

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

Further references.

- Rapoport A, *et al.* Dose range-finding studies with frovatriptan in the acute treatment of migraine. *Headache* 2002; **42** (suppl 2): S74–S83.
- Ryan R, *et al.* Clinical efficacy of frovatriptan: placebo-controlled studies. *Headache* 2002; **42** (suppl 2): S84–S92.
- Poolsup N, *et al.* Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. *J Clin Pharm Ther* 2005; **30**: 521–32.

## Preparations

### Proprietary Preparations (details are given in Part 3)

**Austria:** Eumitan; **Cz:** Fromen; **Recur;** **Fin:** Migard; **Fr:** Tigreat; **Ger:** Al-legro; **Gr:** Migard; **Migralin;** **Irl:** Frovex; **Ital:** Auradol; **Rilamig;** **Neth:** Fromirex; **Migard;** **Port:** Dorlise; **Migard;** **Spain:** Forvey; **Perlic;** **Switz:** Me-namig; **UK:** Migard; **USA:** Frova.

## Iprazochrome (rINN)

Ipratsokromi; Iprazochromum; Iprazocromo; Iprazokrom. 3-Hydroxy-1-isopropyl-5,6-indolinedione 5-semicarbazone.

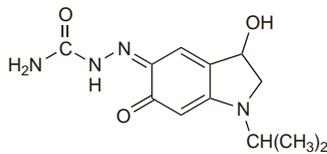
Ипразохром

$C_{12}H_{16}N_4O_3 = 264.3$ .

CAS — 7248-21-7.

ATC — N02CX03.

ATC Vet — QN02CX03.



## Profile

Iprazochrome is a serotonin antagonist used in the prophylaxis of migraine (p.616) and in the management of diabetic retinopathy. It has been given in usual oral doses of 2.5 to 5 mg three times daily.

## Preparations

### Proprietary Preparations (details are given in Part 3)

**Ger:** Divascan†; **Hung:** Divascan; **Pol:** Divascan.

## Methysergide (BAN, USAN, rINN)

1-Methyl-D-lysergic Acid Butanolamide; Méthysergide; Methysergidum; Metisergida; Metysergida; Metysergidi. N-[1-(Hydroxymethyl)propyl]-1-methyl-D-lysergamide; 9,10-Didehydro-N-[1-(hydroxymethyl)propyl]-1,6-dimethylergoline-8β-carboxamide.

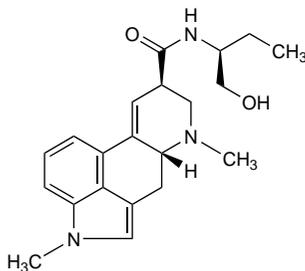
Метизергид

$C_{21}H_{27}N_3O_2 = 353.5$ .

CAS — 361-37-5.

ATC — N02CA04.

ATC Vet — QN02CA04.



## Methysergide Maleate (BANM, rINNM)

Maleato de metisergida; Méthysergide, Maléate de; Methysergidi Maleas.

Метизергида Маллат

$C_{21}H_{27}N_3O_2 \cdot C_4H_4O_4 = 469.5$ .

CAS — 129-49-7.

ATC — N02CA04.

ATC Vet — QN02CA04.

## Pharmacopoeias. In Br and US.

**BP 2008** (Methysergide Maleate). A white or almost white crystalline powder which may have a yellow or pink tinge; odourless or almost odourless. Slightly soluble in water and in methyl alcohol; practically insoluble in chloroform and in ether. A 0.2% solution in water has a pH of 3.7 to 4.7. Store at a temperature of 2° to 8°. Protect from light.

