ranofin and monthly thereafter; licensed product information advises that auranofin should be withdrawn if the platelet count falls below 100 000 cells/mm^3 or if signs and symptoms suggestive of thrombocytopenia, leucopenia or aplastic anaemia occur. US licensed product information states that baseline renal and liver function levels should also be established before starting auranofin therapy. Auranofin should be used with caution in patients with inflammatory bowel disease.

Porphyria. Auranofin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions
As for Sodium Aurothiomalate, p.123.

Pharmacokinetics
Auranofin is incompletely absorbed from the gastrointestinal tract, only about 25% of the gold being absorbed. Gold from auranofin is bound to plasma proteins as well as to red blood cells. After 2 to 3 months of treatment the steady-state concentration of gold in the blood is reported to be about 0.7 micrograms/mL. The average terminal plasma half-life of gold at steady state is about 26 days while the biological half-life is 80 days. Tissue retention and total gold accumulation in the body are less than with intramuscular gold. Gold from auranofin penetrates into synovial fluid.

Most of a dose of auranofin appears in the faeces due to its poor absorption. About 60% of the absorbed gold from auranofin is excreted in the urine and the remainder in the faeces.

◊ Reviews.

1. Blocka KLN, *et al*. Clinical pharmacokinetics of oral and injectable gold compounds. *Clin Pharmacokinet* 1986; **11:** 133–43.
2. Benn HP, *et al.* Pharmacokinetics of auranofin: a single dose study in man. *J Rheumatol* 1990; **17:** 466–8.

Uses and Administration
Auranofin is a gold compound with a gold content of about 29%; it has similar actions and uses to those of sodium aurothiomalate (p.123). It is given orally in active progressive rheumatoid arthritis (below); such oral treatment is less toxic than intramuscular gold but is also much less effective. The usual initial dose of auranofin is 6 mg daily given in two divided doses at first, then, if tolerated, as a single dose. Treatment should be continued for at least 6 months to assess the response; the dose may be increased after 6 months, if the response is inadequate, to 3 mg three times daily. If the response is still inadequate after 3 months at this dosage, then treatment should be stopped.

Asthma. A systematic review[1] found that oral or parenteral gold compounds reduced corticosteroid requirements in the management of asthma (p.1108); however, it was considered that the effect was probably of limited clinical significance and, given the adverse effects and monitoring requirements of gold compounds, their use in asthma could not be recommended.

1. Evans DJ, *et al*. Gold as an oral corticosteroid sparing agent in stable asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 25/10/06).

Lupus. Since the introduction of less toxic drugs gold compounds are now rarely used in the treatment of SLE, however, there have been anecdotal reports suggesting that auranofin may still be of use in patients with discoid lupus erythematosus[1] or cutaneous lupus erythematosus[2] refractory to conventional treatment.

1. Dalziel K, *et al*. Treatment of chronic discoid lupus erythematosus with an oral gold compound (auranofin). *Br J Dermatol* 1986; **115:** 211–16.
2. Farrell AM, Bunker CB. Oral gold therapy in cutaneous lupus erythematosus (revisited). *Br J Dermatol* 1996; **135** (suppl 47): 41.

Pemphigus. A patient with long-standing pemphigus foliaceus being treated with prednisolone and hydroxychloroquine had healing of his lesions within 6 months of auranofin being substituted for the hydroxychloroquine.[1]

1. Bagheri MM, *et al*. Pemphigus foliaceus presenting as eruptive seborrheic keratosis and responding to oral gold treatment. *J Drugs Dermatol* 2002; **1:**333–4.

Psoriasis. Although topical auranofin has been shown in a placebo-controlled study[1] to be effective in the treatment of plaque-type psoriasis (p.1583) the high incidence of adverse skin reactions, such as contact dermatitis, was thought to outweigh any benefit.

1. Helm KF, *et al*. Topical auranofin ointment for the treatment of plaque psoriasis. *J Am Acad Dermatol* 1995; **33:** 517–19.

Rheumatic disorders. Gold compounds are among the disease-modifying antirheumatic drugs (DMARDs) that may be used in the treatment of rheumatoid arthritis (p.11). Oral gold is less toxic than intramuscular gold but is also much less effective. Gold compounds may also be of benefit in psoriatic arthritis (see under Spondyloarthropathies, p.13) and have been used in juvenile idiopathic arthritis (p.10).

References.

1. Suarez-Almazor ME, *et al.* Auranofin versus placebo in rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 09/05/05).

