

USP 31 (Dicyclomine Hydrochloride). A fine white, practically odourless, crystalline powder. Soluble 1 in 13 of water, 1 in 5 of alcohol, 1 in 2 of chloroform and of glacial acetic acid, and 1 in 770 of ether. pH of a 1% solution in water is between 5.0 and 5.5.

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Dicycloverine hydrochloride should not be given to infants younger than 6 months of age.

Apnoea. Reports¹⁻³ of severe apnoea in infants aged 5 to 10 weeks associated with the use of dicycloverine.

1. Williams J, Watkin-Jones R. Dicyclomine: worrying symptoms associated with its use in some small babies. *BMJ* 1984; **288**: 901.
2. Edwards PDL. Dicyclomine in babies. *BMJ* 1984; **288**: 1230.
3. Spoudeas H, Shribman S. Dicyclomine in babies. *BMJ* 1984; **288**: 1230.

Pregnancy. For a review of the risks to the fetus of antiemetic therapy during pregnancy, with particular reference to *Debendox* (*Bendectin*: dicycloverine with doxylamine and pyridoxine), see under Antihistamines on p.563.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220).

Uses and Administration

Dicycloverine hydrochloride is a tertiary amine antimuscarinic with effects similar to but weaker than those of atropine (p.1219); it also has a direct antispasmodic action.

Dicycloverine is used in gastrointestinal spasm, particularly that associated with the irritable bowel syndrome. For adults, 10 to 20 mg of dicycloverine hydrochloride is given orally 3 times daily; in the USA, up to 40 mg four times daily has been recommended where adverse effects permit. Children aged 6 months to 2 years may be given 5 to 10 mg up to 3 or 4 times daily; doses are usually given 15 minutes before meals. Children aged 2 to 12 years may be given 10 mg three times daily.

Dicycloverine hydrochloride may be given intramuscularly in doses of 20 mg given 4 times daily to patients in whom oral therapy is temporarily impractical, but should not be used for longer than 1 to 2 days.

Preparations

BP 2008: Dicycloverine Oral Solution; Dicycloverine Tablets; **USP 31:** Dicyclomine Hydrochloride Capsules; Dicyclomine Hydrochloride Injection; Dicyclomine Hydrochloride Syrup; Dicyclomine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Babypasmil; **Austral.:** Merbentyl†; **Braz.:** Benty; **Canad.:** Bentylo; Formulex†; Lomine; **Hong Kong:** Dicycline; **India:** Cyclominol; Cyclopan; Dymen; Spasmo-Proxylon; Spasmonil; **Irl.:** Merbentyl†; **Israel:** Notensyl; **Mex.:** Benty; Clominal; Dicigon; Diclorimin; Sediclone; **NZ:** Merbentyl†; **Philipp.:** Benty; Dilomin; Relestat; Spasdon; **Port.:** Optimal†; **Rus.:** Trigan (Триган); **S.Afr.:** Clomint; Medicyclomine†; Merbentyl; **Thal.:** Dicomin; Dicymine; **UK:** Merbentyl; **USA:** Antispas; Benty; Byclomine; Dibent; Or-Tyl; **Venez.:** Cidan†; Diclolor†; Mabex.

Multi-ingredient: **Arg.:** Dafine; **Chile:** Profisin; **Hong Kong:** Colimix; Dicycline Co; Eplon; Veragel; **India:** Colimex; Colind; Cyclo-Meff; Cyclopan; Diclospa; Dymen; Nicispas; Normaxin; Parvon-Spas; Spasmo-Proxylon; Spasmo-Proxylon Forte; Spasmocip Plus; Spasmoflexon†; Spasmonil; Spasmonil Plus; Trigan-D; Ze-Spas; **Ital.:** Merankol Pastiglie; **Malaysia:** Colimix; Uphacol†; **Mex.:** Alphalox-D; Exhidrol; Farcolon; **Port.:** Nausefe; **Rus.:** Trigan-D (Триган-Д); **S.Afr.:** Acugel; Alkalite D; Alumag D; Alumite D; Asic; Betaclomin; Co-Gel; Gelumen; Kolantyl; Medigel; Microgel; Neutragel-D; pH 550†; Propan Gel-S; Remotrox; Spasmogel; **Singapore:** Colimix; Meclosi; Veragel DMS; **Spain:** Colchimax; Neocolan; **Thal.:** Berclomine; Biodan†; Cymine; Difemic; Kremil-S; Mainnox; Med-Anspasmic†; Spasticon; Veragel; **UK:** Kolanticon; **Venez.:** Clopina†; Dicigel.

