Plus; ***UK:*** Arheumacare; Digestive; HRI Golden Seal Digestive; Indian Brandee; Indigestion Relief; Neo Baby Gripe Mixture; Neo Gripe Mixture; Traveleeze; Wind & Dyspepsia Relief; Zinopin; ***Venez.:*** Ervossil; Jengimiel; Jengimiel Sabila.

Granisetron Hydrochloride

(BANM, USAN, rINNM)

BRL-43694A; Granisétron, chlorhydrate de; Granisetron-hydrochlorid; Granisetronhydroklorid; Granisetroni hydrochloridum; Granisetronihydrokloridi; Granisetrono hidrocloridas; Hidrocloruro de granisetrón. 1-Methyl-*N*-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1*H*-indazole-3-carboxamide hydrochloride.

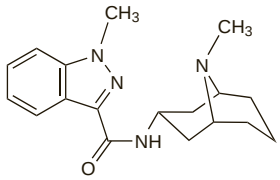
Гранисетрона Гидрохлорид

$C_{18}H_{24}N_4O$, HCl = 348.9.

CAS — 109889-09-0 (granisetron); 107007-99-8 (granisetron hydrochloride).

ATC — A04AA02.

ATC Vet — QA04AA02.



(granisetron)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).

Ph. Eur. 6.2 (Granisetron Hydrochloride). A white or almost white powder. Freely soluble in water; sparingly soluble in dichloromethane; slightly soluble in methyl alcohol. A 1% solution in water has a pH of 4.0 to 6.5.

Adverse Effects and Precautions

As for Ondansetron, p.1757, although no dosage reduction is considered necessary in renal or hepatic impairment.

Carcinogenicity. The manufacturer (*Roche*) has reported an increased incidence of hepatic neoplasms in *rodents* given very high doses of granisetron for prolonged periods, but the clinical relevance of these results is unknown. Although mutagenicity and genotoxicity have not been seen in some tests, others have reported an increased incidence of polyploidy or unscheduled DNA synthesis in exposed cells.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p.1757.

Interactions

The metabolism of granisetron is induced by phenobarbital.

Pharmacokinetics

Granisetron is rapidly absorbed after oral doses, with peak plasma concentrations occurring after about 2 hours. Oral bioavailability is about 60% as a result of first-pass hepatic metabolism. Granisetron has a large volume of distribution of around 3 litres/kg; plasma protein binding is about 65%. The pharmacokinetics exhibit considerable interindividual variation, and the elimination half-life after an intravenous dose is reported to be around 4 to 5 hours in healthy subjects but about 9 to 12 hours in cancer patients. It is metabolised in the liver, primarily by *N*-demethylation, with less than 20% of a dose recovered unchanged in urine, the remainder being excreted in faeces and urine as metabolites. Granisetron clearance is not affected by renal impairment, but is lower in the elderly and in patients with hepatic impairment.

Uses and Administration

Granisetron is a 5-HT_3 antagonist with an antiemetic action similar to that of ondansetron (p.1757). It is used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of postoperative nausea and vomiting (p.1700). Granisetron is given as the hydrochloride, but doses are expressed in terms of the base. Granisetron hydrochloride 1.1 mg is equivalent to about 1 mg of granisetron base.

For acute **nausea and vomiting** associated with **chemotherapy** granisetron is used in *prevention* and *treatment* in similar doses.

- In the UK, a dose equivalent to 3 mg of granisetron is diluted to a volume of 20 to 50 mL with a suitable infusion solution and given intravenously over 5 minutes before the start of chemotherapy; alternatively this dose may be given in 15 mL of infusion solution as a bolus over not less than 30 seconds. The dose may be repeated up to twice in 24 hours; doses should be given at least 10 minutes apart and a total daily dose of 9 mg should not be exceeded. The efficacy of granisetron may be enhanced by the use of dexamethasone. The recommended oral dose is 1 to 2 mg within one hour before therapy begins, then 2 mg daily as a single dose or in 2 divided doses.
- For use in children, an intravenous infusion of 40 micrograms/kg, up to a maximum total dose of 3 mg, has been recommended, diluted in 10 to 30 mL of infusion fluid and given over 5 minutes. This dose may be repeated once within 24 hours, but at least 10 minutes after the original infusion. Alternatively, children may be given 20 micrograms/kg (up to 1 mg) orally twice daily for up to 5 days during therapy; the first dose should be given within 1 hour before the start of chemotherapy.
- In the USA, lower intravenous doses of the equivalent of granisetron 10 micrograms/kg are recommended in both adults and children over 2 years of age, beginning within 30 minutes before chemotherapy. Oral doses are the same as those described for the UK above.

