Of 54 children with haemolytic-uraemic syndrome given intravenous furosemide 2.5 to 4 mg/kg every 3 to 4 hours immediately after diagnosis 24% eventually required dialysis.[1] In contrast, a retrospective analysis of 39 patients treated conservatively showed that 82% had required dialysis. The results therefore suggested that high-dose furosemide could prevent the progression of oliguria to anuria in these patients by increasing urate clearance.

1. Rousseau E, *et al.* Decreased necessity for dialysis with loop diuretic therapy in hemolytic uremic syndrome. *Clin Nephrol* 1990; **34:** 22–5.

Heart failure. Diuretics have been the mainstay in the treatment of heart failure (p.1165) but drugs such as ACE inhibitors that have been shown to improve mortality are now generally recommended for first-line therapy along with diuretics. Diuretics provide very effective symptomatic control in patients with peripheral or pulmonary oedema and rapidly relieve dyspnoea. If symptoms of fluid retention are only mild, a thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide, may be adequate. However, in most cases, especially in moderate or severe fluid retention, a loop diuretic such as furosemide will be necessary. Combination treatment with diuretics that behave synergistically by acting at different sites (the principle of sequential nephron blockade), namely a loop diuretic with a thiazide or potassium-sparing diuretic, may be needed in some patients, especially when there is diuretic resistance.

Patients have been successfully treated using continuous intravenous infusions[1] or high doses (up to 8 g daily) of furosemide given by intravenous infusion[2,3] or orally.[3] A patient who was successfully maintained on intravenous furosemide at home has been described.[4] Combination of furosemide with thiazide diuretics[5] or metolazone[6,7] has been reported. There is a danger of overdiuresis with both of these strategies, and careful monitoring of electrolytes and renal function is essential.[8] Delivery of furosemide to the renal tubules may be enhanced by combined therapy with hydralazine[9] or captopril.[10] The use of captopril and furosemide may also correct hyponatraemia without fluid restriction.[11] In elderly patients not responding adequately to low-dose furosemide together with optimum doses of ACE inhibitors, increasing the dose of furosemide (to an average of 297 mg daily orally) has been reported[12] to be of benefit. However, caution is necessary when using furosemide with antihypertensives and especially ACE inhibitors since these combinations can result in sudden and profound hypotension and renal toxicity. Low-dose dopamine infusion has been suggested as an alternative to high-dose furosemide infusion and may cause less toxicity. In a study[13] in patients with severe refractory heart failure given optimal therapy with ACE inhibitors, oral diuretics, nitrates, and digoxin, additional therapy with low-dose intravenous dopamine (4 micrograms/kg per minute) and low-dose oral furosemide (80 mg daily) was as effective as intravenous high-dose furosemide (10 mg/kg daily) but caused less hypokalaemia and renal impairment. Use of intravenous hypertonic saline has also been reported[14] to augment the effect of furosemide.

1. Lawson DH, *et al.* Continuous infusion of frusemide in refractory oedema. *BMJ* 1978; **2:** 476.
2. O'Rourke MF, *et al.* High-dose furosemide in cardiac failure. *Arch Intern Med* 1984; **144:** 2429.
3. Gerlag PGG, van Meijel JJM. High-dose furosemide in the treatment of refractory congestive heart failure. *Arch Intern Med* 1988; **148:** 286–91.
4. Hattersley AT, *et al.* Home intravenous diuretic therapy for patient with refractory heart failure. *Lancet* 1989; **i:** 446.
5. Channer KS, *et al.* Thiazides with loop diuretics for severe congestive heart failure. *Lancet* 1990; **335:** 922–3.
6. Aravot DJ, *et al.* Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; **i:** 727.
7. Friedland JS, Ledingham JGG. Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; **i:** 727–8.
8. Oster JR, *et al.* Combined therapy with thiazide-type and loop diuretic agents for resistant-sodium retention. *Ann Intern Med* 1983; **99:** 405–6.
9. Nomura A, *et al.* Effect of furosemide in congestive heart failure. *Clin Pharmacol Ther* 1981; **30:** 177–82.
10. Dzau VJ, Hollenberg NK. Renal response to captopril in severe heart failure: role of furosemide in natriuresis and reversal of hyponatremia. *Ann Intern Med* 1984; **100:** 777–82.
11. Hamilton RW, Buckalew VM. Sodium, water, and congestive heart failure. *Ann Intern Med* 1984; **100:** 902–4.
12. Waterer G, Donaldson M. High-dose frusemide for cardiac failure. *Lancet* 1995; **346:** 254.
13. Cotter G, *et al.* Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. *Clin Pharmacol Ther* 1997; **62:** 187–93.
14. Paterna S, *et al.* Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail* 2000; **2:** 305–13.