The symbol † denotes a preparation no longer actively marketed

**USP 31** (Methysergide Maleate). A white to yellowish-white or reddish-white, crystalline powder. Is odourless or has not more than a slight odour. Soluble 1 in 200 of water and 1 in 165 of alcohol; soluble 1 in 3400 of chloroform; practically insoluble in ether. pH of a 1 in 500 solution is between 3.7 and 4.7. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

## Adverse Effects

Gastrointestinal effects such as nausea, vomiting, heartburn, and abdominal pain are common on initial treatment with methysergide maleate, as are dizziness and drowsiness. Other CNS effects reported include ataxia, insomnia, weakness, restlessness, lightheadedness, euphoria, and hallucinations. Peripheral or localised oedema, leg cramps, and weight gain have occurred and there have been occasional reports of skin rashes, loss of hair, joint and muscle pain, neutropenia, and eosinophilia. Orthostatic hypotension and tachycardia have been observed. There have been isolated reports of myocardial infarction particularly in patients with ischaemic heart disease or when given with other vasoconstrictive drugs, both of which are contra-indications for methysergide therapy.

Arterial spasm has occurred in some patients, and may present as paraesthesia of the extremities or angular pain, as with ergotamine (p.620); if such symptoms occur methysergide should be withdrawn, although rebound headaches may be experienced if it is withdrawn suddenly. Vascular insufficiency of the lower limbs may represent arterial spasm or fibrotic changes. Treatment should be stopped at the first signs of impaired peripheral circulation. Retroperitoneal fibrosis, with obstruction of abdominal blood vessels and ureters, pleuropulmonary fibrosis, and fibrotic changes in heart valves have occurred in patients on long-term treatment. Methysergide must be withdrawn immediately if fibrosis occurs. Retroperitoneal fibrosis is usually reversible, but other fibrotic changes are less readily reversed.

**Fibrosis.** Fibrosis has been associated with the long-term use of methysergide maleate. In one early report<sup>1</sup> in 27 patients retroperitoneal fibrosis was attributed to use of methysergide for periods of 9 to 54 months in doses ranging from 2 to 28 mg daily. There was partial or complete regression of fibrosis in 13 of the patients whose treatment was withdrawn. Improvement usually began within a few days, in some cases with the aid of prednisone. The other 14 patients were treated by surgery; those few who continued taking methysergide had difficult postoperative courses. Cardiac murmurs occurred in 7 patients, and regressed wholly or partially in 3 after therapy was stopped. Fibrotic changes affecting the aorta, heart valves, and pulmonary tissues occurred in a few of the patients. Others have reported the development of endocardial fibrosis indicated by cardiac murmurs in 48 patients receiving methysergide.<sup>2</sup> The murmurs gradually regressed in 27 when methysergide was stopped. Retroperitoneal fibrosis was present in 9 patients and pleuropulmonary fibrosis in 2. A patient with fibrosis of the iliac vein has been described.<sup>3</sup>

A few cases of retroperitoneal fibrosis associated with ergotamine tartrate or dihydroergotamine have also been noted.<sup>1</sup> These 2 drugs have also been implicated in a few other cases of retroperitoneal fibrosis or other fibrotic disorders in patients taking high doses for long periods.<sup>4,7</sup>

- Graham JR, *et al.* Fibrotic disorders associated with methysergide therapy for headache. *N Engl J Med* 1966; **274**: 359–68.
- Bana DS, *et al.* Cardiac murmurs and endocardial fibrosis associated with methysergide therapy. *Am Heart J* 1974; **88**: 640–55.
- Bucci JA, Manoharan A. Methysergide-induced retroperitoneal fibrosis: successful outcome and two new laboratory features. *Mayo Clin Proc* 1997; **72**: 1148–50.
- Lepage-Savary D, Vallières A. Ergotamine as a possible cause of retroperitoneal fibrosis. *Clin Pharm* 1982; **1**: 179–80.
- Robert M, *et al.* Fibrotic processes associated with long-term ergotamine therapy. *N Engl J Med* 1984; **311**: 601 and 602.
- Damstrup L, Jensen TT. Retroperitoneal fibrosis after long-term daily use of ergotamine. *Int Urol Nephrol* 1986; **18**: 299–301.
- Malaquin F, *et al.* Pleural and retroperitoneal fibrosis from dihydroergotamine. *N Engl J Med* 1989; **321**: 1760.

