Rabeprazole

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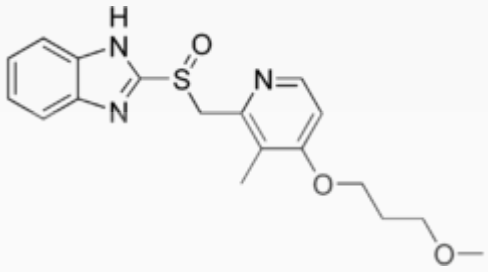

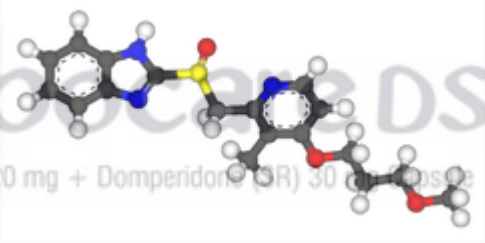

Systematic (IUPAC) name	
(*RS*)-2-([4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl)-1*H*-benzo[*d*]imidazole	
Clinical data	
Trade names	Aciphex, Acifix (by Beximco)
AHFS/Drugs.com	monograph
MedlinePlus	a699060
Licence data	US FDA:Finix&SearchType=BasicSearch link
Pregnancy cat.	B (US)
Legal status	POM (UK) ℞-only (US)
Routes	Oral
Pharmacokinetic data	

Bioavailability	52%
Metabolism	mostly non-enzymatic, partly hepatic (CYP2C19)
Half-life	1 - 1.5 hours
Excretion	90% renal
Identifiers	
CAS number	117976-89-3
ATC code	A02BC04
PubChem	CID 5029
DrugBank	DB01129
ChemSpider	4853
UNII	32828355LL
ChEBI	CHEBI:8768
ChEMBL	CHEMBL1219
PDB ligand ID	RZX (PDBe, RCSB PDB)
Chemical data	
Formula	$C_{18}H_{21}N_3O_3S$
Mol. mass	359.444 g/mol
SMILES	
	• O=S(c2nc1ccccc1n2)Cc3nccc(OCCCOC)c3C
InChI	

InChI=1S/C18H21N3O3S/c1-13-16(19-9-8-17(13)24-11-5-10-23-2)12-25(22)18-20-14-6-3-4-7-15(14)21-18/h3-4,6-9H,5,10-12H2,1-2H3,(H,20,21)

Key:YREYEVIYCVEVJK-UHFFFAOYSA-N

Rabeprazole /ˌræ.ˈbɛp.ræ.zɔːl/ is an antiulcer drug in the class of proton pump inhibitors. It was developed by Eisai Co. and is marketed by Janssen-Cilag as the sodium salt under the brand names **AcipHex** (/ˈæsɨfɛks/, referring to pH) in the US, **Pariet** in Europe, Brazil, Canada, Japan, Russia and Australia. Rabonik in India, and Zechin in Pakistan.In Bangladesh Rabeprazole is sold under the brand name of Acifix by Beximco Pharma

Indications and usage

Short-term treatment in healing and symptomatic relief of duodenal ulcers and erosive or ulcerative gastroesophageal reflux disease (GORD); maintaining healing and reducing relapse rates of heartburn symptoms in patients with GORD; treatment of daytime and nighttime heartburn and other symptoms associated with GORD; long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome and in combination with amoxicillin and clarithromycin to eradicate *Helicobacter pylori*.

- Gastric ulcer (GU)
- Peptic ulcer disease (PUD)
- Maintenance of healing of erosive or ulcerative GORD
- Healing of erosive and ulcerative GORD
- Healing of duodenal ulcers.
- Treatment of symptomatic GORD
- Treatment of pathological hypersecretory conditions (Zollinger-Ellison syndrome)
- *Helicobacter pylori* eradication to reduce risk of duodenal ulcer recurrence

Contraindications

- hypersensitivity to rabeprazole, substituted benzimidazoles or any of components of its pharmaceutical forms.
- lactation: Thomson Lactation Ratings: Infant risk cannot be ruled out.

Restriction of usage

- acute hepatic failure
- pediatric use in patients under 18 years of age (there are insufficient data about safety and efficiency of rabeprazole in this group of patients)

Side effects

Rabeprazole adverse reactions/side effects include[*citation needed*]:

- In clinical trials the most common side effect assessed as possibly or probably related to AcipHex was headache in 2.4% of patients vs 1.6% taking placebo.
- abdominal pains
- anxiety
- arthralgia
- asthenia
- constipation
- diarrhea
- dry mouth
- erythema
- granulocytopenia

- headache
- increased or decreased appetite
- insomnia
- leukocytopenia
- meteorism
- muscle or bone pain
- myalgia
- nausea
- skin eruption
- thrombocytopenia
- vertigo
- vomiting

Antacid preparations such as rabeprazole by suppressing acid mediated break down of proteins, leads to an elevated risk of developing food or drug allergies. This happens due to undigested proteins then passing into the gastrointestinal tract where sensitisation occurs. It is unclear whether this risk occurs with only long-term use or with short-term use as well.[1]

Drug interactions

Rabeprazole decreases the concentration of ketoconazole in the plasma (in 33%), increases the concentration of digoxin (in 22%), and does not interact with liquid antacids. Rabeprazole is compatible with any medicine metabolized by the CYP450 (theophylline, warfarin, diazepam, phenytoin).

