Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Frigol; ***Cz.:*** Xanidil; ***Ger.:*** Complamin spezial; ***Hung.:*** Xavin; ***India:*** Complamina; ***Ital.:*** Complamin; Vedrin†; ***Neth.:*** Complamin; ***Pol.:*** Sadamin; ***Switz.:*** Complamin.

Multi-ingredient: ***Spain:*** Rulun.

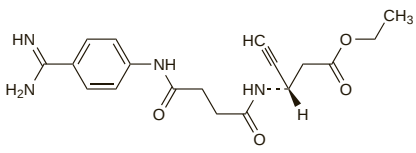
Xemilofiban Hydrochloride *(USAN, rINNM)*

Hidrocloruro de xemilofibán; SC-54684A; Xémilofiban, Chlorhydrate de; Xemilofibani Hydrochloridum. Ethyl (3*S*)-3-{3-[(*p*-amidinophenyl)carbamoyl]propionamido}-4-pentynoate monohydrochloride.

Ксемилофибана Гидрохлорид

$C_{18}H_{22}N_4O_4,HCl$ = 394.9.

CAS — 149820-74-6 (xemilofiban); 156586-91-3 (xemilofiban hydrochloride).



(xemilofiban)

Profile

Xemilofiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an oral antiplatelet drug for the management of thromboembolic disorders such as unstable angina, and after angioplasty, but results have been disappointing.

◊ References.

1. O'Neill WW, *et al.* Long-term treatment with a platelet glycoprotein-receptor antagonist after percutaneous coronary revascularization. *N Engl J Med* 2000; **342:** 1316–24.

Xipamide *(BAN, USAN, rINN)* ⊗

Be-1293; Ksipamidi; MJF-10938; Xipamid; Xipamida; Xipamidum. 4-Chloro-5-sulphamoylsalicylo-2′,6′-xylidide; 5-(Aminosulphonyl)-4-chloro-*N*-(2,6-dimethylphenyl)-2-hydroxy-benzamide.

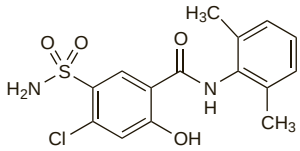
Ксипамид

$C_{15}H_{15}ClN_2O_4S$ = 354.8.

CAS — 14293-44-8.

ATC — C03BA10.

ATC Vet — QC03BA10.



Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p.1307.

Effects on electrolyte balance. Although reductions in plasma-potassium concentrations with xipamide have been shown to be on average comparable with those produced by thiazide and loop diuretics at equipotent doses,[1] there have been several reports of marked hypokalaemia in individual patients. Asymptomatic hypokalaemia was reported in 4 of 5 patients[2] (serum-potassium concentrations of less than 3.4 mmol/litre) and in 3 of 13 patients[3] (serum-potassium concentrations of less than 3.0 mmol/litre). Severe hypokalaemia resulting in ventricular arrhythmias has been reported after xipamide used alone[4] or with indapamide.[5] Profound electrolyte disturbances with altered consciousness and ventricular extrasystoles occurred in a patient taking digoxin after the addition of xipamide for 10 days.[6] A case of hypokalaemic periodic paralysis associated with xipamide use has also been reported.[7]

1. Prichard BNC, Brogden RN. Xipamide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985; **30:** 313–32.
2. Weissberg P, Kendall MJ. Hypokalaemia and xipamide. *BMJ* 1982; **284:** 975.
3. Raftery EB, *et al.* A study of the antihypertensive action of xipamide using ambulatory intra-arterial monitoring. *Br J Clin Pharmacol* 1981; **12:** 381–5.
4. Altmann P, Hamblin JJ. Ventricular fibrillation induced by xipamide. *BMJ* 1982; **284:** 494.
5. Boulton AJM, Hardisty CA. Ventricular arrhythmias precipitated by treatment with non-thiazide diuretics. *Practitioner* 1982; **226:** 125–8.
6. Bentley J. Hypokalaemia and xipamide. *BMJ* 1982; **284:** 975.
7. Boulton AJM, Hardisty CA. Hypokalaemic periodic paralysis precipitated by diuretic therapy and minor surgery. *Postgrad Med J* 1982; **58:** 106–7.

Hepatic impairment. For a recommendation that xipamide should be given with caution to patients with liver disease, see under Pharmacokinetics, below.

Interactions

As for Hydrochlorothiazide, p.1309.

