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-S†; Port.: Kompensan-S.

Diisopromine Hydrochloride (rINNM)

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

Диизопромина Гидрохлорид

 $C_{21}H_{29}N,HCI = 331.9.$

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.: Biliflux†; S.Afr.: Agofell.

Diphenoxylate Hydrochloride

(BANM, rINNM)

Difenoksilaattihydrokloridi; Difenoksilat Hidroklorür; Difenoksilato hidrochloridas; Difenoxilát-hidroklorid; Difenoxiláthydroklorid; Difenoxylát-hydrochlorid; Diphenoxylate, chlorhydrate de; Diphenoxylati hydrochloridum; Hidrocloruro de difenoxilato; R-I132. Ethyl I-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate hydrochloride.

Дифеноксилата Гидрохлорид

 $C_{30}H_{32}N_2O_2$,HCI = 489.0.

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

ATC — AO7DAO1.

ATC Vet - QA07DA01.

(diphenoxylate)

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 diphenoxylic acid (difenoxin, p.1723), which has antidiarrhoeal activity; other metabolites include hydroxydiphenoxylic 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).

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)

Rustral: Lofenoxal; Lomotii; Braz: Lomotii; Candd.: Lomotii; Cz.: Reasec; Fr.: Diarsed; Hong Kong: Dhamotil; Dimotil; Lomotil; Hung.: Reasec; India: Lomotil; Irl.: Lomotil; Malaysia: Atrotil†; Beamotil; Dhamotil; Lomotil†; Str. Diastop; Lomotil†; Pol.: Reasec; Port.: Lomotil†; Str. Disastop; Lomotil†; Pol.: Reasec; Port.: Lomotil†; Thai: Dilomil†; Lomotil; Turk.: Lomotil; UAE: Intard; UK: Dymotil; Lomotil; USA: Logen; Lomotil; Lomo

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

Docusates

Docusatos.

Docusate Calcium (USAN)

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

Докузат Кальция

 $C_{40}H_{74}CaO_{14}S_2 = 883.2.$

CAS — 128-49-4.

Pharmacopoeias. In US.

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

Docusate Potassium (USAN)

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

Докузат Калия

 $C_{20}H_{37}KO_7S = 460.7.$ CAS - 7491-09-0.

Pharmacopoeias. In US.

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

Docusate Sodium (BAN, USAN, rINN)

Dioctyl Sodium Sulfosuccinate; Dioctyl Sodium Sulphosuccinate; Docusate sodique: Docusato de sodio: Docusato sódico: Docusatum Natricum: Dokusaattinatrium: Dokusát sodná sůl: Dokusatnatrium; Dokuzát-nátrium; Dokuzato natrio druska: DSS: Natrii docusas; Sodium Dioctyl Sulphosuccinate; Sodu dokuzynian. Sodium 1,4-bis(2-ethylhexyl) sulphosuccinate.

Докузат Натрий $C_{20}H_{37}NaO_7^{\circ}S = 444.6$ CAS — 577-11-7. ATC - A06AA02. ATC Vet - QA06AA02.

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

• Co-danthrusate (BAN)—docusate sodium 6 parts and dantron

Pharmacopoeias. In *Eur.* (see p.vii) and *US.* **Ph. Eur. 6.2** (Docusate Sodium). White or almost white, hygroscopic, waxy masses or flakes. Sparingly soluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers

USP 31 (Docusate Sodium). A white wax-like plastic solid with a characteristic odour suggestive of octil alcohol. Slowly soluble 1 in 70 of water; freely soluble in alcohol and in glycerol; very soluble in petroleum spirit.

Adverse Effects and Precautions

Adverse effects occur rarely with docusates; diarrhoea, nausea, abdominal cramps, and skin rash have been reported. Anorectal pain or bleeding have occasionally occurred after rectal doses.

Like all laxatives, docusates should not be used when intestinal obstruction or undiagnosed abdominal symptoms are present; prolonged use should be avoided. Docusate sodium should not be given rectally to patients with haemorrhoids or anal fissures.

Docusate sodium should not be used to soften ear wax when the ear is inflamed or the ear drum perforated.