Hypercalcaemia. Hypercalcaemia (p.1668) usually results from an underlying disease and long-term management involves treating the cause. However, if significant symptoms are present, treatment is necessary to reduce plasma-calcium concentrations. This primarily involves rehydration, but loop diuretics such as furosemide have been used after rehydration, to promote urinary calcium excretion. Doses used have ranged from 20 to 240 mg of furosemide daily, given intravenously.

Obstructive airways disease. In patients with *asthma*, furosemide given by oral inhalation has been found to protect against bronchoconstriction induced by exercise[1] and external stimuli,[2,3] although it did not improve bronchial hyperresponsiveness in a 4-week study[4] and provided no additional benefit when added to salbutamol for the treatment of acute asthma in a small study in children.[5] A number of mechanisms have been suggested for the protective effect of furosemide, including inhibition of electrolyte transport across epithelium, inhibition of inflammatory mediators, or an effect on mast cell function.[6] The potential for clinical applications remains unclear[6] and furosemide is not a part of the accepted schedules for the treatment of asthma (p.1108).

A small study[7] in patients with *chronic obstructive pulmonary disease* found that inhalation of furosemide relieved bronchoconstriction and dyspnoea induced by exercise.

Inhaled furosemide has also been used to relieve *dyspnoea in patients with terminal cancer*.[8]

1. Munyard P, *et al.* Inhaled frusemide and exercise-induced bronchoconstriction in children with asthma. *Thorax* 1995; **50:** 677–9.
2. Bianco S, *et al.* Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. *N Engl J Med* 1989; **321:** 1069–73.
3. Seidenberg J, *et al.* Inhaled frusemide against cold air induced bronchoconstriction in asthmatic children. *Arch Dis Child* 1992; **67:** 214–17.
4. Yates DH, *et al.* Effect of acute and chronic inhaled furosemide on bronchial hyperresponsiveness in mild asthma. *Am J Respir Crit Care Med* 1995; **152:** 2173–5.
5. González-Sánchez R, *et al.* Furosemide plus albuterol compared with albuterol alone in children with acute asthma. *Allergy Asthma Proc* 2002; **23:** 181–4.
6. Floreani AA, Rennard SI. Experimental treatments for asthma. *Curr Opin Pulm Med* 1997; **3:** 30–41.
7. Ong K-C, *et al.* Effects of inhaled furosemide on exertional dyspnea in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **169:** 1028–33.
8. Kallet RH. The role of inhaled opioids and furosemide for the treatment of dyspnea. *Respir Care* 2007; **52:** 900–10.

Patent ductus arteriosus. The usual initial treatment for a haemodynamically significant ductus is reduction of fluid intake, correction of anaemia, support of respiration, and giving a diuretic. If that fails to control symptoms then indometacin is generally given to promote closure of the ductus (see p.68).

Furosemide is often the diuretic chosen. It is effective and widely used but there has been concern that it might delay closure (and even increase the incidence of patent ductus arteriosus in infants treated for respiratory distress syndrome — see Effects in Infants and Neonates under Adverse Effects, above). A systematic review[1] of those treated for patent ductus concluded that this did not seem to be the case, and that the diuretic might reduce adverse renal effects of indometacin; however, the evidence for this was limited and it was felt that there was not enough evidence to support the use of furosemide in infants treated with indometacin.

1. Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley, 2001 (accessed 12/07/05).

Raised intracranial pressure. Osmotic diuretics such as mannitol are first-line drugs for the management of raised intracranial pressure (p.1181) but loop diuretics such as furosemide may be used as adjuncts.

Tinnitus. Furosemide is one of many drugs that have been tried in tinnitus (p.1866), but although reported to be effective in some patients, it is rarely used because of problems with adverse effects.

Preparations

BP 2008: Co-amilofruse Tablets; Furosemide Injection; Furosemide Tablets; ***USP 31:*** Furosemide Injection; Furosemide Oral Solution; Furosemide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Eliur†; Errolon; Fabofurox; Frecuental†; Furagrand; Furital; Furix; Fursemida; Furtenk; Kolkin; Lasix; Nuriban; Retep; Viafurox†; ***Austral.:*** Frusehexal; Frusid; Lasix; Uremide; Urex; ***Austria:*** Fural; Furohexal; Furon; Furostad; Lasix; ***Belg.:*** Docfurose; Furotop; Lasix; ***Braz.:*** Diuremida; Diuret†; Diurit†; Diurix; Fluxil; Furesin; Furosan; Furosecord†; Furosem; Furosen†; Furosetron; Furosix; Furozix; Fursemida; Lasix; Neosemid; Normotensor†; Rovelan; Urasix; ***Canad.:*** Lasix; Novo-Semide; ***Chile:*** Asax; Lasix†; ***Cz.:*** Dryptal†; Furanthril†; Furon; Furorese; Lasix†; ***Denm.:*** Diural; Furese; Furix; Lasix; ***Fin.:*** Furesis; Furomin; Lasix; Vesix; ***Fr.:*** Lasilix; ***Ger.:*** Diurapid; durafurid†; Furanthril; Furo; Furo-Puren; Furobeta; Furogamma; Furomed; Furorese; Furosal; Fusid; Jufurix; Lasix; Odemase†; ***Gr.:*** Hydroflux; Lasix; Semid; ***Hong Kong:*** CP-Furo; Lasix; Naqua; Urex; ***Hung.:*** Furon; Humasemide†; ***India:*** Diucontin-K; Frusemix; Frusenex; Frusix; Lasix; Petsix†; ***Indon.:*** Cetasix; Classic; Diurefo; Edemin; Farsix; Furosix; Impugan; Lasix; Uresix; ***Irl.:*** Fruside; Lasix; ***Israel:*** Fusid; Lasix†; Miphar; ***Ital.:*** Lasix; ***Malaysia:*** Dirine; Furmide†; Lasix; Rasitol; Suopinchon; Usix†; ***Mex.:*** Biomisen†; Butosali; Diurmessel; Edenol; Furomil†; Furosan; Furoter†; Henexal; Lasix; Osemin; Selectofur; Zafimida; ***Neth.:*** Lasiletten; Lasix; ***Norw.:*** Diural; Furix; Lasix; ***NZ:*** Diurin; Frusid; Lasix; ***Philipp.:*** Diuril; Diuspec; Edemann; Fremid; Fretic; Frusema; Furoscan; Fusimex; Lasix; Pharmix; Rofunil; ***Port.:*** Aqueduxt; Lasix; Naqua; ***Rus.:*** Lasix (Лазикс); ***S.Afr.:*** Aquarid; Beurises; Lasix; Puresis; Uretic; ***Singapore:*** Dirine; Furmide; Lasix; ***Spain:*** Seguril; ***Swed.:*** Furix; Impugan; Lasix; ***Switz.:*** furo-basan†; Furodrix; Furosifar†; Fursol; Impugan†; Lasix; Oedemex; ***Thai.:*** Aldic†; Dirine; Frusid†; Fudirine†; Furetic; Furide; Furine; Fuseride; H-Mide; Hawkmide†; Impugan†; Lasiven; Lasix; Mediuresix†; Urasin†; ***Turk.:*** Desal; Furomid; Lasix; Lizik; Urex; ***UAE:*** Salurin; ***UK:*** Froop; Frusid; Frusol; Lasix; Rusyde; ***USA:*** Lasix; ***Venez.:*** Biosemida; Edemid; Fromil†; Inclens; Lasix; Lifurox; Nacua†; Resimida†; Salca; Terysol.