Pharmacokinetics

Xipamide has been reported to be well absorbed from the gastrointestinal tract. Absorption is fairly rapid with peak plasma concentrations occurring within 1 or 2 hours of oral doses. It is 99% bound to plasma proteins, and is excreted in the urine, partly unchanged and partly in the form of the glucuronide metabolite. It is reported to have a plasma half-life of about 5 to 8 hours. In patients with renal impairment excretion in the bile becomes more prominent.

◊ References.

1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; **13:** 254–66.

Hepatic impairment. Xipamide was present in the plasma and in ascitic fluid in patients with liver cirrhosis in proportion to the protein content of the respective compartments.[1] The amount of drug excreted into the urine was much greater in patients with liver disease than in healthy control subjects. This was attributed to a diminution in hepatic elimination, which could result in significant effects on the clinical response to xipamide. Thus patients with cholestasis could have an enhanced response to xipamide. On the other hand cirrhotic patients with the hepatorenal syndrome may be resistant to diuretics. Xipamide should be used with caution in patients with liver disease.

1. Knauf H, *et al.* Xipamide disposition in liver cirrhosis. *Clin Pharmacol Ther* 1990; **48:** 628–32.

Renal impairment. After single oral and intravenous doses of xipamide 20 mg the drug appeared to be completely absorbed from the gastrointestinal tract.[1] The mean elimination half-life in healthy subjects was 7 hours and two-thirds of the clearance was by extrarenal routes. There was some accumulation in patients with chronic renal failure, with a calculated elimination half-life of 9 hours in end-stage renal disease.

1. Knauf H, Mutschler E. Pharmacodynamics and pharmacokinetics of xipamide in patients with normal and impaired kidney function. *Eur J Clin Pharmacol* 1984; **26:** 513–20.

Uses and Administration

Xipamide is a diuretic, structurally related to indapamide, with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1310). It is given orally for hypertension (p.1171), and for oedema, including that associated with heart failure (p.1165).

Diuresis begins about 1 or 2 hours after an oral dose, reaches a peak at 4 to 6 hours, and lasts for about 12 hours.

In the treatment of **hypertension** the usual dose is 20 mg daily as a single morning dose, either alone, or with other antihypertensives. In some patients a dose of 10 mg daily may be adequate. In the treatment of **oedema** the usual initial dose is 40 mg daily, subsequently reduced to 20 mg daily, according to response; in resistant cases 80 mg daily may be required.

◊ References.

1. Prichard BNC, Brogden RN. Xipamide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985; **30:** 313–32.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Aquaphoril; ***Fr.:*** Lumitens†; ***Ger.:*** Aquaphor; Aquex; Xipa; Xipalsis; Xipagamma; ***India:*** Xipamid; ***Ital.:*** Aquafor†; ***Port.:*** Diurexan; ***S.Afr.:*** Diurexan†; ***Spain:*** Demiax†; Diurex; ***UK:*** Diurexan.

Multi-ingredient: ***Ger.:*** Durotan†; Neotri.

Zofenopril Calcium *(BANM, USAN, rINNM)*

Calcii Zofenoprilum; SQ-26991; Zofenopril cálcico; Zofénopril Calcique. Calcium salt of (4*S*)-1-[(2*S*)-3-(Benzylthio)-2-methylpropionyl]-4-(phenylthio)-L-proline.

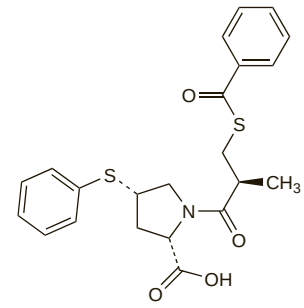
Кальций Зофеноприл

$C_{44}H_{44}CaN_2O_8S_4$ = 897.2.

CAS — 81872-10-8 (zofenopril); 81938-43-4 (zofenopril calcium).

ATC — C09AA15.

ATC Vet — QC09AA15.



(zofenopril)

Profile

Zofenopril is an ACE inhibitor (p.1193) that is used in the management of hypertension (p.1171) and myocardial infarction (p.1175). It owes its activity to the active metabolite zofenoprilat (SQ-26333) to which it is converted after oral doses. It is given orally in a usual daily maintenance dose of 30 to 60 mg of the calcium salt, as a single dose or in two divided doses.

◊ References.