Hypersensitivity. Docusate salts are widely used as anionic surfactants in pharmaceutical formulations. Allergic contact dermatitis has been reported from one such preparation; patch testing confirmed the reaction to docusate sodium.1

 Lee A-Y, Lee K-H. Allergic contact dermatitis from dioctyl so-dium sulfosuccinate in a topical corticosteroid. *Contact Derma*titis 1998; 38: 355-6.

Pregnancy. Hypomagnesaemia in a neonate, manifested by jitteriness, was considered to be secondary to maternal hypomagnesaemia caused by maternal use of docusate sodium during pregnancy.

1. Schindler AM. Isolated neonatal hypomagnesaemia associated with maternal overuse of stool softener. Lancet 1984; ii: 822.

Interactions

Docusates may enhance the gastrointestinal uptake of other drugs, such as liquid paraffin (and the two should not be given together). Dosage of anthraquinone laxatives may need to be reduced if used with docusates. It has also been suggested that giving docusates with aspirin increases the incidence of adverse effects on the gastrointestinal mucosa.

Pharmacokinetics

Docusate salts are absorbed from the gastrointestinal tract and excreted in bile. Docusate sodium is also distributed into breast milk.

Uses and Administration

Docusates are given as the calcium or sodium salt and are used as laxatives in the management of constipation (p.1693) or to reduce straining in patients with haemorrhoids (p.1697) or anal fissure. They are also used as adjuncts for bowel evacuation before abdominal radiological procedures. Docusate potassium has Docusates are anionic surfactants which have been considered to act primarily by increasing the penetration of fluid into the faeces, but may also have other effects on intestinal fluid secretion, and probably act both as stimulants and as faecal softening agents.

The usual daily oral dose of docusate calcium is 240 mg. Docusate sodium is given in usual oral doses of 50 to 300 mg daily in divided doses, although doses of up to 500 mg daily may be used. (For administration in children, see below). The effect is usually seen within 12 to 72 hours. When used as an adjunct to abdominal radiological procedures, an oral dose of 400 mg is given with the barium meal. It is also given rectally as an enema in doses of 120 mg; the effect is usually seen in 5 to 20 minutes. Docusate sodium is also used with anthraguinone stimulant laxatives such as casanthranol (p.1715), dantron (p.1722), and senna (p.1769).

Docusate sodium is used for softening wax in the ear as ear drops containing 0.5 or 5%.

Docusate sodium and other docusate salts are widely used as anionic surfactants in pharmaceutical formulations.

Administration in children. Docusate sodium by mouth is licensed in the UK for the treatment of chronic constipation in children aged 6 months and over. More specific dose details are also provided in the BNFC as follows:

- · 6 months to 2 years: 12.5 mg three times daily
- · 2 to 12 years: 12.5 to 25 mg three times daily

Children aged 12 years and over may be given the adult doses for constipation, either orally or rectally (see Uses and Administration, above). Adult formulations are not licensed for use in children under 12 years.

In the USA, children aged 2 to 12 years may be given docusate sodium in doses of 50 to 150 mg daily, either as a single daily dose or in divided doses. Docusate calcium is generally only used in the USA for children aged 12 years and over

Docusate sodium is also used as an adjunct in abdominal radiological procedures. UK licensed product information suggests that children may be given an oral dose of 75 mg (30 mL of docusate sodium paediatric solution 12.5 mg per 5 mL) with the barium meal. The BNFC recommends that those aged 12 years and over are given the usual adult dose (see above).

Ear wax removal. Cerumen or ear wax is a normal secretion of the ceruminous glands present in the lining of the external auditory canal. Excessive accumulation or impaction of ear wax may decrease hearing acuity, and may also produce dizziness, vertigo, reflex coughing, tinnitus, and otalgia.

Syringing of the external auditory canal with warm water may be used to remove wax from the ear. However, complications include pain, perforation of the ear drum, deafness, dizziness, vertigo, tinnitus, and infection. 1-6 Contra-indications to ear syringing include past perforation, ear infection, previous ear surgery; syringing may be difficult in children.1,

