

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

Preparations for injection may contain, as a solvent, a macrogol which could increase existing acidosis and urea retention in patients with renal impairment; such preparations should not be used in patients with known or suspected renal disease.

Abnormal coloration. Methocarbamol has been reported to cause brown to black or green discoloration of the urine on standing.¹

1. Baran RB, Rowles B. Factors affecting coloration of urine and feces. *J Am Pharm Assoc* 1973; **NS13**: 139-42.

Interactions

The CNS effects of methocarbamol may be potentiated by alcohol or other CNS depressants. Methocarbamol has also been reported to potentiate the effects of anorectics and antimuscarinics, and to inhibit the effect of pyridostigmine.

Pharmacokinetics

Methocarbamol is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses. Its plasma half-life is reported to be about 1 to 2 hours. It is metabolised by dealkylation and hydroxylation and is excreted in urine primarily as the glucuronide and sulfate conjugates of its metabolites. A small amount is excreted in faeces.

Uses and Administration

Methocarbamol is a centrally acting skeletal muscle relaxant whose action may be due to general depressant effects on the CNS.

Methocarbamol is used as an adjunct in the short-term symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions. It is sometimes given with analgesics in compound preparations for the treatment of musculoskeletal pain.

The usual initial oral dose for muscle spasm is 1.5 g four times daily, reduced to a maintenance dose of about 4 g daily after 2 to 3 days. A dose of 750 mg three times daily may be sufficient for a therapeutic effect. Half the maximum daily dose or less may be sufficient for elderly patients.

Methocarbamol has also been given intravenously at a rate of not more than 300 mg/minute, by slow injection or by infusion in sodium chloride 0.9% or glucose 5% injection. The parenteral route should not be used for more than 3 consecutive days and the dose should not exceed 3 g daily. The patient should remain lying down during, and for 10 to 15 minutes after, intravenous doses. The US manufacturers state that the injection is hypertonic and extravasation should be avoided. However, it may also be given by intramuscular injection in a dose of up to 500 mg into each gluteal region at intervals of 8 hours.

Preparations

USP 31: Methocarbamol Injection; Methocarbamol Tablets.

Proprietary Preparations (details are given in Part 3)

Canada: Robaxin; **Fr.:** Lumirelax; **Ger.:** Ortofon; **Hong Kong:** Robaxin; **India:** Robinax; **Mex.:** Remisol; **Rexin;** **S.Afr.:** Robaxin; **Spain:** Robaxin; **Thail.:** Laxan; Manobaxine; Musxan; Myocin; Myomethol; Robaxin; **UK:** Robaxin; **USA:** Robaxin.

Multi-ingredient: **Canada:** Aspirin Backache; Dodds Back Ease; Methocacet; Methocacet-C; Methoxisal; Methoxisal-C; Muscle & Back Pain Relief; Muscle & Back Pain Relief Extra Strength; Muscle & Back Pain Relief-8; Muscle Relaxant and Analgesic; Obusformet; Relaxophen; Robax Platinum; Robaxacet; Robaxacet-8; Robaxisal; Robaxisal-C; Spasmhalt; Spasmhalt-ASA; **Ger.:** Ortofon Plus; **India:** Flexinol; Ibugesic-M; Robiflam; Robinaxol; **Mex.:** Artridol; Carbafer; Carbager-Plus; Carbamox; Dolocam Plus; Flexamol; Malival Compuesto; Morlan; Remisol-Plus; Retoflam F; Reupat; Robaxifen; Robaxisal; Vengesic; **S.Afr.:** Robaxisal; **Spain:** Robaxisal Compuesto; Robaxisal; **Turk.:** Miyolet; **Venez.:** Beseroldos; Robaxifen; Robaxisal.

Pridinol Mesilate (rINN)

C-238 (pridinol); Mesilato de pridinol; Pridinol, Mésilate de; Pridinol Mesylate; Pridinoli Mesilas. 1,1-Diphenyl-3-piperidinopropan-1-ol methanesulphonate.