## Treatment of Adverse Effects

As for Ergotamine Tartrate, p.620.

Methysergide maleate should be withdrawn immediately if fibrosis develops. Corticosteroids have been used to treat fibrosis, although surgery may be required.

## Precautions

As for Ergotamine Tartrate, p.620.

In addition, methysergide maleate is contra-indicated in valvular heart disease, pulmonary and collagen diseases, diseases of the urinary tract, phlebitis and cellulitis of the lower extremities, and debilitated states. It should be used with caution in patients with peptic ulcer disease because it may increase gastric acidity. Patients should be closely supervised. Methysergide should not be given continuously for more than 6 months and should normally be withdrawn gradually (see Uses and Administration, below). However, it should be withdrawn immediately if symptoms of fibrosis or arterial spasm develop.

**Porphyria.** Methysergide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals or *in-vitro* systems.

## Interactions

Interactions involving those ergot alkaloids used primarily in the management of migraine are discussed under ergotamine (p.621). References specific to methysergide may be found there under the headings Antimigraine Drugs and Beta Blockers.

## Pharmacokinetics

Methysergide maleate is rapidly absorbed from the gastrointestinal tract with maximum plasma concentrations being obtained within about one hour of ingestion. It is 66% bound to plasma proteins. Methysergide undergoes extensive first-pass hepatic metabolism to methylergometrine (p.2011). About 50% of an oral dose is excreted in the urine as unchanged drug and metabolites. The elimination of methysergide is biphasic; half-lives of about 2.7 hours and 10 hours have been reported for the 2 phases respectively.

## References

- Bredberg U, *et al.* Pharmacokinetics of methysergide and its metabolite methylergometrine in man. *Eur J Clin Pharmacol* 1986; **30**: 75–7.

## Uses and Administration

Methysergide maleate is a semisynthetic ergot alkaloid. It is a potent serotonin antagonist and, compared with ergotamine, has only weak vasoconstrictor and oxytocic effects. It may be used to prevent severe recurrent migraine (p.616) and headache attacks during cluster periods (p.616), although its use has declined because of adverse effects. It is ineffective in the treatment of acute attacks.

Methysergide is given orally as the maleate but doses are often expressed in terms of the base; 1.33 mg of methysergide maleate is equivalent to about 1 mg of methysergide. A usual dosage is 2 to 6 mg daily given in divided doses with meals. It is suggested that treatment should be started with 1 mg at bedtime and doses increased gradually over about 2 weeks; the minimum effective dose should be used. In some other countries doses are expressed in terms of the maleate, a usual dose of which is 4 to 8 mg daily. Careful and regular observation of the patient is essential because of the high incidence of adverse effects and it is recommended that treatment should only be carried out under hospital supervision. If treatment still proves to be ineffective after 3 weeks, further use is unlikely to be of benefit. Treatment should not be continued for more than 6 months, after which it should be gradually withdrawn over 2 or 3 weeks and then stopped for at least a month for reassessment. Some have considered that treatment courses should not exceed 3 months without a break.

Methysergide maleate has also been used to control diarrhoea associated with carcinoid syndrome (p.643) in high doses equivalent to 12 to 20 mg of methysergide daily.

As a serotonin antagonist, methysergide might be expected to help reverse the serotonin syndrome (p.416).

## Preparations

**BP 2008:** Methysergide Tablets;

**USP 31:** Methysergide Maleate Tablets.

### Proprietary Preparations (details are given in Part 3)

**Austral:** Deseril; **Belg:** Deseril; **Braz:** Deserila; **Canad:** Sansert; **Fr:** Deseril; **Ger:** Deseril†; **Neth:** Deseril; **S.Afr:** Deseril†; **Switz:** Deseril†; **UK:** Deseril.

