Adverse Effects and Precautions
As for Sumatriptan, p.625.

Naratriptan should not be used in patients with severe hepatic or renal impairment (creatinine clearance less than 15 mL/minute) and should be used with caution in mild or moderate renal or hepatic impairment. Patients with hypersensitivity to sulfonamides may theoretically exhibit a similar reaction to naratriptan.

Medication-overuse headache. For a report of an association between naratriptan and medication-overuse headache, see under Adverse Effects of Sumatriptan, p.626.

Interactions
As for Sumatriptan, p.626.

Pharmacokinetics
After oral doses, peak plasma-naratriptan concentrations occur at 2 to 3 hours, and bioavailability is reported to be 63% in men and 74% in women. Plasma protein binding is about 29%. Naratriptan undergoes some hepatic metabolism by a wide range of cytochrome P450 isoenzymes. It is mainly excreted in the urine with 50% of a dose being recovered as unchanged drug and 30% as inactive metabolites. The elimination half-life is 6 hours, and is significantly prolonged in patients with renal or hepatic impairment.

Distribution into milk has been found in studies in *rats*.

Uses and Administration
Naratriptan is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. It is given orally as the hydrochloride, and doses are expressed in terms of the base; naratriptan hydrochloride 1.11 mg is equivalent to about 1 mg of naratriptan.

The recommended dose of naratriptan in the UK is 2.5 mg, and in the USA it is 1 or 2.5 mg. If no response is obtained with the initial dose, a second dose should not be taken for the same attack. If symptoms recur after an initial response, the dose may be repeated after an interval of 4 hours, to a maximum of 5 mg in any 24-hour period. For doses in hepatic or renal impairment see below.

Administration in hepatic or renal impairment. Naratriptan is contra-indicated in patients with severe hepatic or severe renal impairment (creatinine clearance less than 15 mL/minute). In patients with mild to moderate hepatic or renal impairment, the recommended maximum dose in 24 hours is 2.5 mg and a lower starting dose should be considered.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

Further references.

1. Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials. *Pharmacoepidemiol Drug Safety* 2004; **13:** 73–82.

Preparations
USP 31: Naratriptan Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Naramig; ***Austral.:*** Naramig; ***Austria:*** Antimigrin; Naramig; ***Belg.:*** Naramig; ***Braz.:*** Naramig; ***Canad.:*** Amerge; ***Chile:*** Miragran; Naramig; ***Cz.:*** Naramig; ***Denm.:*** Naragran; ***Fin.:*** Naramig; ***Fr.:*** Naramig; ***Ger.:*** Naramig; ***Gr.:*** Naramig; ***Hung.:*** Naramig†; ***Israel:*** Naramig; ***Mex.:*** Naramig; ***Neth.:*** Naramig; ***Norw.:*** Naramig; ***NZ:*** Naramig; ***Port.:*** Naramig; ***Rus.:*** Naramig (Нарамиг); ***S.Afr.:*** Naramig; ***Singapore:*** Naramig; ***Spain:*** Colatan†; Naramig; ***Swed.:*** Naramig; ***Switz.:*** Naramig; ***Thai.:*** Naramig†; ***Turk.:*** Naramig; ***UK:*** Naramig; ***USA:*** Amerge.

Oxetorone Fumarate *(USAN, rINNM)*

Fumarato de oxetorona; L-6257; Oxétorone, Fumarate d'; Oxetoroni Fumaras. 3-(6,12-Dihydrobenzofuro[3,2-*c*][1]benzoxepin-6-ylidene)-*NN*-dimethylpropylamine hydrogen fumarate.

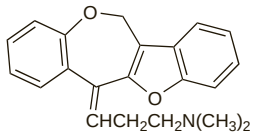
Оксеторона Фумарат

$C_{21}H_{21}NO_2,C_4H_4O_4$ = 435.5.

CAS — 26020-55-3 (oxetorone); 34522-46-8 (oxetorone fumarate).

ATC — N02CX06.

ATC Vet — QN02CX06.



(oxetorone)

Profile
Oxetorone fumarate is an antihistamine and serotonin antagonist used orally in the treatment of migraine (p.616) and cluster headache (p.616) in doses of up to 180 mg daily. Oxetorone was reported to have induced hyperplastic changes in breast tissue and the uterine endometrium of *rodents*.

Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Nocertone; ***Cz.:*** Nocertone†; ***Fr.:*** Nocertone.

Pizotifen *(BAN, rINN)*

BC-105; Pitsotifeeni; Pizotifène; Pizotifeno; Pizotifenum; Pizotyline *(USAN)*. 9,10-Dihydro-4-(1-methylpiperidin-4-ylidene)-4*H*-benzo[4,5]cycloheptа[1,2-*b*]thiophene.

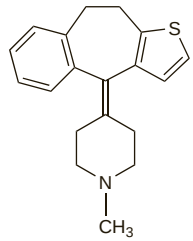
Пизотифен

$C_{19}H_{21}NS$ = 295.4.

CAS — 15574-96-6.

ATC — N02CX01.

ATC Vet — QN02CX01.



Pharmacopoeias. In *Chin.*

Pizotifen Malate *(BANM, rINNM)*

Malato de pizotifeno; Pizotifen Hydrogen Malate; Pizotifène, Malate de; Pizotifeni Malas; Pizotyline Malate.

Пизотифена Малат

$C_{19}H_{21}NS,C_4H_6O_5$ = 429.5.

CAS — 5189-11-7.

ATC — N02CX01.

ATC Vet — QN02CX01.

Pharmacopoeias. In *Br.*
BP 2008 (Pizotifen Malate). A white or slightly yellowish-white, odourless or almost odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in chloroform; sparingly soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions
As for the sedating antihistamines in general, see p.561.

