Pharmacopoeias. In *Swiss*.

Profile
Drofenine hydrochloride is an antimuscarinic available in preparations for the treatment of visceral spasms.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Espasmo Cibalena; ***Austria:*** Spasmoplus; ***Belg.:*** Spasmoplus†; ***Chile:*** Espasmo Cibalgina; Espasmo Cibalgina Compuesta; ***Ger.:*** Spasmo-Cibalgin S†; ***Ital.:*** Spasmo-Cibalgina†; ***Mex.:*** Espasmo Cibalgina; ***Switz.:*** Lunadon; Spasmo-Cibalgin comp†; Spasmo-Cibalgin†.

Dronabinol *(USAN, rINN)* ⊗

Dronabinolum; NSC-134454; Δ^9-Tetrahydrocannabinol; Δ^9-THC. (6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol.

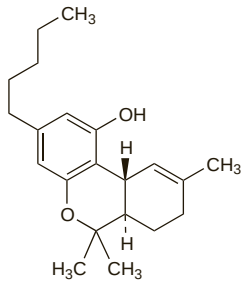
Дронабинол

$C_{21}H_{30}O_2$ = 314.5.

CAS — 1972-08-3.

ATC — A04AD10.

ATC Vet — QA04AD10.



Pharmacopoeias. In *US*.

USP 31 (Dronabinol). Store at a temperature between 8° and 15° in airtight glass containers in an inert atmosphere. Protect from light.

Adverse Effects and Precautions
As for Nabilone, p.1750. The most frequent adverse effects of dronabinol include abdominal pain, nausea and vomiting, dizziness, euphoria, paranoid reactions, and somnolence. Seizures and seizure-like activity have been reported; dronabinol should be used with caution in those with a history of seizure disorders, and therapy should be stopped if seizures occur.

Abuse. The abuse liability of dronabinol was rated as being substantially lower than that of cannabis.[1]

1. WHO. WHO expert committee on drug dependence: thirty-third report. *WHO Tech Rep Ser 915* 2003. Available at: http://libdoc.who.int/trs/WHO_TRS_915.pdf (accessed 03/07/08)

Breast feeding. US licensed product information states that dronabinol is concentrated in breast milk and recommends that it should not be used in breast-feeding mothers.

Pharmacokinetics
After oral doses dronabinol is slowly and erratically absorbed from the gastrointestinal tract; the bioavailability of an oral dose is about 10 to 20%, due to extensive first-pass metabolism. Peak plasma concentrations of dronabinol and its 11-hydroxy metabolite are achieved about 2 to 4 hours after a dose by mouth. It is widely distributed and is extensively protein bound, with a volume of distribution of about 10 litres/kg. Elimination is biphasic, with an initial half-life of about 4 hours, and a terminal half-life of about 25 to 36 hours.

Dronabinol is extensively metabolised, mainly in the liver by cytochrome P450 isoenzymes; the primary metabolite, 11-hydroxydronabinol is also active. The 11-hydroxy metabolite is converted to other, more polar and acidic compounds which are excreted in faeces via the bile, and in the urine. About 50% of an oral dose is recovered in faeces within 72 hours and 10 to 15% in urine. Many of the metabolites have relatively prolonged half-lives, and accumulation may occur with repeated dosage.

Dronabinol is distributed into breast milk and crosses the placenta.

◊ References.

1. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; **42:** 327–60.
2. McGilveray IJ. Pharmacokinetics of cannabinoids. *Pain Res Manag* 2005; **10:** 15A–22A.

Uses and Administration
Dronabinol, the major psychoactive constituent of cannabis (p.2274), has antiemetic properties and is used for the control of **nausea and vomiting** associated with cancer chemotherapy (p.1700) in patients who have failed to respond adequately to conventional antiemetics.

The usual initial oral dose of dronabinol is 5 mg/m^2 given 1 to 3 hours before the first dose of the antineoplastic drug with subsequent doses being given every 2 to 4 hours after chemotherapy to a maximum of 4 to 6 doses daily. If necessary, the dose may be increased by increments of 2.5 mg/m^2 to a maximum dose of 15 mg/m^2, if adverse effects permit.

Dronabinol also has appetite-stimulant effects and is used in the treatment of **anorexia** associated with weight loss in patients with AIDS. For this purpose 2.5 mg may be taken twice daily, before lunch and supper, reduced to a single 2.5-mg dose in the evening in patients who tolerate the drug poorly. If necessary, and if adverse effects permit, doses may also be increased up to 20 mg daily in divided doses.