## Naratriptan Hydrochloride

(BANM, USAN, rINNM)

GR-85548A; GR-85548X (naratriptan); Hidrocloruro de naratriptán; Naratriptan, Chlorhydrate de; Naratriptani Hydrochloridum. N-Methyl-3-(1-methyl-4-piperidyl)indole-5-ethanesulfonamide hydrochloride.

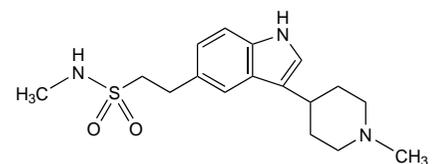
Наратриптана Гидрохлорид

$C_{17}H_{25}N_3O_2 \cdot HCl = 371.9$ .

CAS — 121679-13-8 (naratriptan); 121679-19-4 (naratriptan hydrochloride); 143388-64-1 (naratriptan hydrochloride).

ATC — N02CC02.

ATC Vet — QN02CC02.



(naratriptan)

## Pharmacopoeias. In US.

**USP 31** (Naratriptan Hydrochloride). A white to pale yellow solid. Soluble in water. Store in airtight containers at a temperature not exceeding 30°.

**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-HT<sub>1</sub>) 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. *Pharmacoeconomic 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; **Canada:** 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; **Swed.:** Naramig; **Switz.:** Naramig; **Thai.:** Naramig; **Turk.:** Naramig; **UK:** Naramig; **USA:** Amerge.

**Oxetorone Fumarate** (USAN, rINN)

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.

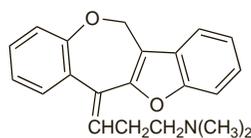
Осеторона Фумарат

C<sub>21</sub>H<sub>21</sub>NO<sub>2</sub>.C<sub>4</sub>H<sub>4</sub>O<sub>4</sub> = 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.:** Nocertonej; **Fr.:** Nocertone.

**Pizotifen** (BAN, rINN)

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

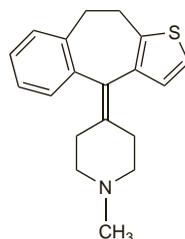
Пизотифен

C<sub>19</sub>H<sub>21</sub>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; Pizotyl-ine Malate.

Пизотифена МАЛАТ

C<sub>19</sub>H<sub>21</sub>NS.C<sub>4</sub>H<sub>6</sub>O<sub>5</sub> = 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.<sup>1</sup> 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<sup>1</sup> of loss of blood pressure control when treatment with pizotifen was started in a patient receiving *debrisoquine* the manufacturer suggested that since piz-

otifen 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 mid-line 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.<sup>1,2</sup> Sleep, and sometimes vomiting, terminate the attack.

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

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/ihsccommon/guidelines/pdfs/ihe\\_IL\\_main\\_no\\_print.pdf](http://216.25.100.131/ihsccommon/guidelines/pdfs/ihe_IL_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; **Canada:** Sandomigran; **Cz.:** Sandomigran; **Denm.:** Sandomigran; **Fr.:** Sanmigran; **Ger.:** Mosegor; **Gr.:** Mosegor; **Hong Kong:** Sandomigran; **Hung.:** Sandomigran; **Indon.:** Lysagor; **Irl.:** Sandomigran; **Ital.:** Sandomigran; **Malaysia:** Sandomigran; **Neth.:** Sandomigran; **NZ:** Sandomigran; **Philipp.:** Litec; Mosegor; **Pol.:** Polomigran; **S.Afr.:** Sandomigran; **Spain:** Mosegor; Sandomigran; **Swed.:** Sandomigran; **Switz.:** Mosegor; **Thai.:** Anorsia; Mosegor; Moselar; Pizomedi; Zofen; **Turk.:** Sandomigran; **UK:** Sandomigran; **Venez.:** Sandomigran.

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