

(ANC <1500 cells/mm³) is rare. Licensed product information recommends that neutrophil counts should be taken before starting anakinra and periodically throughout treatment. UK licensed information recommends monthly monitoring during the first 6 months and then quarterly thereafter; US licensed information requires monthly monitoring for the first 3 months and then quarterly monitoring for a period of up to 1 year. Anakinra should not be started in patients with neutropenia. Small reductions in the total white blood cell and platelets counts and a small increase in eosinophils have also been noted. Anakinra is also associated with an increased incidence of lymphoma in patients with rheumatoid arthritis.

For caution in patients with renal impairment see under Uses and Administration, below.

Effects on the cardiovascular system. A 29-year-old woman with refractory adult-onset Still's disease developed shortness of breath, which progressed to cardiorespiratory failure, 3 months after being started on anakinra;¹ although resuscitation was tried, the patient died. The authors considered that the role of anakinra in this event was unclear, particularly as the patient had shown some evidence of myocardial or pulmonary dysfunction before starting the drug.

- Ruiz PJ, et al. Cardiac death in a patient with adult-onset Still's disease treated with the interleukin 1 receptor inhibitor anakinra. *Ann Rheum Dis* 2007; **66**: 422–3.

Effects on the skin. Inflammatory lesions at injection sites were reported in 5 patients after anakinra use.¹ The lesions were erythematous, oedematous, painful, and itchy plaques, and were seen within 16 days of starting treatment. Treatment with anakinra was completely stopped in 1 patient and interrupted in 2 other patients; when reintroduced, one patient developed abdominal pain, dyspnoea, and facial and abdominal erythema with pruritus.

- Vila AT, et al. Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *Br J Dermatol* 2005; **153**: 417–23.

Interactions

Live vaccines should not be given with anakinra as its effect on vaccine efficacy or the risk of infection transmission is unknown.

The risk of serious infection and neutropenia is increased when anakinra and etanercept are used together (see under Infliximab, p.71); a similar effect may occur with other TNF antagonists. The use of anakinra with etanercept or other TNF inhibitors is not recommended.

Pharmacokinetics

After subcutaneous doses, peak plasma concentrations of anakinra are reached in 3 to 7 hours. Its terminal half-life is about 4 to 6 hours. Anakinra is excreted mainly in the urine.

Uses and Administration

Anakinra is a recombinant receptor antagonist of interleukin-1 (p.2325), an inflammatory mediator found in the plasma and synovial fluid of patients with rheumatoid arthritis.

Anakinra is used for the treatment of the signs and symptoms of moderate to severely active rheumatoid arthritis in patients who have had an inadequate response to methotrexate or another disease-modifying antirheumatic drug (DMARD) alone (but see below). In the UK, it is only licensed for use with methotrexate; however, in the USA, it may be given either alone or with another DMARD, although not one that inhibits TNF (see Interactions, above). The usual dose in adults is 100 mg once daily by subcutaneous injection. The dose should be given at about the same time each day.

Anakinra has been tried in septic shock and graft-versus-host disease in transplant recipients, but results were disappointing.

Administration in renal impairment. Caution may be advisable if anakinra is used in patients with renal impairment. A study¹ in patients with varying degrees of renal function indicated that no dosage adjustment was needed for anakinra in patients with mild or moderate renal impairment but dosage on alternate days appeared advisable in those with severe renal impairment. US licensed product information also recommends alternate-day dosing in patients with severe impairment or end-stage disease (creatinine clearance less than 30 mL/minute). However, in the UK, licensed product information contra-indicates use in those with this degree of impairment.

Dialysis does not affect anakinra concentrations to any significant degree.

- Yang B-B, et al. Pharmacokinetics of anakinra in subjects with different levels of renal function. *Clin Pharmacol Ther* 2003; **74**: 85–94.

Familial Mediterranean fever. For mention of anakinra having been tried in familial Mediterranean fever, see p.557.

