resulting in an increase in sedation, headache, and nausea.[1] Two days after stopping isoniazid there had been a rebound increase in the clearance of chlorzoxazone by 56% over the pre-isoniazid clearance value. Similar but less pronounced effects have also been reported[2] in rapid acetylators with chlorzoxazone's pharmacokinetic parameters returning to baseline values in 2 days.

1. Zand R, *et al.* Inhibition and induction of cytochrome P4502E1-catalyzed oxidation by isoniazid in humans. *Clin Pharmacol Ther* 1993; **54:** 142–9.
2. O'Shea D, *et al.* Modulation of CYP2E1 activity by isoniazid in rapid and slow N-acetylators. *Br J Clin Pharmacol* 1997; **43:** 99–103.

Pharmacokinetics

Chlorzoxazone is reported to be completely absorbed after oral doses and peak plasma concentrations are achieved after 1 to 2 hours. It is rapidly metabolised in the liver via the cytochrome P450 isoenzyme CYP2E1, mainly to 6-hydroxychlorzoxazone, and excreted in the urine primarily as the glucuronide metabolite. The elimination half-life of chlorzoxazone is about 1 hour.

Uses and Administration

Chlorzoxazone is a centrally acting skeletal muscle relaxant with sedative properties. It is claimed to inhibit muscle spasm by exerting an effect primarily at the level of the spinal cord and subcortical areas of the brain. Its effects begin within an hour of an oral dose and last for 3 to 4 hours.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. The usual initial oral dose is 500 mg three or four times daily; the dose can often be reduced subsequently to 250 mg three or four times daily, although doses of up to 750 mg three or four times daily may be given if necessary. Chlorzoxazone is also given with analgesics in compound preparations.

Preparations

USP 31: Chlorzoxazone Tablets.

Proprietary Preparations (details are given in Part 3)
Chile: Fenarol-S†; ***Denm.:*** Paraflex; ***Hong Kong:*** Solaxin; ***Hung.:*** Myoflexin; ***India:*** Parafon DSC; ***Indon.:*** Solaxin; ***S.Afr.:*** Paraflex; ***Swed.:*** Paraflex; ***Thai.:*** Chlorzox†; ***Turk.:*** Paraflex; ***USA:*** Paraflex; Parafon Forte DSC; Remular-S.

Multi-ingredient: ***Arg.:*** Ibupirac Flex; Paraflex AN; Paraflex Plus; Rucaten Forte; ***Austria:*** Parafon; ***Braz.:*** Paralon; ***Canad.:*** Acetazone Forte; Acetazone Forte C8; Back-Aid; Parafon Forte; Tylenol Aches & Strains; ***Chile:*** Beserol-S; Brevex; Desdol; Flectadol; Tonoflex; Winasorb Flex; ***Fin.:*** Paraflex comp†; ***Hong Kong:*** Relaxin-P†; ***India:*** Cip-Zox; Dolocide MR; Duodil; Fenaplus-MR; Flamar-MX; Flexon-MR; Myospaz; Myospaz Forte; New Panazox; Nicip MR; Osteoflam-MR; Pacizox; Parafon; Systaflam; ***Malaysia:*** Paras; ***Mex.:*** Parafon Forte; Reumophan; Tafirol Flex; ***Philipp.:*** Parafon; ***S.Afr.:*** Parafon; ***Swed.:*** Paraflex comp†; ***Thai.:*** Cezox; Myora; Myoserv†; Parafon; ***Turk.:*** Mepadol; Muskazon; Parafon; ***USA:*** Flexaphen.

Cyclobenzaprine Hydrochloride *(USAN, rINNM)*

Cyclobenzaprine, Chlorhydrate de; Cyclobenzaprini Hydrochloridum; Hidrocloruro de ciclobenzaprina; MK-130 (cyclobenzaprine); Proheptatriene Hydrochloride; Ro-4-1557 (cyclobenzaprine); RP-9715 (cyclobenzaprine). 3-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-*NN*-dimethylpropylamine hydrochloride.