Increased appetite and weight gain may occur with pizotifen. Drowsiness may be troublesome.

Incidence of adverse effects. Adverse effects were noted in 22 of 47 patients with severe migraine given pizotifen 1 to 2 mg daily.[1] These reactions included weight increase (15), muscle pain or cramps (3), heavy or restless legs (3), fluid retention (3), drowsiness (2), more frequent milder headaches (2), facial flushing (1), reduced libido (1), exacerbation of epilepsy (1), and dreaming (2). Adverse effects necessitating withdrawal occurred in 11 patients.

1. Peet KMS. Use of pizotifen in severe migraine: a long-term study. *Curr Med Res Opin* 1977; **5:** 192–9.

Interactions
As for the sedating antihistamines in general, see p.563.

Antihypertensives. After a report[1] of loss of blood pressure control when treatment with pizotifen was started in a patient receiving *debrisoquine* the manufacturer suggested that since pizotifen had a similar chemical structure to the tricyclic antidepressants it might antagonise the actions of adrenergic neurone blockers in a similar manner.

1. Bailey RR. Antagonism of debrisoquine sulphate by pizotifen (Sandomigran). *N Z Med J* 1976; **1:** 449.

Pharmacokinetics
Pizotifen is well absorbed from the gastrointestinal tract, peak plasma concentrations occurring about 5 hours after a single oral dose. Over 90% is bound to plasma proteins. Pizotifen undergoes extensive metabolism. Over half of a dose is excreted in the urine, chiefly as metabolites; a significant proportion is excreted in the faeces. The primary metabolite of pizotifen (*N*-glucuronide conjugate) has a long elimination half-life of about 23 hours.

Distribution into milk has been found in *animal* studies.

Uses and Administration
Pizotifen is a sedating antihistamine (p.561) that has strong serotonin antagonist and weak antimuscarinic properties. It also antagonises the action of tryptamine. Pizotifen is used, usually as the malate, for the prophylaxis of migraine and for the prevention of headache attacks during cluster periods. It is not effective in treating an acute attack. Doses of pizotifen malate are expressed in terms of the base; pizotifen malate 1.45 mg is equivalent to about 1 mg of pizotifen.

The usual adult oral dose is 1.5 mg daily either in three divided doses or as a single dose at night; children aged over 2 years may also be given up to 1.5 mg daily, although the maximum single dose (at night) should not exceed 1 mg. Gradual increase from an initial dose of 500 micrograms may help to avoid undue drowsiness. Doses in adults may vary from 500 micrograms up to a maximum of 4.5 mg daily; not more than 3 mg should be given as a single dose.

Pizotifen hydrochloride has also been used in the management of migraine.

Abdominal migraine. Abdominal migraine is a recurrent disorder seen mainly in children and characterised by episodic midline abdominal pain lasting for up to 72 hours. The pain is severe enough to disrupt normal activities and may be associated with pallor, anorexia, nausea, and vomiting.[1,2] Sleep, and sometimes vomiting, terminate the attack.

Pizotifen was found to be effective for the prophylaxis of abdominal pain in children with abdominal migraine.[3] Prophylactic treatment with propranolol or cyproheptadine may also be of benefit.[4]

1. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia* 2004; **24** (suppl 1): 9–160. Also available at: http://216.25.100.131/ihscommon/guidelines/pdfs/ihc_II_main_no_print.pdf (accessed 01/10/04)
2. Russell G, *et al.* The child with recurrent abdominal pain: is it abdominal migraine? *Br J Hosp Med* 2007; **68:** M110–M113.
3. Symon DNK, Russell G. Double blind placebo controlled trial of pizotifen syrup in the treatment of abdominal migraine. *Arch Dis Child* 1995; **72:** 48–50.
4. Worawattanakul M, *et al.* Abdominal migraine: prophylactic treatment and follow-up. *J Pediatr Gastroenterol Nutr* 1999; **28:** 37–40.

Migraine and cluster headache. Pizotifen has been widely used for the prophylaxis of migraine (p.616) but evidence for its efficacy is limited. It has also been tried in the management of cluster headache (p.616) to prevent headache attacks during a cluster period.

References.

1. Cleland PG, *et al.* Studies to assess if pizotifen prophylaxis improves migraine beyond the benefit offered by acute sumatriptan therapy alone. *Eur Neurol* 1997; **38:** 31–8.
2. Barnes N, Millman G. Do pizotifen or propranolol reduce the frequency of migraine headache? *Arch Dis Child* 2004; **89:** 684–5.

Preparations
BP 2008: Pizotifen Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Sandomigran; ***Austral.:*** Sandomigran; ***Belg.:*** Sandomigran; ***Braz.:*** Sandomigran; ***Canad.:*** Sandomigran; ***Cz.:*** Sandomigran; ***Denm.:*** Sandomigrin; ***Fr.:*** Sanmigran; ***Ger.:*** Mosegor†; ***Gr.:*** Mosegor†; ***Hong Kong:*** Sandomigran; ***Hung.:*** Sandomigran†; ***Indon.:*** Lysagor; ***Irl.:*** Sanomigran; ***Ital.:*** Sandomigran; ***Malaysia:*** Sandomigran; ***Neth.:*** Sandomigran; ***NZ:*** Sandomigran; ***Philipp.:*** Litec; Mosegor; ***Pol.:*** Polomigran; ***S.Afr.:*** Sandomigran; ***Spain:*** Mosegor; Sandomigran; ***Swed.:*** Sandomigrin; ***Switz.:*** Mosegor; ***Thai.:*** Anorsia; Mosegor; Moselar; Pizomed; Zofen; ***Turk.:*** Sandomigran; ***UK:*** Sanomigran; ***Venez.:*** Sandomiran†.

Multi-ingredient: ***Philipp.:*** Appetens; Mosegor Vita.