quately to them. The mainstay of treatment of an acute attack is replacement therapy with complement C1 esterase inhibitor. Fresh frozen plasma has been used although there is a risk of initially exacerbating the oedema due to the presence of other complements in the plasma. Tracheostomy or tracheal intubation may be necessary.

Once the acute attack has subsided most patients will not require further treatment, but those who experience life-threatening attacks, repeated episodes of swelling around the face or neck, or incapacitating attacks require long-term **prophylactic therapy**. A synthetic androgen (danazol or stanozolol) or an antifibrinolytic (aminocaproic acid or tranexamic acid) is effective for long-term prophylaxis.[1,2,4,6] Danazol and stanozolol raise serum concentrations of C1 esterase inhibitor possibly by enhancing its synthesis in the liver.[2,6] Aminocaproic acid and tranexamic acid may act by inhibiting plasmin activation.[7] A synthetic androgen is often preferred because these seem to be more effective than antifibrinolytics. In children, however, androgens are generally avoided because of their adverse effects. Nevertheless, they have been used in children, with close monitoring, when antifibrinolytics have been ineffective.[3] In exceptional circumstances, long-term prophylaxis with twice weekly C1 esterase inhibitor may be indicated for adults when antifibrinolytics and androgens are ineffective, not tolerated, or contra-indicated.[6]

Short-term prophylaxis may be used in situations expected to provoke an attack, such as surgery or dental work. Complement C1 esterase inhibitor is given within 24 hours before the procedure, or fresh frozen plasma may be used if this is not available. Alternatively, a synthetic androgen or antifibrinolytic may be used, but these must be started several days before the procedure and continued for 2 days after.

Investigational therapies for the management of hereditary angioedema include a recombinant complement C1 esterase inhibitor, icatibant acetate (a bradykinin receptor antagonist), and ecallantide (an inhibitor of human plasma kallikrein).

1. Nzeako UC, *et al.* Hereditary angioedema: a broad review for clinicians. *Arch Intern Med* 2001; **161:** 2417–29.
2. Fay A, Abinun M. Current management of hereditary angio-oedema (C'1 esterase inhibitor deficiency). *J Clin Pathol* 2002; **55:** 266–70.
3. Farkas H, *et al.* Clinical management of hereditary angio-oedema in children. *Pediatr Allergy Immunol* 2002; **13:** 153–61.
4. Bowen T, *et al.* Canadian 2003 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *J Allergy Clin Immunol* 2004; **114:** 629–37.
5. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol* 2005; **114:** 10–16.
6. Gompels MM, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139:** 379–94. Correction. *ibid.*; **141:** 189–90. [dose]
7. Ritchie BC. Protease inhibitors in the treatment of hereditary angioedema. *Transfus Apheresis Sci* 2003; **29:** 259–67.

Menorrhagia. Tranexamic acid is used in women with menorrhagia (p.2126) who do not require contraception or hormonal therapy. It reduces uterine blood loss in such women when used during menstruation.[1-3] A comparative trial[1] found tranexamic acid 1 g by mouth every 6 hours to be more effective than the NSAID mefenamic acid, a commonly used treatment for the condition, and etamsylate. It is also more effective than cyclical norethisterone[2] (although less so than a progesterone-releasing intra-uterine device[3]). A review,[4] which included these and some other studies, reported that tranexamic acid reduces menstrual blood loss by about 34 to 59% over 2 to 3 cycles.

1. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ* 1996; **313:** 579–82.
2. Preston JT, *et al.* Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. *Br J Obstet Gynaecol* 1995; **102:** 401–406.
3. Milsom I, *et al.* A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *Am J Obstet Gynecol* 1991; **164:** 879–83.
4. Wellington K, Wagstaff AJ. Tranexamic acid: a review of its use in the management of menorrhagia. *Drugs* 2003; **63:** 1417–33.