Dronabinol is used with cannabidiol, another cannabinoid, in a buccal spray preparation as adjunctive treatment for the symptomatic relief of **neuropathic pain** in multiple sclerosis in adults; this combination is also used as adjunctive analgesic treatment in adult patients with advanced cancer and is under investigation for a number of other conditions (see under Cannabis, p.2275).

◊ General references.

1. Voth EA, Schwartz RH. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Ann Intern Med* 1997; **126:** 791–8.
2. Williamson EM, Evans FJ. Cannabinoids in clinical practice. *Drugs* 2000; **60:** 1303–14.
3. Tramer MR, *et al.* Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 2001; **323:** 16–21.
4. Berman JS, *et al.* Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004; **112:** 299–306.
5. Costa B. On the pharmacological properties of Delta9-tetrahydrocannabinol (THC). *Chem Biodivers* 2007; **4:** 1664–77.
6. Beaulieu P, Ware M. Reassessment of the role of cannabinoids in the management of pain. *Curr Opin Anaesthesiol* 2007; **20:** 473–7.

Alzheimer's disease. There is some suggestion[1] that dronabinol may decrease agitation in patients with Alzheimer's disease.

1. Volicer L, *et al.* Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 1997; **12:** 913–19.

Anorexia. Dronabinol is used for the management of anorexia in patients with HIV-associated wasting (p.858). However, although dronabinol may stimulate appetite and prevent weight loss,[1] it does not appear to produce significant weight gain, and may produce less benefit than megestrol acetate.[2] Benefits were also less than those of megestrol in patients with anorexia associated with malignant disease.[3]

1. Beal JE, *et al.* Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 1995; **10:** 89–97.
2. Timpone JG, *et al.* The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Res Hum Retroviruses* 1997; **13:** 305–15.
3. Jatoi A, *et al.* Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002; **20:** 567–73.

Multiple sclerosis. Anecdotal evidence has suggested that cannabinoids might improve symptoms in patients with multiple sclerosis (p.892); a review[1] considered evidence of effectiveness to be lacking. In a large placebo-controlled study, treatment with dronabinol or oral cannabis extract had no benefit on objective assessment of spasticity;[2] however, there were improvements in walking time, and subjective improvements in both spasticity and pain. A subsequent small controlled study found dronabinol to have a modest but clinically relevant effect on central neuropathic pain in patients with multiple sclerosis.[3]

Dronabinol is used with cannabidiol, another cannabinoid, in a buccal spray preparation for the symptomatic relief of neuropathic pain in multiple sclerosis in adults.

1. Killestein J, *et al.* Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs* 2004; **64:** 1–11.
2. Zajicek J, *et al.* Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; **362:** 1517–26.
3. Svendsen KB, *et al.* Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004; **329:** 253–7.

Tourette's syndrome. Preliminary studies[1,2] indicate that dronabinol may reduce tic severity in Tourette's syndrome (see Tics, p.954).

1. Müller-Vahl KR, *et al.* Treatment of Tourette's syndrome with Δ -tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry* 2002; **35:** 57–61.
2. Müller-Vahl KR, *et al.* Δ -Tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry* 2003; **64:** 459–65.

Preparations
USP 31: Dronabinol Capsules.

Proprietary Preparations (details are given in Part 3)

Canad.: Marinol; ***Israel:*** Ronabin†; ***S.Afr.:*** Elevat†; ***USA:*** Marinol.

Multi-ingredient: ***Canad.:*** Sativex.

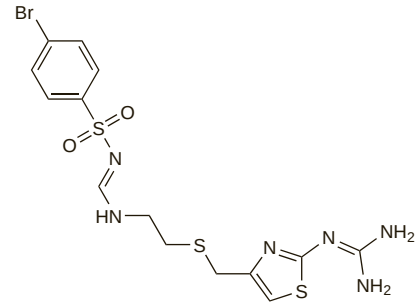
Ebrotidine *(rINN)*

Ebrotidina; Ébrotidine; Ebrotidinum. *p*-Bromo-*N*-[(*E*)-({2-[({2-[(diaminomethylene)amino]-4-thiazolyl}methyl)thio]ethyl}amino)methylene]benzenesulfonamide.

Эбротидин

$C_{14}H_{17}BrN_6O_2S_3$ = 477.4.

CAS — 100981-43-9.