Difemerine Hydrochloride (rINN)

Difémérine, Chlorhydrate de; Difemerini Hydrochloridum; Hidrocloruro de difemerina; UP-57. 2-Dimethylamino-1,1-dimethyl-ethyl benzilate hydrochloride.

Дифемерина Гидрохлорид

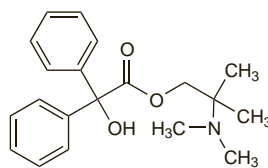
$C_{20}H_{25}NO_3 \cdot HCl = 363.9$.

CAS — 80387-96-8 (difemerine); 70280-88-5 (difemerine hydrochloride).

ATC — A03AA09.

ATC Vet — QA03AA09.

The symbol † denotes a preparation no longer actively marketed



(difemerine)

Profile

Difemerine hydrochloride is an antimuscarinic with effects similar to those of atropine (p.1219) and was used in the symptomatic treatment of visceral spasms.

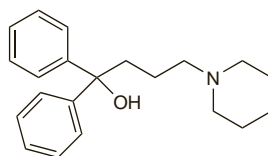
Difenidol Hydrochloride (BANM, rINNM)

Difénidol, Chlorhydrate de; Difenidoli Hydrochloridum; Diphenidol Hydrochloride (USAN); Hidrocloruro de difenidol; SKF-478 (difenidol); SKF-478-A; SKF-478-J (difenidol embonate). 1,1-Diphenyl-4-piperidinobutan-1-ol hydrochloride.

Дифенидола Гидрохлорид

$C_{21}H_{27}NO \cdot HCl = 345.9$.

CAS — 972-02-1 (difenidol); 3254-89-5 (difenidol hydrochloride); 26363-46-2 (difenidol embonate).



(difenidol)

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Difenidol hydrochloride is an antiemetic that probably acts through the chemoreceptor trigger zone. It is claimed to control vertigo by means of a specific effect on the vestibular apparatus. Difenidol also has a weak peripheral antimuscarinic action.

It has been used in the treatment of some forms of nausea and vomiting (p.1700) such as those associated with surgery, radiotherapy, and cancer chemotherapy. It has also been used for the symptomatic treatment of vertigo (p.565), nausea and vomiting due to Ménière's disease (p.564), and other labyrinthine disturbances.

It has been given in oral doses equivalent to 25 to 50 mg of difenidol every 4 hours as required. Difenidol hydrochloride has also been given parenterally.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Vontrol†; **Chile:** Vontrol; **Hong Kong:** Cephadol; **Jpn:** Cephadol; **Malaysia:** Cephadol; **Mex.:** Biomitin; Diphafen; Hemetiken; Lansenol; Nautrol; Normavom; Serratal; Sons; Vontrol; Voxamine; **Philipp.:** Cephadol; **Singapore:** Cephadol†; **Thai:** Cephadol.

Difenoxin (BAN, USAN, rINN)

Difénoxicilic Acid; Difenoxina; Difénoxine; Difenoxinum; Diphenoxyllic Acid; McN-JR-15403-11. 1-(3-Cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid.

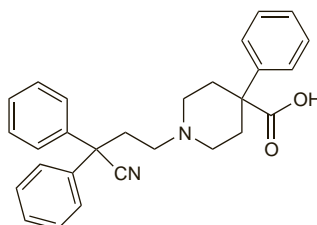
Дифеноксин

$C_{28}H_{28}N_2O_2 = 424.5$.

CAS — 28782-42-5.

ATC — A07DA04.

ATC Vet — QA07DA04.



Difenoxin Hydrochloride (BANM, rINN)

Difénoxine, Chlorhydrate de; Difenoxini Hydrochloridum; Difenoxylic Acid Hydrochloride; Diphenoxyllic Acid Hydrochloride; Hidrocloruro de difenoxina; R-15403.

Дифеноксина Гидрохлорид

$C_{28}H_{28}N_2O_2 \cdot HCl = 461.0$.

CAS — 35607-36-4.

ATC — A07DA04.

ATC Vet — QA07DA04.