Preparations

BP 2008: Tranexamic Acid Injection; Tranexamic Acid Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Cyklokapron; ***Austria:*** Cyklokapron; ***Belg.:*** Exacyl; ***Braz.:*** Hemoblock; Transamin; ***Canad.:*** Cyklokapron; ***Chile:*** Espercil; ***Cz.:*** Cyklokapron†; Exacyl; ***Denm.:*** Cyklokapron; ***Fin.:*** Caprilon; Cyklokapron; ***Fr.:*** Exacyl; Spotof; ***Ger.:*** Anvitoff†; Cyklokapron; ***Gr.:*** Transamin; ***Hong Kong:*** CP-Tran; Cyklokapron; Qualixamin; Transamin; ***Hung.:*** Exacyl; ***India:*** Tranarest; Tranfib; Traxamic†; ***Indon.:*** Asamnex; Clonex; Ditranex; Intermic; Kalnex; Lunex; Nexa; Plasminex; Pytramic; Ronex; Theranex; Tranexid; Transamin; ***Irl.:*** Cyklokapron; ***Israel:*** Hexakapron; ***Ital.:*** Tranex; Ugurol; ***Jpn:*** Transamin; ***Malaysia:*** Transamin; Tren; ***Neth.:*** Cyklokapron; ***Norw.:*** Cyklokapron; ***NZ:*** Cyklokapron; ***Philipp.:*** Cyclotrax; Cyklokapron; Dostan; Fibrinon; Fimoplas; Hemoclot; Hemostan; Hemotrex; Micranex; Proklot; Trenaxin; ***Pol.:*** Exacyl; ***S.Afr.:*** Cyklokapron; ***Singapore:*** Cyklokapron; ***Spain:*** Amchafibrin; ***Swed.:*** Cyklo-F; Cyklokapron; Tranon; ***Switz.:*** Anvitoff†; Cyklokapron; ***Thai.:*** Tramic; Transamin; ***Turk.:*** Transamine; ***UK:*** Cyklokapron; ***USA:*** Cyklokapron; ***Venez.:*** Ciclokapron.

Multi-ingredient: ***Fr.:*** Quixil; ***Ger.:*** Quixil; ***India:*** Tranfib MF; ***Ital.:*** Quixil; ***Jpn:*** Sin Colgen Kowa Kaze; ***Neth.:*** Quixil; ***Port.:*** Quixil.

von Willebrand Factor

Facteur Willebrand humain (human von Willebrand factor); Factor humanus von Willebrandi (human von Willebrand factor); Factor VIII-related Antigen; vWF.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Human von Willebrand Factor). A preparation of a plasma protein fraction that contains the glycoprotein von Willebrand factor with varying amounts of coagulation factor VIII, depending on the method of preparation. It is prepared from human plasma obtained from blood from healthy donors: the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus.

When reconstituted as stated on the label, the potency is not less than 20 international units of von Willebrand factor per mL. It is a white or pale yellow, hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Profile

von Willebrand factor is used in the treatment and prophylaxis of bleeding in von Willebrand's disease (p.1051), usually when desmopressin is ineffective or contra-indicated. It is generally contained in plasma concentrate preparations with factor VIII, but highly purified preparations that contain very little factor VIII are also available in some countries. Dosage depends on the extent and source of bleeding. Hypersensitivity reactions may occur rarely, and as for other plasma-derived preparations, the risk of transmission of infective agents cannot be totally excluded.

◊ References.

1. Smith MP, *et al.* Continuous infusion therapy with very high purity von Willebrand factor concentrate in patients with severe von Willebrand disease. *Blood Coag Fibrinol* 1997; **8:** 6–12.
2. Goudemand J, *et al.* Clinical management of patients with von Willebrand's disease with a VHP vWF concentrate: the French experience. *Haemophilia* 1998; **4** (suppl 3): 48–52.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Wilfactin; Wilstart; ***Gr.:*** Wilfactin.