Profile
Ebrotidine is a histamine H_2-antagonist with general properties similar to those of cimetidine (p.1716), but which also has cytoprotective actions. It has been used in peptic ulcer disease. Serious liver damage has been reported.

◊ References.

1. Patel SS, Wilde MI. Ebrotidine. *Drugs* 1996; **51:** 974–80.
2. Various. Ebrotidine: a new generation H -receptor antagonist and gastroprotective agent. *Arzneimittelforschung* 1997; **47:** 427–590.
3. Andrade RJ, *et al.* Acute liver injury associated with the use of ebrotidine, a new H -receptor antagonist. *J Hepatol* 1999; **31:** 641–6.

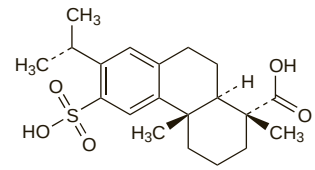
Ecabet Sodium *(rINNM)*

Ecabet sódico; Écabet Sodique; Natrii Ecabetum; 12-Sulphodehydroabietic Acid, Monosodium Salt; TA-2711. 13-Isopropyl-12-sulphopodocarpa-8,11,13-trien-15-oic acid pentahydrate, sodium salt.

Экабет Натрий

$C_{20}H_{27}NaO_5S,5H_2O$ = 492.6.

CAS — 33159-27-2 (ecabet); 86408-72-2 (ecabet sodium).



(ecabet)

Profile
Ecabet sodium is a cytoprotective drug used in the treatment of peptic ulcer disease (p.1702). The suggested oral dose is 1 g of ecabet sodium twice daily.

It is also under investigation as eye drops in the management of dry eye.

◊ References.

1. Murata H, *et al.* Combination therapy of ecabet sodium and cimetidine compared with cimetidine alone for gastric ulcer: prospective randomized multicenter study. *J Gastroenterol Hepatol* 2003; **18:** 1029–33.
2. Lee JH, *et al.* Efficacy and safety of ecabet sodium on functional dyspepsia: a prospective, double-blinded, randomized, multicenter controlled trial. *World J Gastroenterol* 2006; **12:** 2756–61.

Administration. The use of ecabet sodium as a rectal enema has been investigated in patients with ulcerative colitis.[1,2]

1. Kono T, *et al.* Effect of ecabet sodium enema on mildly to moderately active ulcerative proctosigmoiditis: an open-label study. *Am J Gastroenterol* 2001; **96:** 793–7.
2. Iizuka M, *et al.* Efficacy of ecabet sodium enema on steroid resistant or steroid dependent ulcerative colitis. *Gut* 2006; **55:** 1523.

Preparations
Proprietary Preparations (details are given in Part 3)

Jpn: Gastrom.

Enoxolone Aluminium *(BANM, rINNM)*

Aluminii Enoxolonum; Aluminium Glycyrrhetate; Aluminium Glycyrrhetinate; Enoxolona de aluminio; Enoxolone Aluminum; Énoxolone d'Aluminium. 3β-Hydroxy-11-oxo-olean-12-en-30-oic acid, aluminium salt.

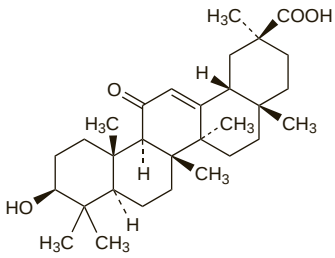
Алюминий Эноксолон

$(C_{30}H_{46}O_4)_3.Al$ = 1439.0.

CAS — 4598-66-7.

ATC — D03AX10.

ATC Vet — QD03AX10.



(enoxolone)

Profile

Enoxolone aluminium is an analogue of carbenoxolone (p.1714) that has been used in preparations for the treatment of peptic ulcer disease and other gastrointestinal disorders. It has also been used in preparations for skin disorders and mouth and throat disorders.

Primary pulmonary hypertension. *In-utero* exposure to enoxolone was implicated in a fatal case of neonatal primary pulmonary hypertension; the mother had used a lotion for prurigo that contained enoxolone and the authors supposed it had contributed at least in part to the pulmonary hypertension.[1]

1. Navarre-Belhassen C, *et al.* An unexpected case of primary pulmonary hypertension of the neonate (PPHN): potential role of topical administration of enoxolone. *J Perinat Med* 2002; **30:** 437–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Spain:*** Gastroalgine.