Profile

Difenoxin is the principal active metabolite of diphenoxylate (p.1724) and has similar actions and uses. It is given orally as the hydrochloride, but doses are in terms of the base; difenoxin hydrochloride 1.1 mg is equivalent to about 1 mg of difenoxin.

In the treatment of diarrhoea (p.1694), the usual dose in adults is the equivalent of difenoxin 2 mg initially, followed by 1 mg after each loose stool or every 3 to 4 hours as required, up to a maximum of 8 mg daily.

Preparations of difenoxin usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse.

Preparations

Proprietary Preparations (details are given in Part 3)

USA: Motofen.

Dihexyverine Hydrochloride (USAN, rINNM)

Dihexiverine Hydrochloride; Dihexyvérine, Chlorhydrate de; Dihexyverini Hydrochloridum; Hidrocloruro de dihexiverina; JL-1078. 2-Piperidinoethyl bicyclohexyl-1-carboxylate hydrochloride.

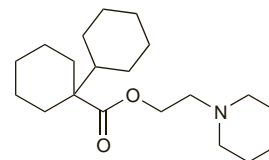
Дигексиверина Гидрохлорид

$C_{26}H_{35}NO_2 \cdot HCl = 358.0$.

CAS — 561-77-3 (dihexyverine); 5588-25-0 (dihexyverine hydrochloride).

ATC — A03AA08.

ATC Vet — QA03AA08.



(dihexyverine)

Profile

Dihexyverine hydrochloride is an antimuscarinic with effects similar to those of atropine (p.1219). It has been given in the symptomatic treatment of gastrointestinal spasm.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Spasmodex†.

Dihydroxyaluminum Sodium Carbonate

Aluminium Sodium Carbonate Hydroxide; Carbonato sódico de dihidroxialuminio; Dihidroksialüminyum Sodyum Karbonat; Dihydroksialuminiumnatriumkarbonaatti; Dihydroksialuminiumnatrii Carbonas; Dihydroksialuminiumnatriumkarbonat; Dihydroksialuminium Sodium Carbonate. Sodium (carbonato)dihydroxyaluminate(1-).

Дигидрооксисилиция Натрия Карбонат

$CH_2AlNaO_5 = 144.0$.

CAS — 41342-54-5 (carbaldrate); 12011-77-7 (dihydroxyaluminium sodium carbonate); 16482-55-6 (dihydroxyaluminium sodium carbonate).

ATC — A02AB04.

ATC Vet — QA02AB04.

NOTE. The name Carbaldrate (rINN) has been applied to $(CH_2AlNaO_5 \cdot nH_2O)$, a form of sodium (carbonato)dihydroxyaluminate(1-) hydrate.

Pharmacopoeias. In *US*.

USP 31 (Dihydroxyaluminum Sodium Carbonate). A fine white odourless powder. It loses not more than 14.5% of its weight on drying. Practically insoluble in water and in organic solvents;

soluble in dilute mineral acids with the evolution of carbon dioxide. A 4% suspension in water has a pH of 9.9 to 10.2. Store in airtight containers.

Profile

Dihydroxyaluminum sodium carbonate is an antacid with general properties similar to aluminium hydroxide (p.1706) that is given in doses of about 300 to 600 mg by mouth.

Preparations

USP 31: Dihydroxyaluminum Sodium Carbonate Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Antacidum; **Denm.:** Noacid; **Ger.:** Kompensan; **Pol.:** Alugastrin; Gastrinal; **Port.:** Kompensan; **Switz.:** Kompensan; **Turk.:** Dank; Kompensan.

Multi-ingredient: **Ger.:** Kompensan-St; **Port.:** Kompensan-S.

Diisopromine Hydrochloride (rINN)

Diisopromine, Chlorhydrate de; Di-isopromine Hydrochloride; Diisopromini Hydrochloridum; Hidrocloruro de diisopromina. NN-Di-isopropyl-3,3-diphenylpropylamine hydrochloride.

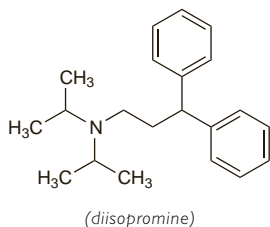
Диизопромина Гидрохлорид

$C_{21}H_{29}N.HCl = 331.9$.

CAS — 5966-41-6 (diisopromine); 24358-65-4 (diisopromine hydrochloride).

ATC — A03AX02.

ATC Vet — QA03AX02.