Multi-ingredient: *Arg.:* Aldactone-D; Diflux; Errolon A; Furdiuren†; Lasilacton; Lasiride; Nuriban A; ***Austria:*** Furo-Aldopur; Furo-Spirobene; Furolacton; Hydrotrix; Lasilacton; Lasitace; Spirono comp; ***Belg.:*** Frusamil; ***Braz.:*** Diurana; Diurisa; Furosemide Composto; Hidrion; Lasilactona; ***Chile:*** Furdiuren; Hidrium; Hidropid; ***Cz.:*** Spiro Compositum†; ***Denm.:*** Frusamil; ***Fin.:*** Furesis comp; ***Fr.:*** Aldalix; Logirene; ***Ger.:*** Betasemid; Diaphal; duraspiron-comp†; Furo-Aldopur; Furorese Comp; Hydrotrix; Osyrol Lasix; Spiro comp; Spiro-D; Spironolacton Plus†; ***Gr.:*** Frumil; ***India:*** Frumil; Lasilactone; Spiromide; ***Irl.:*** Diumide-K Continus; Fru-Co; Frumil; Lasoride†; ***Ital.:*** Fluss 40; Lasitone; Spirofur; ***Mex.:*** Lasilacton; ***NZ:*** Frumil; ***Philipp.:*** Diumide-K; ***Spain:*** Salidur; ***Switz.:*** Frumil†; Furocombin; Furospir; Lasilactone; ***UK:*** Aridil; Froop Co†; Fru-Co; Frumil; Frusene; Komil; Lasikal; Lasilactone; Lasoride†; ***Venez.:*** Furdiuren.

Gallopamil Hydrochloride *(BANM, rINNM)*

D-600 (gallopamil); Gallopamil, Chlorhydrate de; Gallopamilhydroklorid; Gallopamilli Hydrochloridum; Gallopamillihydrokloridi; Hidrocloruro de galopamilo; Methoxyverapamil Hydrochloride. 5-[*N*-(3,4-Dimethoxyphenethyl)-*N*-methylamino]-2-(3,4,5-trimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

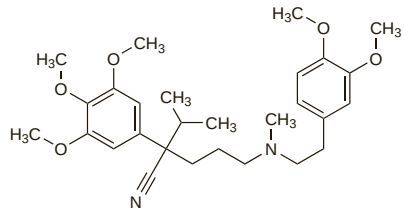
Галопамила Гидрохлорид

$C_{28}H_{40}N_2O_5,HCl$ = 521.1.

CAS — 16662-47-8 (gallopamil); 16662-46-7 (gallopamil hydrochloride).

ATC — C08DA02.

ATC Vet — QC08DA02.



(gallopamil)

Profile

Gallopamil is a calcium-channel blocker (see p.1154) with antiarrhythmic activity and is chemically related to verapamil. It is used in the management of angina pectoris (p.1157), cardiac arrhythmias (p.1160), and hypertension (p.1171). Gallopamil hydrochloride is given by mouth in doses of 25 to 50 mg every 6 to 12 hours up to a maximum total dose of 200 mg daily. Modified-release preparations are also available and are given once or twice daily in similar total daily doses.

◊ General references.

1. Brogden RN, Benfield P. Gallopamil: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in ischaemic heart disease. *Drugs* 1994; **47:** 93–115.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Procorum; ***Ger.:*** Gallobeta; Procorum; ***Hung.:*** Procorum; ***Ital.:*** Algocor; Procorum; ***Mex.:*** Procorum; ***Philipp.:*** Procorum; ***Thai.:*** Procorum.

Gemfibrozil *(BAN, USAN, rINN)*

CI-719; Gemfibrotsiili; Gemfibrozilo; Gemfibrozilum; Gemfibrozyl. 2,2-Dimethyl-5-(2,5-xylyloxy)valeric acid.