Overdosage

Studies in mice and rats indicated the symptoms of acute toxicity due to overdose included: hypoactivity, labored respiration, convulsion, diarrhea, tremor, and coma. A study in dogs indicated that a dose of 2000mg/kg was not lethal.

References

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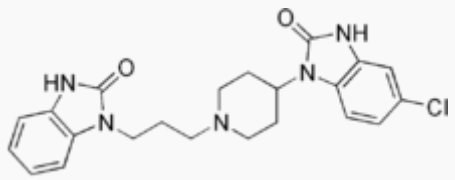
Domperidone

Domperidone



Systematic (IUPAC) name

5-chloro-1-(1-[3-(2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)propyl]piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one

Clinical data	
Trade names	Motilium
AHFS/Drugs.com	Micromedex Detailed Consumer Information
Pregnancy cat.	Not classified (US)
Legal status	Not approved for use or sale: US; prescription medicine (POM): India, Australia, Canada, Israel, Belgium; Over the Counter (OTC): UK (Pharmacy only), Egypt, Ireland, Italy, Japan, Netherlands, South Africa, Switzerland, China, Russia, Slovakia, Thailand, Malta, South Korea, and Romania[1]
Routes	Oral, intravenous, rectal
Pharmacokinetic data	
Bioavailability	High
Protein binding	91–93%
Metabolism	Hepatic and intestinal (first-pass)
Half-life	7 hours
Excretion	Breast milk, renal
Identifiers	
CAS number	57808-66-9
ATC code	A03FA03 QP51AX24
PubChem	CID 3151
IUPHAR ligand	965
DrugBank	DB01184

ChemSpider	3039
UNII	5587267Z69
KEGG	D01745
ChEBI	CHEBI:31515
ChEMBL	CHEMBL219916

Chemical data

Formula	$C_{22}H_{24}ClN_5O_2$
Mol. mass	425.911 g/mol

SMILES

- Clc1cc2c(cc1)N(C(=O)N2)C5CCN(CCCN4c3ccccc3NC4=O)CC5

InChI

InChI=1S/C22H24ClN5O2/c23-15-6-7-20-18(14-15)25-22(30)28(20)16-8-12-26(13-9-16)10-3-11-27-19-5-2-1-4-17(19)24-21(27)29/h1-2,4-7,14,16H,3,8-13H2,(H,24,29)(H,25,30)

Key:FGXWKSZFVQUSTL-UHFFFAOYSA-N

Domperidone (trade names **Motilium**, **Motillium, Motinorm Costi**, **Nomit** and **Molax**) is a medication developed by Janssen Pharmaceutica that is a peripheral, specific blocker of dopamine receptors. It is administered orally, rectally, or intravenously. Domperidone is given in order to relieve nausea and vomiting; to increase the transit of food through the stomach (as aprokinetic agent through increase in gastrointestinal peristalsis); and to increase lactation (breast milk production) by release of prolactin. It is also used in the scientific study of the way dopamine (an important neurotransmitter) acts in the body.

Mechanism of Action

Domperidone is a peripheral dopamine (D2) and (D3) receptor antagonist. It provides relief from nausea by blocking receptors at the chemo-receptor trigger zone (a location in the nervous system that registers nausea) at the floor of the fourth ventricle (a location near the brain). It increases motility in the upper gastrointestinal tract to a moderate degree and lowers esophageal sphincter pressure by blocking dopamine receptors in the gastric antrum and the duodenum. It blocks dopamine receptors in the posterior pituitary gland increasing release of prolactin which in turn increases lactation.[2][3] Domperidone may be more useful in some patients and cause harm in others by way of the genetic characteristic of the person, such as polymorphisms in thedrug transporter gene ABCB1, the potassium channel KCNH2 gene, and α1D--adrenoceptor ADRA1D gene.[4]

Uses

The uses or *indications* of domperidone vary between nations. For instance, in Italy it is used in the treatment of gastroesophageal reflux disease and in Canada, the drug is indicated in upper gastrointestinal motility disorders and to prevent gastrointestinal symptoms associated with the use of dopamine agonist antiparkinsonian agents.[5] In the United States domperidone's use is not approved, though patients with various gastrointestinal conditions may qualify for access through the Expanded Access to Investigational Drugs program.[6]

Nausea and vomiting

There is some evidence that domperidone has antiemetic activity.[7] It is recommended in the Canadian Headache Society's guidelines for treatment of nausea associated with acute migraine.[8]

Gastroparesis

Gastroparesis is a medical condition characterised by delayed emptying of the stomach when there is no mechanical gastric outlet obstruction. Its cause is most commonly idiopathic, a diabetic complication or a result of abdominal surgery. The condition causes nausea, vomiting, fullness after eating, early satiety (feeling full before the meal is finished), abdominal pain and bloating.