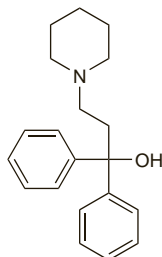
ПРИДИНОЛА Мезимат

$C_{20}H_{25}NO \cdot CH_3SO_3H = 391.5$.

CAS — 511-45-5 (pridinol); 968-58-1 (pridinol hydrochloride); 6856-31-1 (pridinol mesilate).

ATC — M03BX03.

ATC Vet — QM03BX03.



(pridinol)

Profile

Pridinol mesilate is a centrally acting muscle relaxant used in the symptomatic treatment of muscle spasm (p.1887). The usual initial oral dose is 2 to 8 mg three times daily, reduced to 4 to 8 mg daily for maintenance treatment. It is also given by intramuscular injection or rectally, and has been applied in compound topical preparations.

Pridinol has been used as the hydrochloride for its antimuscarinic properties in the management of parkinsonism (p.791).

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Myoson; **Parkst.:** **Hong Kong:** Konlax; **Ital.:** Lyseen; **Pol.:** Polmesilat.

Multi-ingredient: **Arg.:** Blokium Flex; Cuninflex Plus; Didogestic Relax; Didomar Flex; Didonex Relax; Dioxaflex Plus; Dolvan Flex; Doxtran Flex; Flexidol Relax; Iglodine Flex; Metaflex Plus NF; Mextran Flex; Mio Aldoron NF; Mio-Vibrobron NF; Nalgiflex Relax; Oxa Sport; Oxadisten; Panchoflex; Rodinac Flex; Silfox Flex; Tomanil Flex; Vesalion Flex; Viartil Flex; Voltaren Flex; Xedenol Flex; **Ital.:** Algolisinaf.

Thiocolchicoside (rINN)

Thiocolchicosidum; Tiocolchicósido; Tiyokolşikozid. 3,10-Di(dimethoxy)-3-glucopyranosyloxy-10-methylthiocolchicine.

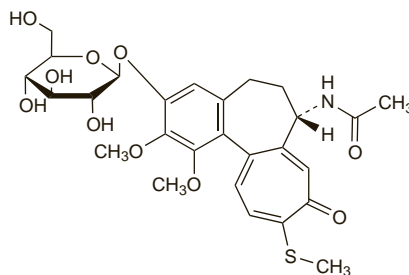
ТИКОЛЬХИКОЗИД

$C_{27}H_{33}NO_{10}S = 563.6$.

CAS — 602-41-5.

ATC — M03BX05.

ATC Vet — QM03BX05.



Pharmacopoeias. In Fr.

Profile

Thiocolchicoside is a muscle relaxant that has been claimed to possess GABA-mimetic and glycinergic actions. It is used in the symptomatic treatment of painful muscle spasm (p.1887). The usual initial oral dose is 16 mg daily given in 2 divided doses. It has also been given intramuscularly, in doses up to 8 mg daily, or applied as cream or ointment. Photosensitivity reactions may occur.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Coltrax; **Musconi:** **Cz.:** Musconi; **Fr.:** Coltramy; **Myolege;** **Gr.:** Disintryl; Haliver; Klesidren; Musco-rit; Thiacomint; **India:** Myoni; **Ital.:** Decontri; Miotens; Muscoflex; Musconi; Sciomi; Strialsin; Teraside; Ticathion; Tionlene; Tioside; **Pol.:** Musconi; **Port.:** Coltramy; **Relmus;** **Turk.:** Muscoflex; **Musconi:** **Venez.:** Biocolchidi; Coltrax; Colval; Cosiden; Eusilen; Lampral; Tiochax; Tractil.

Multi-ingredient: **Ital.:** Musconi Trauma; **Mex.:** Neuroflax; **Port.:** Adalgur N; **Reimus Compositum;** **Spain:** Adalgur; **Venez.:** Colfene.

Tizanidine Hydrochloride (BANM, USAN, rINN)

AN-021; DS-103-282; DS-103-282-ch; Hidrocloruro de tizanidina; Tizanidine, Chlorhydrate de; Tizanidini Hydrochloridum. 5-Chloro-N-(2-imidazolin-2-yl)-2,1,3-benzothiadiazol-4-ylamine hydrochloride.