1. Ambrosioni E, *et al.* The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995; **332:** 80–5.
2. Borghi C, *et al.* Effects of the administration of an angiotensin-converting enzyme inhibitor during the acute phase of myocardial infarction in patients with arterial hypertension: SMILE study investigators: Survival of Myocardial Infarction Long-term Evaluation. *Am J Hypertens* 1999; **12:** 665–72.
3. Borghi C, *et al.* A review of the angiotensin-converting enzyme inhibitor, zofenopril, in the treatment of cardiovascular diseases. *Expert Opin Pharmacother* 2004; **5:** 1965–77.
4. Buikema H. Use of the ACE inhibitor zofenopril in the treatment of ischemic heart disease. *Expert Rev Cardiovasc Ther* 2006; **4:** 631–47.
5. Ambrosioni E. Defining the role of zofenopril in the management of hypertension and ischemic heart disorders. *Am J Cardiovasc Drugs* 2007; **7:** 17–24.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Bifril; ***Fr.:*** Zofenil; ***Gr.:*** Zofepril; Zopranol; ***Irl.:*** Zofenil; ***Ital.:*** Bifril; Zantipres; Zopranol; ***Neth.:*** Zofil; Zopranol; ***Port.:*** Zofenil; Zopranol; ***Rus.:*** Zocardis (Зокардис); ***Spain:*** Zofenil; Zopranol; ***Swed.:*** Bifril†; ***Switz.:*** Zofenil; ***Turk.:*** Zoprotec.

Multi-ingredient: ***Fr.:*** Zofenilduo; ***Gr.:*** Zofepril Plus; Zopranol Plus; ***Ital.:*** Bifrizide; Zantipride; Zoprazide; ***Port.:*** Zofenil Plus.

Chelators Antidotes and Antagonists

The drugs included in this chapter act in a variety of ways to counter the toxic effects of exogenous and endogenous substances in the body. They are therefore used in the management of poisoning and overdosage, to protect against the toxicity of drugs such as antineoplastics, and in the management of metabolic disorders such as Wilson's disease where toxic substances accumulate.

The main groups of drugs used include:

- antagonists, such as the opioid antagonist naloxone, that compete with the poison for receptor sites. Other antagonists act by blocking substances that mediate the effects of the toxin; atropine (p.1219) acts in this way
- chelators and other drugs that form complexes with the toxin. This may reduce absorption of the toxin from the gastrointestinal tract, inactivate or reduce the activity of the toxin, or increase its elimination
- drugs that affect the metabolism of the toxin. Some antidotes, such as fomepizole in methyl alcohol poisoning, act by reducing the rate of metabolism to a toxic metabolite; alcohol (p.1625) has a similar action. Others, such as methionine and glutathione, promote the formation of inactive metabolites; acetylcysteine (p.1548) also acts in this way
- drugs that bypass the effect of the toxin. Calcium folinate (p.1943) is used for this purpose in methotrexate overdosage.

Acute poisoning

In the management of suspected acute poisoning it is often impossible to determine the identity of the poison or the size of the dose received with any certainty. Moreover, few poisons have specific antidotes or methods of elimination, and the mainstay of treatment for patients with suspected acute poisoning is therefore supportive and symptomatic therapy; in many cases nothing further is required. Symptoms of acute poisoning are frequently non-specific, particularly in the early stages. Maintenance of the airway and ventilation is the most important initial measure; other treatment, for example for cardiovascular or neurological symptoms, may be added as appropriate. Patients who are unconscious or who have respiratory depression may be given naloxone, particularly if opioid overdosage is a possibility. Some centres also recommend the routine administration of glucose to all unconscious patients since hypoglycaemia may be a cause of unconsciousness, although blood glucose measurements should be obtained first where facilities are immediately available; thiamine may be given in addition since glucose may precipitate Wernicke's encephalopathy.

Specific antidotes are available for a number of poisons and are the primary treatment where there is severe poisoning with a known toxin. They may be life-saving in such cases but their use is not without hazard and in many situations they are not necessary; their use does not preclude relevant supportive treatment.

Measures to reduce or prevent the absorption of the poison are widely advocated. For inhalational poisoning the victim is removed from the source of poisoning. Some toxins, in particular pesticides, may be absorbed through the skin, and clothing should be removed and the skin thoroughly washed to avoid continued absorption. Caustic substances are removed from the skin or eyes with copious irrigation. However, for orally ingested poisons the best method for gastrointestinal decontamination remains controversial.