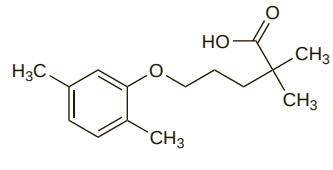
Гемфиброзил

$C_{15}H_{22}O_3$ = 250.3.

CAS — 25812-30-0.

ATC — C10AB04.

ATC Vet — QC10AB04.



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

Ph. Eur. 6.2 (Gemfibrozil). A white or almost white, waxy, crystalline powder. M.p. 58° to 61°. Practically insoluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; very soluble in dichloromethane. Protect from light.

USP 31 (Gemfibrozil). A white waxy crystalline solid. M.p. 58° to 61°. Practically insoluble in water; soluble in alcohol, in methyl alcohol, and in chloroform. Store in airtight containers.

Adverse Effects and Precautions

As for Bezafibrate, p.1232.

Incidence of adverse effects. In the Helsinki Heart Study,[1] 11.3% of 2051 patients taking gemfibrozil reported various moderate to severe upper gastrointestinal tract symptoms during the first year of treatment compared with 7% of 2030 patients taking placebo. No differences were seen between gemfibrozil and placebo groups in haemoglobin concentrations, urinary-protein, or urinary-sugar concentrations.

There was no significant difference in the total number of cancers between the gemfibrozil and placebo groups nor in the number of operations for gallstones or for cataract surgery. A higher number of deaths in the gemfibrozil group was mainly due to accident or violence and intracranial haemorrhage.

A follow-up study[2] reported that gastrointestinal symptoms remained more common in patients taking gemfibrozil. Although there was no significant difference between the gemfibrozil and placebo groups cholecystectomies were consistently more common in those receiving gemfibrozil during the entire 8.5-year observation period. Cancer occurred equally in both groups, but there was increased mortality attributable to cancer in the gemfibrozil group, mainly during the last 1.5 years of follow-up; this difference was no longer apparent after 18 years.[3]

1. Frick MH, *et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317:** 1237–45.
2. Huttunen JK, *et al.* The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. *J Intern Med* 1994; **235:** 31–9.
3. Tenkanen L, *et al.* Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study. *Arch Intern Med* 2006; **166:** 743–8.

Effects on the skin. Psoriasis was exacerbated in a patient within 2 weeks of starting gemfibrozil therapy and recurred when gemfibrozil was subsequently reintroduced.[1]

1. Fisher DA, *et al.* Exacerbation of psoriasis by the hypolipidemic agent, gemfibrozil. *Arch Dermatol* 1988; **124:** 854–5.

Interactions

As for Bezafibrate, p.1232.

Gemfibrozil is an inhibitor of a number of cytochrome P450 isoenzymes, including CYP2C8, CYP2C9, CYP2C19, and CYP1A2 and may increase the plasma concentration of drugs metabolised by these isoenzymes; it also inhibits some UDP-glucuronosyltransferases. Increased plasma concentration of bexarotene (see p.686), pioglitazone (see p.456), and rosiglitazone (see p.459) have been reported with gemfibrozil, and use of gemfibrozil in patients receiving repaglinide is contra-indicated due to the risk of serious hypoglycaemia (see p.458).

Pharmacokinetics

Gemfibrozil is readily absorbed from the gastrointestinal tract; bioavailability is close to 100% and is highest when gemfibrozil is taken 30 minutes before food. Peak concentrations in plasma occur within 1 to 2 hours; the half-life is about 1.5 hours. Plasma protein binding of gemfibrozil is about 98%. About 70% of a dose is excreted in the urine mainly as glucuronide conjugates of gemfibrozil and its metabolites; little is excreted in the faeces.

Uses and Administration

Gemfibrozil, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p.1233).