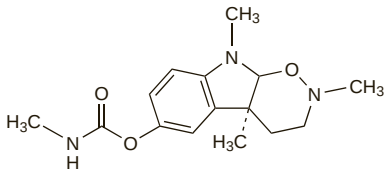
Eseridine Salicylate *(rINNM)*

Éséridine, Salicylate d'; Eseridini Salicylas; Eserine Aminoxide Salicylate; Eserine Oxide Salicylate; Physostigmine Aminoxide Salicylate; Physostigmine *N*-Oxide Salicylate; Salicilato de eseridina. (4a*S*,9a*S*)-2,3,4,4a,9,9a-Hexahydro-2,4a,9-trimethyl-1,2-oxazino[6,5-*b*]indol-6-ylmethylcarbamate salicylate.

Эзеридина Салицилат

$C_{15}H_{21}N_3O_3.C_7H_6O_3$ = 429.5.

CAS — 25573-43-7 (eseridine); 5995-96-0 (eseridine salicylate).



(eseridine)

Profile

Eseridine salicylate, a derivative of physostigmine, is an inhibitor of cholinesterase activity that has been given orally for dyspepsia in doses of up to 4.5 mg 3 times daily, taken 30 minutes before meals.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Geneserine.

Esomeprazole *(BAN, rINN)*

Esomepratsoli; Esomeprazol; Ésoméprazole; Esomeprazolum; H-199/18; Perprazole. 5-Methoxy-2-{(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazole.

Эзомепразол

$C_{17}H_{19}N_3O_3S$ = 345.4.

CAS — 119141-88-7.

ATC — A02BC05.

ATC Vet — QA02BC05.

Esomeprazole Magnesium *(BANM, USAN, rINNM)*

Esomeprazol; Esomeprazol magnésico; Ésoméprazole magnésique; Ésoméprazole Magnesique; Esomeprazolum magnesicum; H199/18 (esomeprazole); Magnesii Esomeprazolum; Perprazole (esomeprazole). 5-Methoxy-2-{(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazole magnesium (2:1) trihydrate.

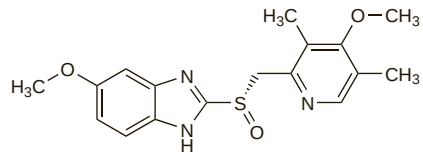
Магния Эзомепразол

$C_{34}H_{36}MgN_6O_6S_2.3H_2O$ = 767.2.

CAS — 217087-09-7.

ATC — A02BC05.

ATC Vet — QA02BC05.



(esomeprazole)

Pharmacopoeias. In *US.*

USP 31 (Esomeprazole Magnesium). A white to slightly coloured powder. Slightly soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

Esomeprazole Sodium *(BANM, USAN, rINNM)*

Esomeprazol sódico; Ésoméprazole Sodique; Natrii Esomeprazolum.

Натрий Эзомепразол

$C_{17}H_{19}N_3NaO_3S$ = 368.4.

CAS — 161796-78-7.

ATC — A02BC05.

ATC Vet — QA02BC05.

Adverse Effects and Precautions

As for Omeprazole, p.1753.

◊ General references.

1. Davies M, *et al.* Safety profile of esomeprazole: results of a prescription-event monitoring study of 11 595 patients in England. *Drug Safety* 2008; **31:** 313–23.

Effects on the cardiovascular system. For discussion of cardiac effects ostensibly seen with esomeprazole, see under Omeprazole, p.1753.

Effects on the kidneys. For reports of interstitial nephritis associated with esomeprazole see p.1753.

Effects on the skin. For mention of exacerbation of vitiligo with esomeprazole, see p.1754.

Fever. For a report of hyperpyrexia associated with esomeprazole, see under Omeprazole, p.1754.

Interactions

As for Omeprazole, p.1755.

◊ References.

1. Andersson T, *et al.* Drug interaction studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet* 2001; **40:** 523–37.

Pharmacokinetics

Esomeprazole is rapidly absorbed after oral doses, with peak plasma levels occurring after about 1 to 2 hours. It is acid labile and an enteric-coated formulation has been developed. Bioavailability of esomeprazole increases with both dose and repeated administration to about 68 and 89% for doses of 20 and 40 mg respectively. Food delays and decreases the absorption of esomeprazole, but this does not significantly change its effect on intragastric acidity. Esomeprazole is about 97% bound to plasma proteins. It is extensively metabolised in the liver by the cytochrome P450 isoenzyme CYP2C19 to hydroxy and desmethyl metabolites, which have no effect on gastric acid secretion. The remainder is metabolised by the cytochrome P450 isoenzyme CYP3A4 to esomeprazole sulfone. With repeated dosage, there is a decrease in first-pass metabolism and systemic clearance, probably caused by an inhibition of the CYP2C19 isoenzyme. However, there is no accumulation during once daily use. The plasma elimination half-life is about 1.3 hours. Almost 80% of an oral dose is eliminated as metabolites in the urine, the remainder in the faeces.