Тизанидина Гидрохлорид

$C_9H_9ClN_5S \cdot HCl = 290.2$.

CAS — 51322-75-9 (tizanidine); 64461-82-1 (tizanidine hydrochloride).

ATC — M03BX02.

ATC Vet — QM03BX02.



(tizanidine)

Pharmacopoeias. In Jpn and US.

USP 31 (Tizanidine Hydrochloride). Store in airtight containers.

Adverse Effects and Precautions

Tizanidine hydrochloride may cause drowsiness; patients affected should not drive or operate machinery. Other adverse effects include dry mouth, fatigue, dizziness or vertigo, muscle pain and weakness, insomnia, anxiety, headache, bradycardia, nausea, and gastrointestinal disturbances. Hallucinations have occurred on rare occasions. Many adverse effects have been found to be dose related and slow titration of doses appears to reduce the frequency of occurrence. Hypotension may occur.

Increases in liver enzymes and rarely acute hepatitis have been associated with tizanidine and it is contra-indicated in patients with severe hepatic dysfunction. In the UK it is recommended that liver function should be monitored monthly in all patients for the first 4 months and in those who develop symptoms suggestive of hepatic dysfunction; similarly, in the USA baseline assessment and monitoring at 1, 3, and 6 months is advised. Treatment should be stopped if liver enzymes are persistently raised. Caution is required in the elderly and in patients with renal insufficiency.

Interactions

Tizanidine is metabolised by the cytochrome P450 isoenzyme CYP1A2 and use with ciprofloxacin or fluvoxamine, both potent inhibitors of this isoenzyme, is contra-indicated. Use with other more moderate inhibitors of CYP1A2 (such as other quinolone antibacterials, cimetidine, and antiarrhythmics such as amiodarone, mexiletine, propafenone, and verapamil) should be avoided unless clinically necessary. The CNS effects of tizanidine may be enhanced by alcohol or other CNS depressants. There may be an additive hypotensive effect when tizanidine is used in patients receiving antihypertensive therapy; bradycardia may also be enhanced if given with beta blockers or digoxin. Caution should be exercised when tizanidine is given with drugs known to increase the QT interval. The clearance of tizanidine has been reported to be lower in women receiving hormonal contraceptives.

Antibacterials. In a study of healthy subjects,¹ ciprofloxacin, an inhibitor of the cytochrome P450 isoenzyme CYP1A2, was reported to elevate the plasma concentrations of tizanidine thereby potentiating its hypotensive and sedative effects.

1. Granfors MT, *et al.* Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. *Clin Pharmacol Ther* 2004; **76**: 598-606.

Antidepressants. In a study¹ in 10 healthy subjects, fluvoxamine, a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2, was reported to increase tizanidine's peak plasma concentrations and elimination half-life 12-fold and 3-fold, respectively. An increased incidence of adverse effects associated with tizanidine such as hypotension, bradycardia, drowsiness, and dizziness was noted in these subjects.

A 70-year-old woman receiving fluvoxamine 150 mg daily and other medications developed bradycardia, dry mouth, urinary retention, and a low body temperature when given tizanidine 3 mg daily;² the patient improved when tizanidine was stopped. In a retrospective survey of medical records, the authors reported adverse effects associated with tizanidine in 6 of 23 patients also receiving fluvoxamine.

1. Granfors MT, *et al.* Fluvoxamine drastically increases concentrations and effects of tizanidine: a potentially hazardous interaction. *Clin Pharmacol Ther* 2004; **75**: 331-41.
2. Momo K, *et al.* Drug interaction of tizanidine and fluvoxamine. *Clin Pharmacol Ther* 2004; **76**: 509-10.

Antiepileptics. For reference to an interaction between tizanidine and phenytoin, see p.500.

Cardiovascular drugs. Severe hypotension, occurring 2 hours after treatment with tizanidine, has been reported in a patient receiving antihypertensives, including lisinopril, and other medications.¹ The patient improved after tizanidine and antihypertensives were stopped; they were later resumed without lisinopril, and caused no problems.