A ceruminolytic agent may be given as ear drops to soften, loosen, or dissolve cerumen instead. They may also be used immediately before syringing, or for several days beforehand. $^{1-3.5,6}$ Traditionally, fixed oils such as arachis oil, olive oil, or almond oil have been used.1 Some still advocate the use of olive oil to reduce the recurrence of impacted cerumen,3 while others consider it to be ineffective. Other ceruminolytics that have been reported as effective include docusates, 4.7.8 peroxides such as hydrogen peroxide or urea hydrogen peroxide, 4.9 and trolamine polypeptide oleate-condensate, 4.8 although some studies have found these to be no more effective in removing wax than a saline control. 10,11 Other agents that have been used include acetic acid,4 choline salicylate, ¹² methyltrypsin solution, ⁵ and an oily solution of paradichlorobenzene and chlorobutanol. ^{4,12} Glycerol and sodium bicarbonate solution have also been used. However, a comparative study in vitro of the efficacy of various wax dispersing agents found the most effective to be water, which had originally been included as a control,13 and a systematic review14 concluded that saline or water ear drops seemed to be as good as proprietary agents for the removal of ear wax, although there was a lack of good quality studies on which to base recommendations. Ear candling is a traditional folk remedy that has been used to

remove cerumen, but studies indicate it is ineffective, and may deposit wax in the ear canal or cause burn injuries.^{3,4}

- 1. Sharp JF, *et al.* Ear wax removal: a survey of current practice. *BMJ* 1990; **301**: 1251–3.
- Grossan M. Cerumen removal—current challenges. Ear Nose Throat J 1998; 77: 541-6, 548.
 Grossan M. Safe, effective techniques for cerumen removal. Geriatrics 2000; 55: 80, 83-6.
- Dimmitt P. Cerumen removal products. J Pediatr Health Care 2005; 19: 332–6.
- Midani A, et al. Safety and efficacy of Sofenz ceruminolytic solution. Ear Nose Throat J 2006; 85: 87–8, 90–2.
- 6. Aung T, Mulley GP. Removal of ear wax. BMJ 2002; 325: 27.
- Chen DA, Caparosa RJ. A nonprescription cerumenolytic. Am J Otol 1991; 12: 475–6.

- 8. Singer AJ, et al. Ceruminolytic effects of docusate sodium: randomized, controlled trial. Ann Emerg Med 2000; 36: 228–32
- Fahmey S, Whitefield M. Multicentre clinical trial of Exterol as a cerumenolytic. Br J Clin Pract 1982; 36: 197–204.
- Whatley VN, et al. Randomized clinical trial of docusate, trieth-anolamine polypeptide, and irrigation in cerumen removal in children. Arch Pediatr Adolesc Med 2003; 157: 1177–80.
- Roland PS, et al. Randomized, placebo-controlled evaluation of Cerumenex and Murine earwax removal products. Arch Otolaryngol Head Neck Surg 2004; 130: 1175–7.
- 12. Dummer DS, et al. A single-blind, randomized study to compare the efficacy of two ear drop preparations ('Audax' and 'Cerumol') in the softening of ear wax. Curr Med Res Opin 1992: **13:** 26-30
- 13. Andaz C, Whittet HB. An in vitro study to determine efficacy of different wax-dispersing agents. ORL J Otorhinolaryngol Relat Spec 1993; 55: 97–9.
- Spec 1993; 53: 97-9.
 Burton MJ, Dorée CJ. Ear drops for the removal of ear wax. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 13/11/06).

Preparations

BP 2008: Co-danthrusate Capsules; Compound Docusate Enema; Docusate Capsules; Docusate Oral Solution; Paediatric Docusate Oral Solution; USP 31: Docusate Calcium Capsules; Docusate Potassium Capsules; Docusate Sodium Syrup; Docusate Sodium Syrup; Docusate Sodium Syrup; Docusate Sodium Syrup; Docusate Sodium Tablets; Ferrous Fumarate and Docusate Sodium Extended-release Tablets

Proprietary Preparations (details are given in Part 3)