Activated charcoal adsorbs a wide range of toxins and is often given to reduce absorption from the gastrointestinal tract. A single dose is generally effective, particularly if it is given within one hour of ingestion, although delayed use may be beneficial for modified-release preparations or for drugs that slow gastrointestinal transit time, such as those with antimuscarinic properties. Charcoal is generally well tolerated, although vomiting is common and there is a risk of aspiration if the airway is not adequately protected. Repeated doses may be of use to eliminate some substances even after systemic absorption has occurred.

Active removal of poisons from the stomach by induction of emesis or gastric lavage has been widely used, but there is little evidence to support its role (see under Ipecacuanha, p.1563). Induction of emesis with an emetic such as syrup of ipecacuanha has been used but is no longer recommended for either the home or hospital situation since there is no evidence that it improves outcomes and it may increase the risk of aspiration. If used at all, it should only be in fully conscious patients, where a potentially toxic amount has been ingested within the previous hour, and where other measures are unavailable or inappropriate. Emesis should not be induced if the poison is corrosive or petroleum based, nor if the poison is removable by treatment with activated charcoal. Gastric lavage may occasionally be indicated for ingestion of non-caustic poisons that are not absorbed by activated charcoal, but only if less than one hour has elapsed since ingestion; it should not be attempted if the airway is not adequately protected.

Whole-bowel irrigation using a non-absorbable osmotic agent such as a macrogol has also been used, particularly for substances that pass beyond the stomach before being absorbed, such as iron preparations or enteric-coated or modified-release formulations, but its role is not established.

Techniques intended to promote the elimination of poisons from the body, such as haemodialysis or haemoperfusion, are only of value for a limited number of poisons in a few severely poisoned patients. Forced diuresis is no longer recommended, although alkalinisation of the urine using sodium bicarbonate infusion may have a role for selected poisons. Repeated oral doses of activated charcoal may be as effective as these more invasive methods for some drugs that undergo enterohepatic or enteroenteric recycling.

Poisons Information Centres exist in many countries and should be consulted for more detailed information in specific situations.

Activated Charcoal

Aktif Kömür; Aktiivihiili; Aktivált szén; Aktyvintosios anglys; Carbo activatus; Carbo Medicinalis; Carbón activado; Charbon activé; Decolorising Charcoal; Kol, aktivt; Medicinal Charcoal; Uhlí aktivní; Węgiel leczniczy.

CAS — 16291-96-6 (charcoal).

ATC — A07BA01.

ATC Vet — QA07BA01.

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

Ph. Eur. 6.2 (Charcoal, Activated). It is obtained from vegetable matter by suitable carbonisation processes intended to confer a high adsorption power. A black, light powder free from grittiness. Practically insoluble in all usual solvents. It adsorbs not less than 40% of its own weight of phenazone, calculated with reference to the dried substance. Store in airtight containers.

USP 31 (Activated Charcoal). The residue from the destructive distillation of various organic materials, treated to increase its adsorptive power. A fine, black, odourless, tasteless powder, free from gritty matter. The USP 31 has tests for adsorptive power in respect of alkaloids and dyes.

Adverse Effects and Precautions

Activated charcoal is relatively non-toxic when given by mouth but gastrointestinal disturbances such as vomiting, constipation, or diarrhoea have been reported. It may colour the faeces black. Activated charcoal should be used with caution in patients at risk of gastrointestinal obstruction as it may reduce gastrointestinal motility.

Haemoperfusion with activated charcoal has produced various adverse effects including platelet aggregation, charcoal embolism, thrombocytopenia, haemorrhage, hypoglycaemia, hypocalcaemia, hypothermia, and hypotension.

Care is needed if activated charcoal is used in patients receiving specific oral antidotes such as methionine (see Interactions, below). As with any treatment given by mouth for poisoning the risk of aspiration should be considered in drowsy or comatose patients.

Effects on the gastrointestinal tract. Gastrointestinal adverse effects are the main complication of oral activated charcoal. Vomiting may occur and is a risk factor for pulmonary aspiration (see Effects on the Lungs, below). Although some preparations may cause diarrhoea, activated charcoal may reduce gastrointestinal motility and multiple doses have been associated with intestinal obstruction or faecal impaction,[1-4] in some cases leading to ulceration[5] or perforation;[6] overdosage with drugs that reduce gastrointestinal motility may increase the risk.[2,3,6] Two cases of pseudo-obstruction, one of which was fatal, have also been reported[7] after the use of activated charcoal and sorbitol with opioid sedation for theophylline poisoning. In another report,[8] severe peritonitis developed in a patient given oral activated charcoal following gastric lavage; charcoal was found in the peritoneum, although the site of perforation could not be detected. Acute appendicitis has also been reported after multiple doses of activated charcoal.[9]