1. Kao C-D, *et al.* Hypotension due to interaction between lisinopril and tizanidine. *Ann Pharmacother* 2004; **38**: 1840-3.

Oral contraceptives. Mean peak plasma concentrations after a single 4-mg dose of tizanidine were 3 times greater in 15 women using an oral contraceptive containing ethinylestradiol and gestodene than in controls;¹ the elimination half-life was not, however, significantly different. The effect appeared to be due to inhibition of the cytochrome P450 isoenzyme CYP1A2 by the contraceptive, resulting in reduced presystemic metabolism of tizanidine. Because the therapeutic range of tizanidine is narrow, care should be exercised if it is given to patients taking oral contraceptives.

1. Granfors MT, *et al.* Oral contraceptives containing ethinyl estradiol and gestodene markedly increase plasma concentrations and effects of tizanidine by inhibiting cytochrome P450 1A2. *Clin Pharmacol Ther* 2005; **78**: 400-11.

Pharmacokinetics

Tizanidine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after oral doses. It is about 30% bound to plasma proteins. Tizanidine undergoes extensive first-pass metabolism in the liver mainly via the cytochrome P450 isoenzyme CYP1A2 and is excreted mainly in the urine as inactive metabolites. Elimination half-lives of 2 to 4 hours have been reported.

Uses and Administration

Tizanidine hydrochloride is a centrally acting skeletal muscle relaxant. It is an α_2 -adrenergic agonist structurally related to clonidine (p.1247) and acts mainly at spinal and supraspinal levels to inhibit excitatory interneurons. It is used for the symptomatic relief of spasticity associated with multiple sclerosis or with spinal cord injury or disease. It is also used in the symptomatic treatment of painful muscle spasm (p.1887) associated with musculoskeletal conditions.

Tizanidine hydrochloride is given orally, usually in divided doses; doses are expressed in terms of the base. Tizanidine hydrochloride 1.14 mg is equivalent to about 1 mg of tizanidine. The usual initial daily dose in the UK in the management of spasticity is the equivalent of 2 mg of the base given as a single dose. The dose may be increased thereafter according to response in steps of 2 mg at intervals of at least 3 to 4 days, usually up to 24 mg daily given in 3 or 4 divided doses. A similar schedule, with an initial daily dose of 4 mg, increased as required in steps of 2 to 4 mg, is used in the USA. The maximum recommended dose is 36 mg daily. Maintenance doses have been given in some countries in the form of modified-release preparations. For dosage in renal impairment, see below.

In the treatment of painful muscle spasm tizanidine hydrochloride is given in doses equivalent to 2 to 4 mg of the base three times daily.

Administration in renal impairment. In the UK, licensed product information recommends that in patients with renal insufficiency, treatment with tizanidine hydrochloride should be started with the equivalent of 2 mg of the base once daily; thereafter it advises a slow increase in the once-daily dose before increasing the frequency of administration. Similar recommendations are made in the USA.

Headache. Results from an open-label study¹ and a later controlled study² suggested that tizanidine might be of value in the prophylaxis of chronic daily headache. However, an earlier controlled study³ failed to show any significant advantage over placebo in the treatment of chronic tension-type headache. In another study⁴ tizanidine was also effective when given with a long-acting NSAID as part of a detoxification regimen for patients with chronic daily headaches induced by analgesic overuse.

1. Saper JR, *et al.* An open-label dose-titration study of the efficacy and tolerability of tizanidine hydrochloride tablets in the prophylaxis of chronic daily headache. *Headache* 2001; **41**: 357–68.

2. Saper JR, *et al.* Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache* 2002; **42**: 470–82.
3. Murros K, *et al.* Modified-release formulation of tizanidine in chronic tension-type headache. *Headache* 2000; **40**: 633–7.
4. Smith TR. Low-dose tizanidine with nonsteroidal anti-inflammatory drugs for detoxification from analgesic rebound headache. *Headache* 2002; **42**: 175–7.

Premedication. The value of tizanidine as a premedicant is being studied.¹ A dose of tizanidine 12 mg appears to have sedative and sympatholytic effects comparable with clonidine 150 micrograms.