4. Winer KK, *et al.* Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism: results of a short-term randomized crossover trial. *JAMA* 1996; **276:** 631–6.
5. Winer KK, *et al.* Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *J Clin Endocrinol Metab* 2003; **88:** 4214–20.
6. Decker GAG, *et al.* Allotransplantation of parathyroid cells. *Lancet* 1995; **345:** 124. Correction. *ibid.*; 464.
7. Hasse C, *et al.* Parathyroid allotransplantation without immunosuppression. *Lancet* 1997; **350:** 1296–7.

Alendronate

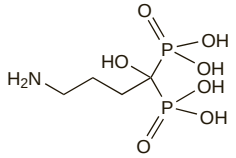
ATC — M05BA04.
ATC Vet — QM05BA04.

Alendronic Acid *(BAN, rINN)*

Acide Alendronique; Ácido alendrónico; Acidum Alendronicum; AHButBP; Alendronihappo; Alendronik Asit; Alendronsyra; Aminohydroxybutylidene Diphosphonic Acid. 4-Amino-1-hydroxybutane-1,1-diylbis(phosphonic acid).

Алендроновая Кислота

$C_4H_{13}NO_7P_2$ = 249.1.
CAS — 66376-36-1.
ATC — M05BA04.
ATC Vet — QM05BA04.



Alendronate Sodium *(USAN, rINNM)*

Alendronat Sodyum; Alendronate de Sodium; Alendronato sódico; G-704650; L-670452; MK-0217; MK-217; Monosodium alendronate; Natrii alendronas; Natrii Alendronas Trihydricus; Natrio alendronatas; Natriumalendronaatti; Natriumalendronat; Nátrium-alendronát; Natrium-alendronát trihydrát; Sodium Alendronate *(BANM)*; Sodium, alendronate de. Sodium trihydrogen (4-amino-1-hydroxybutylidene)diphosphonate trihydrate.

Натрий Алендронат

$C_4H_{12}NNaO_7P_2,3H_2O$ = 325.1.
CAS — 121268-17-5.
ATC — M05BA04.
ATC Vet — QM05BA04.

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

Ph. Eur. 6.2 (Sodium Alendronate). A white or almost white crystalline powder. Soluble in water; practically insoluble in dichloromethane; very slightly soluble in methyl alcohol. A 1% solution in water has a pH of 4.0 to 5.0.

USP 31 (Alendronate Sodium). A white, free-flowing powder. Soluble in water; practically insoluble in alcohol, in acetone, in acetonitrile, in chloroform, and in isopropyl alcohol; very slightly soluble in dimethyl sulfoxide, in methyl alcohol, and in propylene glycol.

Adverse Effects, Treatment, and Precautions

As for the bisphosphonates in general, p.1089. Gastrointestinal symptoms such as abdominal pain, dyspepsia, diarrhoea or constipation are the most frequent adverse effects with alendronate. Severe oesophageal reactions such as oesophagitis, erosions, ulceration, and stricture have occurred (see below); patients should be advised to stop taking the tablets and seek medical attention if they develop symptoms such as dysphagia, new or worsening heartburn, pain on swallowing, or retrosternal pain. Peptic ulceration has also been reported.

Alendronate should not be given to patients with abnormalities of the oesophagus or other factors that might delay oesophageal emptying, or those unable to stand or sit upright for at least 30 minutes. It should be used with caution in patients with upper gastrointestinal abnormalities. To minimise the risk of oesophageal reactions:

- patients should be instructed to swallow alendronate tablets whole with plenty of water (not less than 200 mL), in an upright position (standing or sitting). Mineral water with a high concentration of calcium should be avoided
- tablets should be taken on rising for the day, on an empty stomach, at least 30 minutes before breakfast and any other oral medication
- patients should remain upright after taking the tablets (the *BNF* recommends standing or sitting upright for at least 30 minutes), and should not lie down before eating the first meal of the day
- alendronate should not be taken at bedtime, or before getting up for the day

Hypocalcaemia should be corrected before starting alendronate therapy, and other disorders affecting mineral metabolism such as vitamin D deficiency or hypoparathyroidism should also be treated; serum calcium in these patients should be monitored during therapy.