Profile

Diisopromine hydrochloride is an antispasmodic used with sorbitol in various gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: **Braz.:** Biflux; **S.Afr.:** Agofell.

Diphenoxylate Hydrochloride

(BANM, rINN)

Difenoksilatihidroklorid; Difenoksilat Hidroklorür; Difenoksilato hidrokloridas; Difenoksilat-hidroklorid; Difenoksilatihidroklorid; Difenoksylát-hidroklorid; Diphénoxylate, chlorhydrate de; Diphenoxylati hydrochloridum; Hidrocloruro de difenoxilato; R-1132. Ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate hydrochloride.

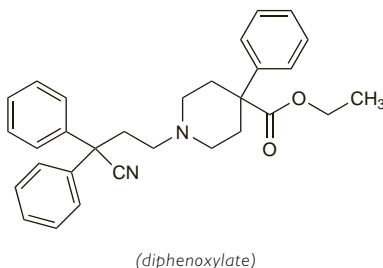
Дифеноксилата Гидрохлорид

$C_{30}H_{32}N_2O_2.HCl = 489.0$.

CAS — 915-30-0 (diphenoxylate); 3810-80-8 (diphenoxylate hydrochloride).

ATC — A07DA01.

ATC Vet — QA07DA01.



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

- Co-phenotrope (BAN)—diphenoxylate hydrochloride 100 parts and atropine sulfate 1 part (w/w).

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

Ph. Eur. 6.2 (Diphenoxylate Hydrochloride). A white or almost white, crystalline powder. Very slightly soluble in water; sparing-

ly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 31 (Diphenoxylate Hydrochloride). A white odourless crystalline powder. Slightly soluble in water and in isopropyl alcohol; sparingly soluble in alcohol and in acetone; freely soluble in chloroform; practically insoluble in ether and in petroleum spirit; soluble in methyl alcohol. A saturated solution in water has a pH of about 3.3.

Dependence and Withdrawal

Preparations of diphenoxylate usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse. Short-term use of diphenoxylate with atropine in the recommended dosage carries a negligible risk of dependence, although prolonged use or use of high doses may produce dependence of the morphine type (see p.101).

Adverse Effects and Treatment

Diphenoxylate is related to the opioid analgesics (p.102), and its adverse effects and their treatment are similar, particularly in overdosage. Reported adverse effects include: gastrointestinal effects such as anorexia, nausea and vomiting, abdominal distension or discomfort, paralytic ileus, toxic megacolon, and pancreatitis; nervous system effects such as headache, drowsiness, dizziness, restlessness, euphoria, depression, numbness of the extremities; and hypersensitivity reactions including angioedema, urticaria, pruritus, and swelling of the gums. Signs of overdosage may be delayed and patients should be observed for at least 48 hours. Young children are particularly susceptible to the effects of overdosage.

The presence of subclinical doses of atropine sulfate in preparations containing diphenoxylate may give rise to the adverse effects of atropine in susceptible individuals or in overdosage—see Atropine Sulfate, p.1219.

Precautions

Diphenoxylate hydrochloride should be avoided in patients with jaundice, intestinal obstruction, antibiotic-associated colitis, or diarrhoea associated with enterotoxin-producing bacteria, and should be used with caution in patients with hepatic impairment. It should also be used with caution in young children, in whom response is more variable, and is not generally recommended for use in infants. Patients with inflammatory bowel disease receiving diphenoxylate should be carefully observed for signs of toxic megacolon and diphenoxylate stopped promptly should abdominal distension occur.

Interactions

Because of the structural relationship of diphenoxylate to pethidine (p.113) there is a theoretical risk of hypertensive crisis if diphenoxylate is used with MAOIs. Diphenoxylate may potentiate the effects of other CNS depressants such as alcohol, barbiturates, and some anxiolytics.

Pharmacokinetics

Diphenoxylate hydrochloride is well absorbed from the gastrointestinal tract. It is rapidly and extensively metabolised in the liver, mainly to diphenoxylate acid (difenoxin, p.1723), which has antidiarrhoeal activity; other metabolites include hydroxydiphenoxylate acid. It is excreted mainly as metabolites and their conjugates in the faeces; lesser amounts are excreted in urine. It may be distributed into breast milk.