1. Meittinen TJ, *et al.* The sedative and sympatholytic effects of oral tizanidine in healthy volunteers. *Anesth Analg* 1996; **82**: 817–20.

Spasticity. The efficacy of tizanidine for spasticity (p.1887) associated with cerebral and spinal disorders^{1,2} has been shown in several placebo-controlled studies and in comparative studies it has produced similar improvements in muscle tone to baclofen or diazepam. Carefully titrated doses of tizanidine and baclofen used together may have additive beneficial effects^{1,2} but use with benzodiazepines is not recommended because of potential interactions.¹ It was considered that tizanidine might have the advantage of being better tolerated than baclofen.

1. Wagstaff AJ, Bryson HM. Tizanidine: a review of its pharmacology, clinical efficacy and tolerability in the management of spasticity associated with cerebral and spinal disorders. *Drugs* 1997; **53**: 435–52.
2. Kamen L, *et al.* A practical overview of tizanidine use for spasticity secondary to multiple sclerosis, stroke, and spinal cord injury. *Curr Med Res Opin* 2008; **24**: 425–39.

Preparations

USP 31: Tizanidine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Sirdalud; **Austria:** Sirdalud; **Belg.:** Sirdalud; **Braz.:** Sirdalud; **Canad.:** Zanaflex; **Chile:** Sirdalud; **Cz.:** Sirdalud; **Denm.:** Sirdalud; **Fin.:** Sirdalud; **Ger.:** Sirdalud; **Gr.:** Sirdalud; **Hung.:** Sirdalud; **India:** Sirdalud; **Indon.:** Myores; Sirdalud; Zitanid; **Irl.:** Zanaflex; **Ital.:** Sirdalud; **Mex.:** Sirdalud; **Neth.:** Sirdalud; **Philipp.:** Sirdalud; Temelax; **Pol.:** Sirdalud; **Port.:** Sirdalud; **Rus.:** Sirdalud (Сипаланы); **Spain:** Sirdalud; **Switz.:** Sirdalud; **Thai.:** Sirdalud; **Tiz.:** Sirdalud; **Turk.:** Sirdalud; **UK:** Zanaflex; **USA:** Zanaflex; **Venez.:** Sirdalud.

Multi-ingredient: **India:** Kinectine-MR; Movon-MR; Niciflex-T; Nicip T; Nimulid MR; Valus-XT†; Vorth-XT†; Zerodol-MR.

Tolperisone Hydrochloride (BANM, rINNM)

Hidrocloruro de tolperisone; N-553; Tolpérisone, Chlorhydrate de; Tolperisoni Hydrochloridum. 2,4'-Dimethyl-3-piperidinopropiophenone hydrochloride.

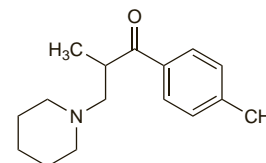
Тольперизона Гидрохлорид

$C_{16}H_{23}NO \cdot HCl = 281.8$.

CAS — 728-88-1 (tolperisone); 3644-61-9 (tolperisone hydrochloride).

ATC — M03BX04.

ATC Vet — QM03BX04.



(tolperisone)

Pharmacopoeias. In Jpn.

Profile

Tolperisone hydrochloride is a centrally acting muscle relaxant that has been used for the symptomatic treatment of spasticity (p.1887) and muscle spasm (p.1887), in usual doses of 50 to 150 mg three times daily by mouth. It has also been given by injection.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Miodom; **Austria:** Mydocalm; **Cz.:** Mydocalm; **Ger.:** Mydocalm; **Hong Kong:** Mydocalm; **Hung.:** Myderison; Mydeton; **Jpn.:** Muscalm; **Pol.:** Mydocalm; Tolperis; **Rus.:** Mydocalm (Мидокалм); **Switz.:** Mydocalm; **Thai.:** Biocalm; Musocalm; Mydocalm; Mydono; Mydosone; Myoxan; Riscalin; Shiwalax†; Soneriper; Spamus†; Tanderon.

Multi-ingredient: **Mex.:** Mydocalm-A.