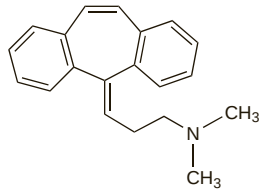
Циклобензаприна Гидрохлорид

$C_{20}H_{21}N,HCl = 311.8$.

CAS — 303-53-7 (cyclobenzaprine); 6202-23-9 (cyclobenzaprine hydrochloride).

ATC — M03BX08.

ATC Vet — QM03BX08.



(cyclobenzaprine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of cyclobenzaprine hydrochloride:
Cyclo; Cyclone.

Pharmacopoeias. In *US*.
USP 31 (Cyclobenzaprine Hydrochloride). A white to off-white, odourless, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in isopropyl alcohol; slightly soluble in chloroform and in dichloromethane; insoluble in hydrocarbons.

Adverse Effects, Treatment, and Precautions

Cyclobenzaprine is structurally related to the tricyclic antidepressants and shares their adverse effects and precautions (see Amitriptyline, p.376). Cyclobenzaprine should be used with caution in the elderly and patients with hepatic impairment; use in moderate to severe hepatic impairment is not recommended.

It may cause drowsiness; patients affected should not drive or operate machinery.

The elderly. Symptoms of toxicity[1] (hallucinations, insomnia, and restlessness) were seen in a 76-year-old patient taking cyclobenzaprine at therapeutic doses. US licensed product information states that the elderly may be more likely to experience adverse effects such as hallucinations and confusion..

In another study[2] the mean elimination half-life of cyclobenzaprine in the elderly was longer than in younger subjects and clearance was reduced. It was suggested that it should be used in a reduced dose or frequency in the elderly.

1. Douglass MA, Levine DP. Hallucinations in an elderly patient taking recommended doses of cyclobenzaprine. *Arch Intern Med* 2000; **160:** 1373.
2. Winchell GA, *et al.* Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency. *J Clin Pharmacol* 2002; **42:** 61–9.

Neuroleptic malignant syndrome. Report of a neuroleptic malignant-like syndrome associated with cyclobenzaprine in a 36-year-old man.[1] It was not clear whether the syndrome was due to an idiosyncratic reaction or to an overdose.

1. Theoharides TC, *et al.* Neuroleptic malignant-like syndrome due to cyclobenzaprine. *J Clin Psychopharmacol* 1995; **15:** 79–81.

Overdosage. Treatment of cyclobenzaprine overdose is mainly symptomatic and supportive. A large retrospective study[1] found that cyclobenzaprine hydrochloride overdoses of up to 1 g rarely present with the serious cardiovascular and neurological effects seen with tricyclic antidepressant overdoses. There were no reports of seizures, life-threatening arrhythmias, or fatalities. However, 150 patients required treatment in the intensive care unit, 13 patients needed assisted ventilation, and 8 were unresponsive to stimuli. It was noted that observation may be sufficient for overdoses of under 50 mg in children.

1. Spiller HA, *et al.* Five-year multicentre retrospective review of cyclobenzaprine toxicity. *J Emerg Med* 1995; **13:** 781–5.

Interactions

Cyclobenzaprine is structurally related to the tricyclic antidepressants and may be subject to similar interactions (see Amitriptyline, p.379). The CNS effects of cyclobenzaprine may be enhanced by alcohol or other CNS depressants.

Antidepressants. A patient who already had QT prolongation associated with use of cyclobenzaprine and *fluoxetine*. developed torsade de pointes, progressing into ventricular fibrillation, when given *droperidol* as premedication prior to surgery.[1] QT abnormalities resolved on stopping cyclobenzaprine.

1. Michalets EL, *et al.* Torsade de pointes resulting from the addition of droperidol to an existing cytochrome P450 drug interaction. *Ann Pharmacother* 1998; **32:** 761–5.