Proprietary Preparations (details are given in Part 3)
Arg.: Cerumex: Otoclean Solucion de Limpieza†; Phillips†, Austral.:
Coloxyl; Rectalad; Waxsol; Belg.: Norgalax; Canad.: Calax Colace; Correctol Stool Softener; Ex-Lax Stool Softener; Regulex†; Selax; Silace; Softax Surfak; Chile: Regalf; Fr.: Jamylene; Norgalax†; Ger.: Ottex; Otowaxol; Hong Kong: Norgalax†; Waxsol; India: Desol; Laxicon; Indon.: Forumen; Waxsol; Int. Norgalax; Waxsol; Maloysia: Soluwax Waxsol; Mex.: Correctol†; Neth.: Norgalax; NZ: Coloxyl; Waxsol; Phillipp.: Otosol; Pol.: Laxolp; Port.: Norgalax; Soluvax; Waxsol; Papin: Dama-Lax†; Switzx: Norgalax; Thai.: Cusate; Dewax; Waxsol; UK: Clear Ear; Dioctyl; Docusol; Dufosas: Fletchers Enemette; Molcer: Norgalax; Goluvax; Colace: Docase: Defoase: Patchers Enemette; Molcer: Norgalax; Soluvaxol; Maxol; Golace: Docase: Defoase: Defoas coEase; Fletchers Enemette†; Molcer; Norgalax; Waxsol; **USA**: Colace; D-S-S; DC Softgels; Dioctyn; Docusoft; DOK; DOS Softgel; Dulcolax Stool Softener; Ex-Lax Stool Softener; Regulax SS; Silace; Sof-lax; Sulfolax; Surfak.

Multi-ingredient: Arg.: Candilax, Nigalax, Austral.: Chemists Own Nat-ural Laxative with Softener; Coloxyl: Coloxyl with Senna; Combiliax, Sen-nesoft; Soflax, Austria: Purigoa†, Yal; Belg.: Laxavit; Softener; Braz.: Ventre Livre†; Canad.: Fruitatives†; Gentlax S; Peri-Colace†, Senna-S; Senokot-S; Cz.: Yal; Denm.: Analka; Glyoktyl: Klyx, Fin.: Klyx; Fir.: Doculyse; Ger.: Nor-galax Minikitister; Yal; Gr.: Florisan; Hung.: Yal†, India: Hepasules; Pursen-nid-In†, Israel: Migraleve; Ital.: Macrolax; Sorbiclis; Mex.: Clyss-Go; Neth.: nicl-In; Israel: Migraleve, Ital.: Macrolax Sorbiciis, Mex.: Člyss-Go; Neth.: Klyx. Norw.: Work.: Emulax; Klyx.; Switz.: Klyx. Magnum; Yal; Thair.: Bioalax; Hemorini; UK: Capsuvac; Normax; USA: Docusoft Plus; Doxidan†; Dulcolax Bowel Prep Klt; Ex-Lax Gentle Strength; Genasoft Plus Softgels†; Laxative & Stool Softener; Nu-Natal Advanced; Peri-Colace; Peri-Dos Softgels†; Senna Plus; Senna-S; Senokot-S; Silace-C†; Therevac Plus; Therevac SB; X-Prep Bowel Evacuant Kit-I; Venez; Clyx-Grd; Senokot-Op. Docustati. ez.: Clys-Go†; Senokot con Docusato.

Used as an adjunct in: India: Softeron; Softeron-Z; Indon.: Fercee; Viliron; Philipp.: Ti-HEMIC; USA: Anemagen OB†; Citracal Prenatal; Citracal Prenatal + DHA; Ferro-Dok; Hem Fe; Hemaspan†; Natal Extra†; Nephron FA; Obstetrix; Optinate Omega-3; Prenatal; Ti-HEMIC; Vinate GT.

Dolasetron Mesilate (BANM, rINNM)

Dolasétron, Mésilate de; Dolasetron Mesylate (USAN); Dolasetroni Mesilas; MDL-73147EF (dolasetron or dolasetron mesilate); Mesilato de dolasetrón. (6R,8r,9aS)-3-Oxoperhydro-2H-2,6-methanoquinolizin-8-yl indole-3-carboxylate methanesulphonate.

Доласетрона Мезилат

 $C_{19}H_{20}N_2O_3$, $CH_4O_3S = 420.5$.

CAS — 115956-12-2 (dolasetron); 115956-13-3 (dolasetron mesilate).

ATC - A04AA04.

ATC Vet - QA04AA04.

(dolasetron)

Pharmacopoeias. In US.

USP 31 (Dolasetron Mesylate). A white to off-white powder. Freely soluble in water and in propylene glycol; slightly soluble in alcohol and in sodium chloride 0.9%. Protect from light.

Stability. A study¹ of the stability of two extemporaneous oral suspensions of dolasetron mesilate 10 mg/mL prepared from