Rheumatoid arthritis. In the UK, anakinra is licensed for the treatment of rheumatoid arthritis (p.11) in patients with an inadequate response to methotrexate alone; however, NICE does not recommend its use except in the context of a controlled, long-term clinical study.

References

- Bresnahan B, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998; **41**: 2196–2204.

- Cohen S, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46**: 614–24.
- Nuki G, et al. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46**: 2838–46.
- Fleischmann RM, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003; **48**: 927–34.
- NICE. Anakinra for rheumatoid arthritis: Technology Appraisal Guidance 72 (issued November 2003). Available at: <http://www.nice.org.uk/nicemedia/pdf/TA072guidance.pdf> (accessed 22/06/07)
- Schiff MH. Durability and rapidity of response to anakinra in patients with rheumatoid arthritis. *Drugs* 2004; **64**: 2493–2501.
- Waugh J, Perry CM. Anakinra: a review of its use in the management of rheumatoid arthritis. *BioDrugs* 2005; **19**: 189–202.
- Reiff A. The use of anakinra in juvenile arthritis. *Curr Rheumatol Rep* 2005; **7**: 434–40.
- den Broeder AA, et al. Observational study on efficacy, safety, and drug survival of anakinra in rheumatoid arthritis patients in clinical practice. *Ann Rheum Dis* 2006; **65**: 760–2.
- Burger D, et al. Is IL-1 a good therapeutic target in the treatment of arthritis? *Best Pract Res Clin Rheumatol* 2006; **20**: 879–96.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Kineret; **Canad.:** Kineret; **Cz.:** Kineret; **Denm.:** Kineret; **Fin.:** Kineret; **Fr.:** Kineret; **Ger.:** Kineret; **Gr.:** Kineret; **Irl.:** Kineret; **Ital.:** Kineret; **Neth.:** Kineret; **Norw.:** Kineret; **Pol.:** Kineret; **Port.:** Kineret; **Spain:** Kineret; **Swed.:** Kineret; **UK:** Kineret; **USA:** Kineret.

Anileridine (BAN, rINNM)

Anileridini; Anileridin; Anileridina; Anileridine; Anileridinum. Ethyl 1-(4-aminophenethyl)-4-phenylpiperidine-4-carboxylate.

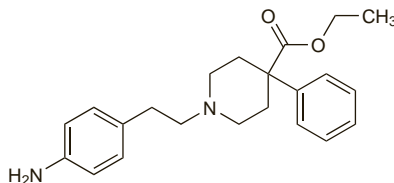
АНИЛЕРИДИН

C₂₂H₂₈N₂O₂ = 352.5.

CAS — 144-14-9.

ATC — N01AH05.

ATC Vet — QN01AH05.



Pharmacopoeias. In *US*.

USP 31 (Anileridine). A white to yellowish-white, odourless or practically odourless, crystalline powder. When exposed to light and air it oxidises and darkens in colour. It exhibits polymorphism, and of two crystalline forms observed, one melts at about 80° and the other at about 89°. Very slightly soluble in water; soluble 1 in 2 of alcohol and 1 in 1 of chloroform; soluble in ether but solutions may be turbid. Store in airtight containers. Protect from light.

Anileridine Hydrochloride (BANM, rINNM)

Anileridine, Chlorhydrate d'; Anileridini Hydrochloridum; Hidrocloruro de anileridina.

АНИЛЕРИДИНА Гидрохлорид

C₂₂H₂₈N₂O₂·2HCl = 425.4.

CAS — 126-12-5.

Pharmacopoeias. In *US*.

USP 31 (Anileridine Hydrochloride). A white or nearly white odourless crystalline powder. Soluble 1 in 5 of water and 1 in 80 of alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is 2.5 to 3.0. Store in airtight containers. Protect from light.

Anileridine Phosphate (BANM, rINNM)

Anileridine, Phosphate d'; Anileridini Fosphas; Fosfato de anileridina.

АНИЛЕРИДИНА Фосфат

C₂₂H₂₈N₂O₂·H₃PO₄ = 450.5.

CAS — 4268-37-5.