Antipsychotics. For a report of an interaction between cyclobenzaprine and *droperidol*, see Antidepressants above.

Pharmacokinetics

Cyclobenzaprine hydrochloride is readily and almost completely absorbed from the gastrointestinal tract, although plasma concentrations vary considerably among individuals given the same dose. About 93% is bound to plasma proteins and has a reported effective half-life of 8 to 37 hours. It is extensively metabolised, principally to glucuronide conjugates, and excreted in the urine. Cytochrome P450 isoenzymes CYP3A4, CYP1A2, and to a lesser extent CYP2D6 mediate its demethylation. Some unchanged drug appears in the bile and is excreted in the faeces.

◊ References.

1. Winchell GA, *et al.* Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency. *J Clin Pharmacol* 2002; **42:** 61–9.

Uses and Administration

Cyclobenzaprine hydrochloride is a centrally acting skeletal muscle relaxant, related to the tricyclic antidepressants. It acts mainly at the brain stem to decrease tonic somatic motor activity influencing both alpha and gamma motor systems. Additional activity at spinal cord sites may be involved. Effects begin within 1 hour of a dose by mouth; the effects of a single dose have been reported to last as long as 12 to 24 hours.

It is used as an adjunct in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. The usual dose is 5 mg three times daily given by mouth, increased if necessary to 10 mg three times daily. Treatment for more than 2 or 3 weeks is not recommended. A starting dose of 5 mg with less frequent dosing is recommended for elderly patients. For doses in patients with hepatic impairment, see below. A modified-release preparation of cyclobenzaprine hydrochloride is also available for once-daily dosing.

Administration in hepatic impairment. A starting dose of 5 mg of cyclobenzaprine hydrochloride by mouth, and perhaps less frequent dosing than usual (see above), is recommended for those with mild hepatic impairment; use in moderate to severe hepatic impairment is not recommended.

Back pain. A meta-analysis[1] of 14 studies concluded that cyclobenzaprine hydrochloride, in the short term, improves low back pain (p.7). Doses given to patients were titrated and ranged from 10 to 60 mg daily with a median dose of 30 mg daily. Patients improved moderately in the first 4 days of treatment, with the effects of cyclobenzaprine hydrochloride gradually declining with time although there was some evidence of continued improvement at 2 weeks. Further studies are needed to determine the optimal length of use in the management of acute back pain. Adverse effects were common, occurring in at least 53% of patients.

1. Browning R, *et al.* Cyclobenzaprine and back pain: a meta-analysis. *Arch Intern Med* 2001; **161:** 1613–20.

Fibromyalgia. Studies of the efficacy of cyclobenzaprine in the management of fibromyalgia, a painful musculoskeletal disorder which usually responds poorly to analgesics (see Soft-tissue Rheumatism, p.13), have produced conflicting results but a meta-analysis[1] of 5 such studies suggested that cyclobenzaprine had some modest benefit in the condition. Patients were more likely to report overall improvement and moderate reductions in individual symptoms, particularly sleep, while taking the drug.

1. Tofferi JK, *et al.* Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. *Arthritis Rheum* 2004; **51:** 9–13.

Preparations

USP 31: Cyclobenzaprine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Miosan; Mirtax; Musculare; ***Canad.:*** Flexeril†; Flexitec†; Novo-Cycloprine; ***Chile:*** Ciclamil; Masterelax†; Medarex; Nostaden; Reflexan; Relexil; Tensamon; Tensiomax; Tensodox; Tonalgen; Ziclob; ***Ital.:*** Flexiban; ***Port.:*** Flexiban; ***Spain:*** Yurelax; ***USA:*** Amrix; Fexmid; Flexeril.

Multi-ingredient: ***Arg.:*** Dorixina Relax; ***Braz.:*** Dolamin Flex; ***Mex.:*** Yuredol; ***Venez.:*** Dorixina Flex.