Gemfibrozil is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p.1169), including type IIa, type IIb, type III, type IV, and type V hyperlipoproteinaemias. It is also indicated for the primary prevention of ischaemic heart disease (see Cardiovascular Risk Reduction, p.1164) in hyperlipidaemic men: in the USA this use is restricted to type IIb patients who also have low HDL-cholesterol concentrations and who have not responded to dietary and other measures. The usual oral dose is 1.2 g daily in 2 divided doses given 30 minutes before the morning and evening meals. Alternatively, a single daily dose of 900 mg has been given 30 minutes before the evening meal.

◊ Reviews.

1. Spencer CM, Barradell LB. Gemfibrozil: a reappraisal of its pharmacological properties and place in the management of dyslipidaemia. *Drugs* 1996; **51:** 982–1018.

Administration in renal impairment. Gemfibrozil is contra-indicated in patients with severe renal impairment. However, UK licensed prescribing information allows its use in patients with mild to moderate impairment (glomerular filtration rate 30 to 80 mL/minute per 1.73 m^2); the initial dose should be reduced to 900 mg daily and renal function should be assessed before increasing the dose.

In a study[1] of the pharmacokinetics of gemfibrozil in 17 patients with stable chronic renal failure the mean plasma half-life was 1.8 and 1.9 hours after multiple and single doses respectively, which was comparable with that reported in patients with normal renal function. Gemfibrozil clearance was independent of renal function, but the kinetics of gemfibrozil metabolites were not evaluated.

Beneficial responses[2] were seen in lipid and lipoprotein concentrations in 5 of 6 uraemic patients treated with gemfibrozil 1.2 g daily for six months and in 6 nephrotic patients given gemfibrozil 800 mg daily for 4 months. No significant adverse effects or signs of organ toxicity were seen. Results of a secondary prevention study[3] also suggested that gemfibrozil at a dose of 1.2 g daily was safe and effective in patients with mild to moderate renal impairment.

1. Evans JR, *et al.* The effect of renal function on the pharmacokinetics of gemfibrozil. *J Clin Pharmacol* 1987; **27:** 994–1000.
2. Manninen V, *et al.* Gemfibrozil treatment of dyslipidaemias in renal failure with uraemia or in the nephrotic syndrome. *Res Clin Forums* 1982; **4:** 113–18.
3. Tonelli M, *et al.* for the Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) Investigators. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int* 2004; **66:** 1123–30.

Preparations

BP 2008: Gemfibrozil Capsules; Gemfibrozil Tablets;
USP 31: Gemfibrozil Capsules; Gemfibrozil Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Gedun; Hipolixan; Lopid; ***Austral.:*** Ausgem; Gemhexal; Jezil; Lipazil; Lopid; ***Austria:*** Gevilon; ***Braz.:*** Lopid; Lozil; ***Canad.:*** Lopid; ***Chile:*** Grifogemzilo; Lipotril; Lopid; ***Cz.:*** Gevilon†; Innogem†; Ipolipid†; ***Denm.:*** Lopid; ***Fin.:*** Gevilon; Lopid; ***Fr.:*** Lipur; ***Ger.:*** Gemfi; Gevilon; Lipox Gemfi†; ***Gr.:*** Adratan†; Amedran; Antilipid; Cholhepan; Clipostat; Dosamont; Drisofal†; Eklipid; Entianthe†; Fibrolip; Fibrospes; Gebrozil†; Gedizil; Gemfolid; Gemlipid; Gineton; Hobatolex; Lisolip; Lopid; Noxobran†; Parnoxil; Prelisin; Renolip; Solulip; Terostrant; Tiazam; ***Hong Kong:*** Gemzil; Ipolipid; Lipison; Lipistorol; Lipofor; Lopid; Lowin; Marbrozil; Qualipid; Saffid; Synbrozil; ***Hung.:*** Innogem; Minilip; ***India:*** Lopid; Normolip; ***Indon.:*** Detrichol; Fetinor; Fibralip; Hypofil; Inobes; Lapibroz; Lifibron; Lipira; Lipitrop; Lokoles; Lopid; Lowlip; Mersikol; Nufalemzil; Progemzal; Renabrazin; Scantipid; Zilop; ***Irl.:*** Lopid; ***Ital.:*** Fibrocit; Gemlipid; Genlip; Genozil; Lipogen; Lipozid; Lopid; ***Malaysia:*** Brozil; Fibrol†; Ipolipid; Lipistorol†; Lipofor; Lopid†; Mariston†; ***Mex.:*** Apo-Fide; Lopid; Raypid; ***Neth.:*** Lopid; ***NZ:*** Gemizol†; ***Philipp.:*** Lipigem; Lipison; Lipizile; Lipozid; Lopid; Reducel; ***Port.:*** Lipoite; Lopid; ***Rus.:*** Ipolipid (Иполипид); ***S.Afr.:*** Lopid; ***Singapore:*** Brozil; Gemd†; Hidil; Ipolipid; Lipison†; Lipofor; Lopid†; Recozil; ***Spain:*** Bolutol†; Decrelip†; Lopid; Pilder; Trialmin; ***Swed.:*** Lopid; ***Switz.:*** Gevilon; ***Thai.:*** Bisil; Chlorestrol†; Deopid†; Dropid; Gemfibril; GFB; Gozid; Hidil; Lipidys; Lipison; Lipolo; Lipozil; Locholes; Lopid; Manobrozil; Mariston; Norpid; Pharzil; Poli-Fibrozil; Polyxit; Tiba; ***Turk.:*** Lopid; ***UK:*** Lopid; ***USA:*** Lopid; ***Venez.:*** Lipontal; Lopid.