Profile

Anileridine, a phenylpiperidine derivative, is an opioid analgesic (p.101) chemically related to pethidine (p.113) and with similar actions. It has been used as the hydrochloride in the management of moderate to severe pain. Anileridine has also been given by injection as the phosphate.

Preparations

USP 31: Anileridine Hydrochloride Tablets; Anileridine Injection.

Aspirin (BAN)

Acetilsalicílico, ácido; Acetilsalicilo rūgštis; Acetilszalicilsav; Acetylsal. Acid; Acetylsalicylic Acid; Acetylsalicylsyra; Acide acétylsalicylique; Acidum acetylsalicylicum; Asetilsalisilik Asit; Asetylisalisylilhapoo; Kwas acetylosalicylowy; Kyselina acetylsalicylová; Polopiryna; Salicylic Acid Acetate. O-Acetylsalicylic acid; 2-Acetoxybenzoic acid.

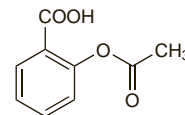
Аспирин

C₉H₈O₄ = 180.2.

CAS — 50-78-2.

ATC — A01AD05; B01AC06; N02BA01.

ATC Vet — QA01AD05; QB01AC06; QN02BA01.



NOTE. The use of the name Aspirin is limited; in some countries it is a trade-mark.

Compounded preparations of aspirin may be represented by the following names:

- Co-codaprin (BAN)—aspirin 50 parts and codeine phosphate 1 part (w/w)
- Co-codaprin (PEN)—aspirin and codeine phosphate.

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

Ph. Eur. 6.2 (Acetylsalicylic Acid; Aspirin BP 2008). White or almost white, crystalline powder or colourless crystals. Slightly soluble in water; freely soluble in alcohol. Store in airtight containers.

USP 31 (Aspirin). White crystals, commonly tubular or needle-like, or white crystalline powder; odourless or has a faint odour. Is stable in dry air; in moist air it gradually hydrolyses to salicylic and acetic acids. Soluble 1 in 300 of water, 1 in 5 of alcohol, 1 in 17 of chloroform, and 1 in 10 to 15 of ether; sparingly soluble in absolute ether. Store in airtight containers.

Adverse Effects and Treatment

Aspirin has many properties in common with the non-aspirin NSAIDs, the adverse effects of which are described on p.96.

The most common adverse effects of therapeutic doses of aspirin are gastrointestinal disturbances such as nausea, dyspepsia, and vomiting. Gastrointestinal symptoms may be minimised by giving aspirin with food. Irritation of the gastric mucosa with erosion, ulceration, haematemesis, and melaena may occur. Histamine H₂-antagonists, proton pump inhibitors, and prostaglandin analogues such as misoprostol may be used in the management of NSAID-induced ulceration (see Peptic Ulcer Disease, p.1702), including that caused by aspirin. Slight blood loss, which is often asymptomatic, may occur in about 70% of patients; it is not usually of clinical significance but may, in a few patients, cause iron-deficiency anaemia during long-term therapy. Such occult blood loss is not affected by giving aspirin with food but may be reduced by use of enteric-coated or other modified-release tablets, H₂-antagonists, or high doses of antacids. Major upper gastrointestinal bleeding occurs rarely.

Some persons, especially those with asthma, chronic urticaria, or chronic rhinitis, exhibit notable hypersensitivity to aspirin (see also below), which may provoke reactions including urticaria and other skin eruptions, angioedema, rhinitis, and severe, even fatal, paroxysmal bronchospasm and dyspnoea. Persons sensitive to aspirin often exhibit cross-sensitivity to other NSAIDs.

Aspirin increases bleeding time, decreases platelet adhesiveness, and, in large doses, can cause hypoprothrombinaemia. It may cause other blood disorders, including thrombocytopenia.

Aspirin and other salicylates may cause hepatotoxicity, particularly in patients with juvenile idiopathic arthritis or other connective tissue disorders. In children the use of aspirin has been implicated in some cases of Reye's syndrome, leading to severe restrictions on the indications for aspirin therapy in children. For further details see under Reye's Syndrome, below.