Effects on the eyes. For reports of ocular effects with the bisphosphonates, including alendronate, see under Bisphosphonates, p.1090.

Effects on the heart. For a report of a possible association between alendronate and atrial fibrillation, see Effects on the Heart, under Bisphosphonates, p.1090.

Effects on the kidneys. Renal failure has been associated with the aminobisphosphonates, including alendronate, see under Bisphosphonates, p.1091.

Effects on the liver. Hepatitis[1,2] and hepatocellular damage with raised liver enzyme concentrations[3,4] have been reported after therapy with alendronate.

1. Lieverse RJ. Hepatitis after alendronate. *Neth J Med* 1998; **53:** 271–2.
2. Carrère C, *et al.* Hépatite aiguë sévère imputable á l'alendronate. *Gastroenterol Clin Biol* 2002; **26:** 179–80.
3. Halabe A, *et al.* Liver damage due to alendronate. *N Engl J Med* 2000; **343:** 365.
4. de la Serna Higuera C, *et al.* Lesión hepatocelular inducida por alendronato. *Gastroenterol Hepatol* 2001; **24:** 244–6.

Effects on mental state. Auditory hallucinations and red-coloured visual disturbances were reported[1] in a patient taking alendronate for osteoporosis.

1. Coleman CI, *et al.* Alendronate-induced auditory hallucinations and visual disturbances. *Pharmacotherapy* 2004; **24:** 799–802.

Effects on the musculoskeletal system. A 63-year old woman given alendronate 70 mg once weekly for osteoporosis developed diffuse severe myalgia and transient acute symmetrical polyarthritis 12 hours after ingestion. Symptoms did not recur after stopping the drug.[1] From the initial marketing of alendronate up until November 2002, the FDA had received reports of severe bone, joint, and/or muscle pain in 118 patients, including a child given the drug in error. Of 83 patients for whom information was available, 55 improved after stopping alendronate; in most of these improvement was gradual, although some experienced immediate relief. Nine of these 83 patients had recurrence of pain when given alendronate again. It was suggested that pain might tend to be under-reported since it is subjective, and might be attributed to underlying osteoporosis.[2] As of May 2006, 7 cases of synovitis linked to alendronate use had been reported in New Zealand; in one case, severe synovitis caused carpal tunnel syndrome that required urgent decompression.[3]

Concerns have been raised about potential oversuppression of bone turnover during long-term therapy with alendronate. In a report on 9 patients who developed spontaneous non-spinal fractures while taking alendronate, fracture healing was absent or incomplete in 6 patients who continued therapy for between 3 months and 2 years after fracture onset. When alendronate was stopped, fracture healing was still incomplete in 4 patients after 8 to 12 months. Use of estrogen (in 3 cases) or the presence of glucocorticoid-induced osteoporosis (in 2) may have contributed to the development of bone turnover suppression in some, but 4 patients had received alendronate as monotherapy; duration of therapy was also considered to be a factor as bone suppression might be cumulative.[4]

Osteonecrosis of the jaw has been reported after the use of bisphosphonates, including alendronate (see Effects on the Musculoskeletal System, under Adverse Effects of Bisphosphonates, p.1091).

1. Gerster JC, Nicole F. Acute polyarthritis related to once-weekly alendronate in a woman with osteoporosis. *J Rheumatol* 2004; **31:** 829–30.
2. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 2005; **165:** 346–7.
3. Savage R. Alendronate and inflammatory adverse reactions (issued May 2006). Available at: http://www.medsafe.govt.nz/profs/puarticles/alendinflam.htm#Myalgia (accessed 15/04/08)
4. Odvina CV, *et al.* Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 2005; **90:** 1294–1301.