◊ References.

1. Andersson T, *et al.* Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. *Clin Pharmacokinet* 2001; **40:** 411–26.
2. Sostek MB, *et al.* Effect of timing of dosing in relation to food intake on the pharmacokinetics of esomeprazole. *Br J Clin Pharmacol* 2007; **64:** 386–90.

Metabolism. As for omeprazole (p.1755), the cytochrome P450 isoenzyme CYP2C19 is involved in the metabolism of esomeprazole, and individuals who are deficient in this enzyme are poor metabolisers of esomeprazole. However, there is some suggestion that the metabolism of esomeprazole is less dependent on this genotype, as there may be a metabolic shift towards the CYP3A4-mediated pathway.[1]

1. Schwab M, *et al.* Esomeprazole-induced healing of gastro-esophageal reflux disease is unrelated to the genotype of CYP2C19: evidence from clinical and pharmacokinetic data. *Clin Pharmacol Ther* 2005; **78:** 627–34.

Uses and Administration

Esomeprazole is the *S*-isomer of the proton pump inhibitor omeprazole (p.1753) and is used similarly in the treatment of peptic ulcer disease and NSAID-associated ulceration (p.1702), in gastro-oesophageal reflux disease (p.1696), and the Zollinger-Ellison syndrome (p.1704). It is given as the magnesium or sodium salt but doses are calculated in terms of esomeprazole. Esomeprazole magnesium 22.2 mg and esomeprazole sodium 21.3 mg are each equivalent to about 20 mg of esomeprazole.

Usual doses for **peptic ulcer disease**, as a component of a triple therapy regimen with amoxicillin and clarithromycin, are the equivalent of 20 mg esomeprazole orally twice daily for 7 days, or 40 mg once daily for 10 days.

Oral doses of 20 mg daily, for 4 to 8 weeks, are used in the treatment of **NSAID-associated ulceration**; a dose of 20 mg daily may also be used for prophylaxis in patients at risk of such lesions who require continued NSAID treatment.

In the UK, the dose for treatment of severe (erosive) **gastro-oesophageal reflux disease** is 40 mg once daily for 4 weeks, extended for a further 4 weeks if necessary; in the USA, where doses of 20 or 40 mg daily are permitted for initial treatment, a further 4 to 8 weeks of treatment may be considered for patients who do not heal after 4 to 8 weeks. For maintenance, or for symptomatic disease without erosive oesophagitis, doses equivalent to 20 mg of esomeprazole daily may be used in both countries.

For the treatment of **Zollinger-Ellison syndrome**, the recommended initial oral dose of esomeprazole is 40 mg twice daily, which is then adjusted as needed. The majority of patients can be controlled on doses between 80 and 160 mg daily, although doses of 240 mg have been given. Doses above 80 mg daily should be given in 2 divided doses.

PARENTERAL DOSAGE.

Similar doses to the above may be given intravenously for gastro-oesophageal reflux disease and NSAID-associated ulceration. Esomeprazole is given as the sodium salt by slow intravenous injection over at least 3 minutes or by intravenous infusion over 10 to 30 minutes.

Doses of esomeprazole may need to be reduced in patients with hepatic impairment (see below).

◊ References.

1. Maton PN, *et al.* Safety and efficacy of long term esomeprazole therapy in patients with healed erosive oesophagitis. *Drug Safety* 2001; **24:** 625–35.
2. Scott LJ, *et al.* Esomeprazole: a review of its use in the management of acid-related disorders. *Drugs* 2002; **62:** 1503–38.
3. Keating GM, Figgitt DP. Intravenous esomeprazole. *Drugs* 2004; **64:** 875–82.
4. Metz DC, *et al.* Comparison of the effects of intravenously and orally administered esomeprazole on acid output in patients with symptoms of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2005; **22:** 813–21.
5. Edwards SJ, *et al.* Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs. *Aliment Pharmacol Ther* 2006; **24:** 743–50.