Uses and Administration

Diphenoxylate hydrochloride is a synthetic derivative of pethidine (p.113) with little or no analgesic activity; it reduces intestinal motility and is used in the symptomatic treatment of acute and chronic diarrhoea (p.1694). It may also be used to reduce the frequency

and fluidity of the stools in patients with colostomies or ileostomies.

Preparations of diphenoxylate usually contain subclinical amounts of atropine sulfate in an attempt to discourage abuse; UK preparations are all in the form of co-phenotrope (see above).

In **acute diarrhoea** the usual initial dose for adults is 10 mg orally, followed by 5 mg every six hours, later reduced as the diarrhoea is controlled. In the UK, diphenoxylate hydrochloride is not licensed for children under 4 years of age. Suggested initial doses for children are: 4 to 8 years, 2.5 mg three times daily; 9 to 12 years, 2.5 mg four times daily; over 12 years, 5 mg three times daily. While emphasising that antimotility drugs are not recommended for acute diarrhoea in children under 12 years of age, the *BNFC* allows for a dose of 1.25 mg three times daily for children aged 2 to 4 years. In the USA, diphenoxylate is not recommended for children under the age of 2 years and an initial dose of 0.3 to 0.4 mg/kg (up to an effective maximum of 10 mg) daily in 4 divided doses is suggested for children aged 2 to 12 years. (For the view that antidiarrhoeal drugs should not be used at all in children, see p.1694.)

Similar initial doses are used for **chronic diarrhoea**, and subsequently reduced as necessary. If clinical improvement is not seen after 10 days of treatment with the maximum daily dose of 20 mg (in adults) further use is unlikely to result in any benefit.

Diarrhoea. Co-phenotrope (see above) may be considered as an alternative to loperamide in the management of faecal incontinence in adults, see Diarrhoea, under Loperamide, p.1742.

Substance dependence. Diphenoxylate may be useful¹ in the symptomatic management of diarrhoea associated with opioid withdrawal syndromes (p.101).

1. DOH. *Drug misuse and dependence: guidelines on clinical management*. London: HMSO, 1999. Also available at: <http://www.dh.gov.uk/assetRoot/04/07/81/98/04078198.pdf> (accessed 18/01/06)

Preparations

USP 31: Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution; Diphenoxylate Hydrochloride and Atropine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Lofenoxal; Lomotil; **Braz.:** Lomotil; **Canad.:** Lomotil; **Cz.:** Reasec; **Fr.:** Diarsed; **Hong Kong:** Dhamotil; Dimotil; Lomotil; **Hung.:** Reasec; **India:** Lomotil; **Irl.:** Lomotil; **Malaysia:** Atrottil; Beamotil; Dhamotil; Lomotil; Setmotil; **NZ:** Diastop; Lomotil; **Pol.:** Reasec; **Port.:** Lomotil; **S.Afr.:** Lomotil; **Singapore:** Beamotil; Dhamotil; Lomotil; Remodil; **Thai:** Dilomil; Lomotil; **Turk.:** Lomotil; **UAE:** Intard; **UK:** Dymotil; Lomotil; **USA:** Logen; Lomotil; Lonox; **Venez.:** Lomotil.

Multi-ingredient: **Braz.:** Colestase; **India:** Lomofen.

Docusates

Docusatos.

Docusate Calcium (USAN)

Diocetyl Calcium Sulfosuccinate; Diocetyl Calcium Sulphosuccinate; Docusato cálcico. Calcium 1,4-bis(2-ethylhexyl) sulphosuccinate.

Докузат Кальция

$C_{40}H_{74}CaO_4S_2 = 883.2$.

CAS — 128-49-4.

Pharmacopoeias. In *US*.

USP 31 (Docusate Calcium). A white amorphous solid with the characteristic odour of octyl alcohol. Soluble 1 in 3300 of water; very soluble in alcohol, in macrogol 400, and in maize oil.

Docusate Potassium (USAN)

Diocetyl Potassium Sulfosuccinate; Diocetyl Potassium Sulphosuccinate; Docusato potásico. Potassium 1,4-bis(2-ethylhexyl) sulphosuccinate.

Докузат Калия

$C_{40}H_{73}KO_4S = 460.7$.

CAS — 7491-09-0.

Pharmacopoeias. In *US*.

USP 31 (Docusate Potassium). A white amorphous solid with a characteristic odour suggestive of octyl alcohol. Sparingly soluble in water; soluble in alcohol and in glycerol; very soluble in petroleum spirit.