1. Watson WA, *et al.* Gastrointestinal obstruction associated with multiple-dose activated charcoal. *J Emerg Med* 1986; **4:** 401–7.
2. Anderson IM, Ware C. Syrup of ipecacuanha. *BMJ* 1987; **294:** 578.
3. Ray MJ, *et al.* Charcoal bezoar: small-bowel obstruction secondary to amitriptyline overdose therapy. *Dig Dis Sci* 1988; **33:** 106–7.
4. Atkinson SW, *et al.* Treatment with activated charcoal complicated by gastrointestinal obstruction requiring surgery. *BMJ* 1992; **305:** 563.
5. Mizutani T, *et al.* Rectal ulcer with massive haemorrhage due to activated charcoal treatment in oral organophosphate poisoning. *Hum Exp Toxicol* 1991; **10:** 385–6.
6. Gomez HF, *et al.* Charcoal stercolith with intestinal perforation in a patient treated for amitriptyline ingestion. *J Emerg Med* 1994; **12:** 57–60.
7. Longdon P, Henderson A. Intestinal pseudo-obstruction following the use of enteral charcoal and sorbitol and mechanical ventilation with papaveretum sedation for theophylline poisoning. *Drug Safety* 1992; **7:** 74–7.
8. Mariani PJ, Pook N. Gastrointestinal tract perforation with charcoal peritoneum complicating orogastric intubation and lavage. *Ann Emerg Med* 1993; **22:** 606–9.
9. Eroglu A, *et al.* Multiple dose-activated charcoal as a cause of acute appendicitis. *J Toxicol Clin Toxicol* 2003; **41:** 71–3.

Effects on the lungs. Vomiting after oral activated charcoal for acute poisoning has been associated with pulmonary aspiration of gastric contents, sometimes with fatal results.[1-3] Vomiting may be related to the formulation used and may be increased with sorbitol-containing preparations,[4] although a study in children[5] failed to confirm this. The use of a cuffed endotracheal tube has been recommended for any patient with impaired laryngeal reflexes to prevent aspiration;[3] however, there have been reports of aspiration despite a protected airway, including a case of obstructive laryngitis in a child.[6] Acute[7] and chronic[8] pulmonary toxicity has also been reported after accidental administration of charcoal into the lung due to misplacement of the nasogastric tube.

1. Harsch HH. Aspiration of activated charcoal. *N Engl J Med* 1986; **314:** 318.
2. Menzies DG, *et al.* Fatal pulmonary aspiration of oral activated charcoal. *BMJ* 1988; **297:** 459–60.
3. Rau NR, *et al.* Fatal pulmonary aspiration of oral activated charcoal. *BMJ* 1988; **297:** 918–19.
4. McFarland AK, Chyka PA. Selection of activated charcoal products for the treatment of poisonings. *Ann Pharmacother* 1993; **27:** 358–61.
5. Osterhoudt KC, *et al.* Risk factors for emesis after therapeutic use of activated charcoal in acutely poisoned children. *Pediatrics* 2004; **113:** 806–10.
6. Donoso A, *et al.* Activated charcoal laryngitis in an intubated patient. *Pediatr Emerg Care* 2003; **19:** 420–1.
7. Harris CR, Filandrinos D. Accidental administration of activated charcoal into the lung: aspiration by proxy. *Ann Emerg Med* 1993; **22:** 1470–3.
8. Graff GR, *et al.* Chronic lung disease after activated charcoal aspiration. *Pediatrics* 2002; **109:** 959–61.

Interactions

Activated charcoal has the potential to reduce the absorption of many drugs from the gastrointestinal tract and simultaneous oral therapy should therefore be avoided. In the management of acute poisoning, concurrent medication should be given parenterally. Care is needed if a specific oral antidote such as methionine is given since adsorption of the antidote may decrease its effectiveness; it has been recommended that activated charcoal should be cleared from the stomach or avoided if oral antidotes are to be used.

Uses and Administration

Activated charcoal can adsorb a wide range of plant and inorganic poisons and many drugs including salicylates, paracetamol, barbiturates, and tricyclic antidepressants; when given orally it reduces their systemic absorption from the gastrointestinal tract and is therefore used in the treatment of acute oral poisoning. It is of no value for poisoning by strong acids, alkalis, or other corrosive substances and its adsorptive capacity is too low to be of use in poisoning with iron salts,