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

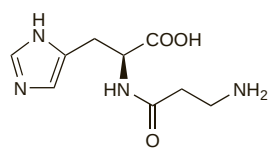
Ph. Eur.: Botulinum Toxin Type A for Injection.

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.

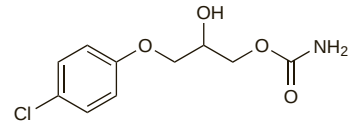
Proprietary Preparations (details are given in Part 3)
Arg.: Listaflex; ***Canad.:*** Soma†; ***Denm.:*** Somadril†; ***India:*** Carisoma; ***Mex.:*** Somacid; ***Norw.:*** Somadril†; ***Spain:*** Mio Relax†; ***Swed.:*** Somadril†; ***Thai.:*** Myolax†; ***UK:*** Carisoma†; ***USA:*** Soma.

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.