Glyceryl Trinitrate

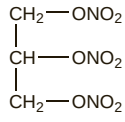
Glicerin-trinitrát; Glicerolio trinitratas; Gliseril Trinitrat; Glonoin; Glyceroli Trinitras; Glyceroli trinitratis; Glycerol-trinitrát; Glycéryle, trinitrate de; Glyceryltrinitrat; Glyseryylitrinitraatti; GTN; Nitroglicerina; Nitrogliserin; Nitroglycerin; Nitroglycerol; NTG; Trinitrin; Trinitroglycerin. Propane-1,2,3-triol trinitrate.

$C_3H_5(NO_3)_3$ = 227.1.

CAS — 55-63-0.

ATC — C01DA02; C05AE01.

ATC Vet — QC01DA02; QC05AE01.



Pharmacopoeias. *Chin., Eur.* (see p.vii), *US*, and *Viet.* include glyceryl trinitrate as diluted solutions.

Ph. Eur. 6.2 (Glyceryl Trinitrate Solution). An ethanolic solution containing 1 to 10% w/w of glyceryl trinitrate. It is a clear, colourless or slightly yellow solution. Miscible with dehydrated alcohol and with acetone.

Pure glyceryl trinitrate is practically insoluble in water; freely soluble in dehydrated alcohol; miscible with acetone.

Protect from light. Diluted solutions (1%) should be stored at 2° to 15°; more concentrated solutions may be stored at 15° to 20°.

USP 31 (Diluted Nitroglycerin). A mixture of glyceryl trinitrate with lactose, glucose, alcohol, propylene glycol, or other suitable inert excipient, usually containing not more than 10% glyceryl trinitrate. When diluted in either alcohol or propylene glycol it is a clear, colourless, or pale yellow liquid. When diluted with lactose, it is a white odourless powder. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Prevent exposure to temperatures above 40°. Protect from light.

Undiluted glyceryl trinitrate is a white to pale yellow, thick, flammable, explosive liquid. Slightly soluble in water; soluble in alcohol, in acetone, in carbon disulfide, in chloroform, in dichloromethane, in ether, in ethyl acetate, in glacial acetic acid, in methyl alcohol, in benzene, in toluene, in nitrobenzene, and in phenol.

Handling. Undiluted glyceryl trinitrate can be exploded by percussion or excessive heat and only exceedingly small amounts should be isolated.