For the *prevention* of nausea and vomiting associated with **radiotherapy** the recommended adult oral dosage is 2 mg daily taken within 1 hour of irradiation. The drug has also been given intravenously for the *treatment and prevention* of nausea and vomiting associated with radiotherapy, in similar doses to those recommended above for emetogenic chemotherapy. In the UK, the *BNFC* has recommended similar oral and intravenous doses to those given above (for chemotherapy-induced nausea and vomiting) in both the treatment and prevention of radiotherapy-induced nausea and vomiting in children.

For the *prevention* of **postoperative** nausea and vomiting in adults 1 mg is diluted to 5 mL and given by intravenous injection over 30 seconds. Injection should be completed before induction of anaesthesia. The same dose may be given up to twice daily for the *treatment* of established postoperative nausea and vomiting.

Transdermal and intranasal formulations of granisetron are under investigation.

◊ References.

1. Adams VR, Valley AW. Granisetron: the second serotonin-receptor antagonist. *Ann Pharmacother* 1995; **29:** 1240–51. Correction. *ibid.* 1996; **30:** 1043.
2. Wilson AJ, *et al.* Single-dose i.v. granisetron in the prevention of postoperative nausea and vomiting. *Br J Anaesth* 1996; **76:** 515–18.
3. Taylor AM, *et al.* A double-blind, parallel-group, placebo-controlled, dose-ranging, multicenter study of intravenous granisetron in the treatment of postoperative nausea and vomiting in patients undergoing surgery with general anesthesia. *J Clin Anesth* 1997; **9:** 658–63.
4. Blower PR. Granisetron: relating pharmacology to clinical efficacy. *Support Care Cancer* 2003; **11:** 93–100.
5. Minami M. Granisetron: is there a dose-response effect on nausea and vomiting? *Cancer Chemother Pharmacol* 2003; **52:** 89–98.
6. Prentice HG. Granisetron in the control of nausea and vomiting associated with bone marrow transplantation: a review of its efficacy and tolerability. *Support Care Cancer* 2003; **11:** 501–8.
7. Corman SL, *et al.* Low-dose granisetron for postoperative nausea and vomiting prophylaxis. *Ann Pharmacother* 2004; **38:** 710–13.
8. Goldsmith B. First choice for radiation-induced nausea and vomiting—the efficacy and safety of granisetron. *Acta Oncol* 2004; **43** (suppl 15): 19–22.
9. Aapro M. Granisetron: an update on its clinical use in the management of nausea and vomiting. *Oncologist* 2004; **9:** 673–86.

Pain. For reference to the use of granisetron in various painful syndromes see under Uses and Administration of Ondansetron, p.1758

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aludal; Eumetic†; Granitron; Kytril†; Rigmoz†; ***Austral.:*** Kytril; ***Austria:*** Kytril; ***Belg.:*** Kytril; ***Braz.:*** Kytril; ***Canad.:*** Kytril; ***Chile:*** Kytril; ***Cz.:*** Emegar; Kytril; ***Denm.:*** Kytril; ***Fin.:*** Kytril; ***Fr.:*** Kytril; ***Ger.:*** Kevatril; ***Gr.:*** Granitron; Kytril; ***Hong Kong:*** Kytril; ***Hung.:*** Granigen; Kytril; ***India:*** Granicip; ***Indon.:*** Kytril; ***Irl.:*** Kytril; ***Israel:*** Kytril; Setron; ***Ital.:*** Kytril; ***Jpn:*** Kytril; ***Malaysia:*** Kytril; ***Mex.:*** Kytril; ***Neth.:*** Kytril; ***Norw.:*** Kytril†; ***NZ:*** Kytril; ***Philipp.:*** Kytril; ***Port.:*** Kytril; ***Rus.:*** Kytril (Китрил); ***S.Afr.:*** Kytril; ***Singapore:*** Kytril; ***Spain:*** Kytril; ***Swed.:*** Kytril; ***Switz.:*** Kytril; ***Thai.:*** Kytril; ***Turk.:*** Kytril; Setron; ***UK:*** Kytril; ***USA:*** Kytril; ***Venez.:*** Granicip; Kytril; Rubrum.