Effects on the oesophagus. Between September 1995 and March 1996 the UK CSM had received 10 reports of adverse effects on the oesophagus in patients receiving alendronate sodium.[1] Of these, 4 were of oesophageal reflux, 4 of oesophagitis, and 2 of oesophageal ulceration. As of March 1996, worldwide an estimated 475 000 patients had received alendronate and 199 patients had oesophageal reactions reported to the manufacturer, of which 51 were serious or severe.[2] Endoscopic findings included erosions, ulcerations, exudative inflammation, and thickening of the oesophagus. Bleeding was rare, and oesophageal perforation was not reported. Most oesophageal reactions occurred within 1 week to 2 months of starting alendronate therapy. Recovery occurred when alendronate was stopped; however, it was considered important that patients be followed up for the possible development of strictures.[2] In about 60% of the cases where the information was available, alendronate had not been taken in accordance with the precautions for use (see above).

The CSM subsequently noted[3] that it had continued to receive reports of reactions; by July 1998 there had been 97 reports in the UK, in 1 case associated with a fatality. It was estimated that 1 to 2% of patients might experience oesophageal reactions even when following the precautions for use. Some have reported a much higher incidence of unacceptable upper gastrointestinal symptoms in clinical practice.[4] However, a large placebo-controlled trial of alendronate did not find any increase in upper gastrointestinal events in patients taking alendronate.[5]

1. Committee on Safety of Medicines/Medicines Control Agency. Oesophageal reactions with alendronate sodium (Fosamax). *Current Problems* 1996; **22:** 5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015620&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
2. de Groen PC, *et al.* Esophagitis associated with the use of alendronate. *N Engl J Med* 1996; **335:** 1016–21.
3. Committee on Safety of Medicines/Medicines Control Agency. Reminder: severe oesophageal reactions with alendronate sodium (Fosamax). *Current Problems* 1998; **24:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 25/05/06)
4. Kelly R, Taggart H. Incidence of gastrointestinal side effects due to alendronate is high in clinical practice. *BMJ* 1997; **315:** 1235.
5. Bauer DC, *et al.* Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. *Arch Intern Med* 2000; **160:** 517–25.

Hypersensitivity. Allergic reactions to bisphosphonates do occur but appear to be rare, see p.1091.

Interactions

As for the bisphosphonates in general, p.1091.

Pharmacokinetics

Like other bisphosphonates, alendronate is poorly absorbed after oral doses. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. Bioavailability is about 0.4% when taken half an hour before food, reduced from 0.7% in the fasting state; absorption is negligible when taken up to 2 hours after a meal. Plasma protein binding is about 78%. Bisphosphonates do not appear to be metabolised. About half of the absorbed portion is excreted in the urine; the remainder is sequestered to bone for a prolonged period.

◊ References.

1. Gertz BJ, *et al.* Studies of the oral bioavailability of alendronate. *Clin Pharmacol Ther* 1995; **58:** 288–98.
2. Cocquyt V, *et al.* Pharmacokinetics of intravenous alendronate. *J Clin Pharmacol* 1999; **39:** 385–93.
3. Porras AG, *et al.* Pharmacokinetics of alendronate. *Clin Pharmacokinet* 1999; **36:** 315–28.

Uses and Administration

Alendronate is an aminobisphosphonate with general properties similar to those of the other bisphosphonates (p.1091). It is a potent inhibitor of bone resorption and is given in the management of osteoporosis either alone or with vitamin D. Alendronate is used for the treatment of Paget's disease of bone. It has also been given in the treatment of bone metastases and hypercalcaemia of malignancy.

Alendronate is given orally as the sodium salt, but doses are expressed in terms of alendronic acid; alendronate sodium 1.3 mg is equivalent to about 1 mg of alendronic acid. The specific instructions given in Adverse Effects and Precautions, above should be followed to minimise adverse effects and permit adequate absorption.

The usual dosage for the treatment of **osteoporosis** in men and women is 10 mg daily. Postmenopausal women may be given 5 mg daily for prophylaxis. It may also be given once weekly to postmenopausal women in a dose of 70 mg for treatment of osteoporosis, or 35 mg for prophylaxis. Men with osteoporosis may be treated with 70 mg once weekly.