Incompatibility. Studies have found glyceryl trinitrate to be incompatible with phenytoin,[1] alteplase,[2] and levofloxacin.[3]

1. Klamerus KJ, *et al.* Stability of nitroglycerin in intravenous admixtures. *Am J Hosp Pharm* 1984; **41:** 303–5.
2. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.
3. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; **56:** 1458–9.

Stability. ***INTRAVENOUS SOLUTIONS.*** The loss of glyceryl trinitrate from solution by adsorption or absorption into some plastics of intravenous giving sets has been recognised for some years,[1,2] although adsorption does not appear to occur to any great extent with polyolefin[3,4] or polyethylene.[5-7] It is not only infusion containers and plastic tubing that may be involved; some in-line filters can adsorb glyceryl trinitrate.[8,9]

1. Grouthamel WG, *et al.* Loss of nitroglycerin from plastic intravenous bags. *N Engl J Med* 1978; **299:** 262.
2. Roberts MS, *et al.* The availability of nitroglycerin from parenteral solutions. *J Pharm Pharmacol* 1980; **32:** 237–44.
3. Wagenknecht DM, *et al.* Stability of nitroglycerin solutions in polyolefin and glass containers. *Am J Hosp Pharm* 1984; **41:** 1807–11.
4. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; **63:** 2379–82.
5. Schaber DE, *et al.* Nitroglycerin adsorption to a combination polyvinyl chloride, polyethylene intravenous administration set. *Drug Intell Clin Pharm* 1985; **19:** 572–5.
6. Tracy TS, *et al.* Nitroglycerin delivery through a polyethylene-lined intravenous administration set. *Am J Hosp Pharm* 1989; **46:** 2031–5.
7. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.
8. Baaske DM, *et al.* Nitroglycerin compatibility with intravenous fluid filters, containers, and administration sets. *Am J Hosp Pharm* 1980; **37:** 201–5.
9. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; **40:** 1323–8.

TABLETS. Many studies have shown that glyceryl trinitrate tablets are unstable and subject to considerable loss of potency in contact with packaging components such as adhesive labels, cotton and rayon fillers, and plastic bottles and caps. Both the Council of the Royal Pharmaceutical Society of Great Britain and the FDA in the USA have issued packaging and dispensing guidelines. Glyceryl trinitrate tablets should be dispensed only in glass containers sealed with a foil lined cap and containing no cotton wool wadding. In addition, the Council of the Royal Pharmaceutical Society of Great Britain recommends that no more than 100 tablets should be supplied and that the container should be labelled with an indication that any tablets should be discarded after 8 weeks in use.

Adverse Effects

Glyceryl trinitrate may cause flushing of the face, dizziness, tachycardia, and throbbing headache. Large doses cause vomiting, restlessness, blurred vision, hypotension (which can be severe), syncope, and rarely cyanosis, and methaemoglobinaemia; impairment of respiration and bradycardia may ensue. Contact dermatitis has been reported in patients using topical glyceryl trinitrate preparations; local irritation and erythema may also occur. Preparations applied to the oral mucosa frequently produce a localised burning sensation.

Chronic poisoning may occur in industry but tolerance develops when glyceryl trinitrate is regularly handled and nitrate dependence can lead to severe withdrawal symptoms in subjects abruptly removed from chronic exposure. Loss of such tolerance is rapid and may cause poisoning on re-exposure. Tolerance may occur during clinical use and is usually associated with preparations that produce sustained plasma concentrations.

Effects on the heart. Tachycardia, hypotension, and bradycardia are recognised adverse cardiac effects of glyceryl trinitrate. Rarely reported adverse effects include asystole[1] and complete heart block.[2]

1. Ong EA, *et al.* Nitroglycerin-induced asystole. *Arch Intern Med* 1985; **145:** 954.
2. Lancaster L, Fenster PE. Complete heart block after sublingual nitroglycerin. *Chest* 1983; **84:** 111–12.

Effects on taste. A 61-year-old man experienced loss of bitter and salty taste sensations 2 weeks after addition of glyceryl trinitrate patches to his post-myocardial infarction drug regimen.[1] The patient had complete loss of taste after 6 weeks; his taste