Hydrotalcite *(BAN, rINN)*

Hidrotalcita; Hidrotalsit; Hydrotalcit; Hydrotalcitum; Hydrotalsiiti. Aluminium magnesium carbonate hydroxide hydrate.

Гидроталцит

$Mg_6Al_2(OH)_{16}CO_3{,}4H_2O$ = 604.0.

CAS — 12304-65-3.

ATC — A02AD04.

ATC Vet — QA02AD04.

NOTE. Compounded preparations of hydrotalcite may be represented by the following names:

- Co-simalcite *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of simeticone and hydrotalcite respectively.

Pharmacopoeias. In *Br.*

BP 2008 (Hydrotalcite). A hydrated form of an aluminium magnesium basic carbonate corresponding to the formula $Al_2Mg_6(OH)_{16}CO_3{,}4H_2O$. It contains not less than 15.3% and not more than 18.7% of Al_2O_3 and not less than 36.0% and not more than 44.0% of MgO. The ratio of Al_2O_3 to MgO is not less than 0.40 and not more than 0.45. A white or almost white, free-flowing, granular powder. Practically insoluble in water; it dissolves in dilute mineral acids with slight effervescence. A 4% suspension in water has a pH of 8.0 to 10.0.

Profile

Hydrotalcite is an antacid (see p.1692) that is given in oral doses of up to about 1 g.

Preparations

BP 2008: Hydrotalcite Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Talcid; Talidat; ***Cz.:*** Rutacid; Talcid; Talidat; ***Ger.:*** Ancid; Megalac; Talcid; Talidat; ***Gr.:*** Talcid; ***Hung.:*** Talcid; Tisacid; ***Israel:*** Talcid†; ***Malaysia:*** Swecon; ***Mex.:*** Talcid; ***Neth.:*** Talcid; Talidat; Ultacit; ***Pol.:*** Malgacid; Rutacid; Talcid; Ulcetal; ***Port.:*** Talidat†; ***Rus.:*** Rutacid (Рутацид); Talcid (Тальцид); ***S.Afr.:*** Altacite; ***Spain:*** Talcid; ***Turk.:*** Talcid; ***Venez.:*** Baytalcid†.

Multi-ingredient: ***Indon.:*** Promag; ***Jpn:*** Eki Cabe; ***Philipp.:*** Simeco; ***UK:*** Altacite Plus.

Hyoscine *(BAN)*

Escopolamina; Hioscina; Hioscyna; Hyoscin; Hyoscinum; Hyoskiini; Scopolamine; Scopolaminum; Skopolamiini; Skopolamin; Skopolamina; Tropato de epoxitropina. (−)-(1*S*,3*s*,5*R*,6*R*,7*S*,8*s*)-6,7-Epoxy-3[(*S*)-tropoyloxy] tropane.

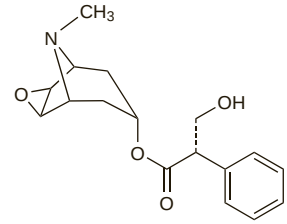
Гиосцин

$C_{17}H_{21}NO_4$ = 303.4.

CAS — 51-34-3.

ATC — A04AD01; N05CM05; S01FA02.

ATC Vet — QA04AD01; QN05CM05; QS01FA02.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of hyoscine:
Burundanga.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Hyoscine). A white or almost white, crystalline powder or colourless crystals. M.p. 66° to 70°. Soluble in water; freely soluble in alcohol.