Domperidone may be useful in diabetic and idiopathic gastroparesis.[9][10]

However, increased rate of gastric emptying induced by drugs like domperidone does not always correlate (equate) well with relief of symptoms.[11]

Parkinson's disease

Parkinson's disease is a chronic neurological condition where a decrease in dopamine in the brain leads to rigidity (stiffness of movement), tremor and other symptoms and signs. Poor gastrointestinal function, nausea and vomiting is a major problem for people with Parkinson's disease because most medications used to treat Parkinson's disease are given by mouth. These medications, such as levodopa can cause nausea as a side effect. Furthermore, anti-nausea drugs, such as metoclopramide, which do cross the blood brain barrier may worsen the extra-pyramidal symptoms of Parkinson's disease.

Domperidone can be used to relieve gastrointestinal symptoms in Parkinson's disease, because, even though it blocks dopamine receptors (which would be expected to worse Parkinson's disease), it does not cross the blood brain barrier (the barrier between the blood circulation of the brain and the rest of the body).[12] In addition to this, domperidone may enhance thebioavailability (effect) of levodopa (one of the main treatments in Parkinson's disease.)[13]

Although these features make domperidone a useful drug in Parkinson's disease, caution is needed due to the cardiotoxic side effects of domperidone when given intravenously, in elderly people and in high doses (> 30mg per day).[14] A clinical sign of domperidone's potential toxicity to the heart is the prolongation (lengthening) of the QT interval (a segment of the heart's electrical pattern).[15]

Functional dyspepsia

Domperidone may be used in functional dyspepsia in both adults and children.[16][17]

Lactation

The hormone prolactin stimulates lactation (production of breast milk). Dopamine, released by the hypothalamus stops the release of prolactin from the pituitary gland. Domperidone, by acting as an anti-dopaminergic agent, results in increased prolactin secretion, and thus promotes lactation (that is, it is a galactogogue). In some nations, including Australia, domperidone is used off label, based on uncertain and anecdotal evidence of its usefulness, as a therapy for mothers who are having difficulty breastfeeding.[18][19] In the United States, domperidone is not approved for this or any other use.[20][21] A study called the *EMPOWER* trial has been designed to

assess the effectiveness and safety of domperidone in assisting mothers of preterm babies to supply breast milk for their infants.[22]

Adverse effects

QT prolongation

Domperidone use is associated with an increased risk of sudden cardiac death most likely through its prolonging effect of the cardiac QT interval and ventricular arrhythmias.[23][24]

QT prolongation in neonates and infants is controversial and uncertain.[25][26]

Penetration of immature blood brain barrier

In Britain a legal case involved the death of two children of a mother whose three children had all had hypernatraemia. She was charged with poisoning the children with salt. One of the children, who was born at 28 weeks gestation withrespiratory complications and had a fundoplication for gastroesophageal reflux and failure to thrive was prescribed domperidone. An advocate for the mother suggested the child may have suffered neurolept malignant syndrome as a side effect of domperidone due to the drug crossing the child's immature blood brain barrier.[27]

Interactions

Itraconazole and ketoconazole, both used to treat fungal infections increase the plasma concentration of domperidone.[28][29]

Erythromycin and other macrolide antibiotics inhibit the metabolism of domperidone (in-vitro) thus increasing the concentration of domperidone and potential side effects of the drug. This is of concern as both drugs may be used to treatgastroparesis.[30]

Contraindications

- Prolactin secreting pituitary tumor.
- Triazole antifungal medications such as ketoconazole, itraconazole, fluconazole.
- Macrolide antibiotics such as erythromycin and clarithromycin.
- Potent CYP3A4 inhibitors.
- Amiodarone
- Mechanical bowel disorders such as bowel obstruction, gastrointestinal haemorrhage or bowel perforation
- Moderate hepatic impairment (liver disease).[31]

History

Janssen Pharmaceutical has brought domperidone before the United States Federal Drug Administration (FDA) several times, including in the 1990s.

See also

- Benzamide
- Cisapride
- Itopride
- Metoclopramide

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