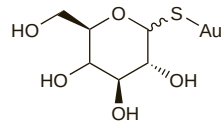
Preparations
Proprietary Preparations (details are given in Part 3)
Austral.: Ridaura; ***Austria:*** Ridaura; ***Belg.:*** Ridaura; ***Braz.:*** Ridaura†; ***Canad.:*** Ridaura†; ***Denm.:*** Ridaura†; ***Fin.:*** Ridaura; ***Fr.:*** Ridauran; ***Ger.:*** Ridaura; ***Gr.:*** Ridaura; ***Hong Kong:*** Ridaura; ***India:*** Goldar; ***Irl.:*** Ridaura; ***Israel:*** Ridaura; ***Ital.:*** Ridaura; ***Neth.:*** Ridaura; ***Norw.:*** Ridaura; ***NZ:*** Ridaura; ***Port.:*** Ridaura; ***Rus.:*** Auropan (Ауропан); ***S.Afr.:*** Ridaura; ***Spain:*** Ridaura; ***Swed.:*** Ridaura†; ***Switz.:*** Ridaura; ***UK:*** Ridaura; ***USA:*** Ridaura.

Aurothioglucose

1-Aurothio-D-glucopyranose; Aurotioglucosa; (D-Glucosylthio)-gold; Gold Thioglucose. (1-Thio-D-glucopyranosato)gold.

Ауротиоглюкоза

$C_6H_{11}AuO_5S$ = 392.2.
CAS — 12192-57-3.
ATC — M01CB04.
ATC Vet — QM01CB04.



Pharmacopoeias. In *US.*
USP 31 (Aurothioglucose). A yellow odourless or practically odourless powder. An aqueous solution is unstable on long standing. It is stabilised by the addition of a small amount of sodium acetate. pH of a 1% solution in water is about 6.3. Freely soluble in water; practically insoluble in alcohol, in acetone, in chloroform, and in ether. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions
As for Sodium Aurothiomalate, p.122.

Effects on the blood. Thrombocytopenia developed in 2 patients treated with intramuscular aurothioglucose.[1]

1. Levin M-D, *et al*. Two patients with acute thrombocytopenia following gold administration and five-year follow-up. *Neth J Med* 2003; **61:** 223–5.

Interactions
As for Sodium Aurothiomalate, p.123.

Pharmacokinetics
As for Sodium Aurothiomalate, p.123; absorption is slower and more irregular.

Uses and Administration
Aurothioglucose is a gold compound with a gold content of about 50%; it has similar actions and uses to those of sodium aurothiomalate (p.123). It is used in the treatment of active rheumatoid arthritis (p.11) and juvenile idiopathic arthritis (p.10). Aurothioglucose is given intramuscularly as a suspension in oil in an initial weekly dose of 10 mg increasing gradually to up to 50 mg weekly. Therapy is continued at weekly intervals until a total dose of 0.8 to 1 g has been given; if improvement has occurred with no signs of toxicity 50 mg may then be given at intervals of 3 to 4 weeks. Children aged 6 to 12 years have been given one-quarter the adult dose, to a maximum of 25 mg per dose.

◊ For comment on the relative efficacy and tolerability of aurothioglucose and aurothiomalate see Rheumatic Disorders, under Sodium Aurothiomalate, p.124.

Preparations
USP 31: Aurothioglucose Injectable Suspension.

Proprietary Preparations (details are given in Part 3)
Canad.: Solganal†; ***Israel:*** Solganal; ***Neth.:*** Auromyose†; ***USA:*** Solganal.

Aurotioprol

Sodium 3-aurothio-2-hydroxypropane-1-sulphonate.

Ауротиопрол

$C_3H_6AuNaO_4S_2$ = 390.2.
CAS — 27279-43-2.
ATC — M01CB05.
ATC Vet — QM01CB05.

Profile
Aurotioprol is a gold compound with a gold content of about 50%; it has similar actions and uses to those of sodium aurothiomalate (p.122). It is given by intramuscular injection for the treatment of rheumatoid arthritis (p.11). The initial dose is 25 mg weekly, increased to 50 to 100 mg weekly, until a total dose of 1.2 to 1.5 g has been given. If improvement has occurred with no signs of toxicity, this may be followed by a dose of 50 to 100 mg intramuscularly every month.

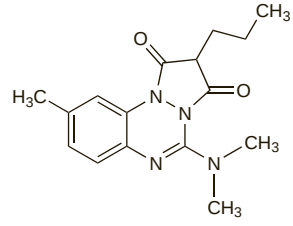
Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Allochrysine†; ***Fr.:*** Allochrysine.

Azapropazone *(BAN, rINN)*

AHR-3018; Apazone *(USAN)*; Atsapropatsoni; Azapropazon; Azapropazona; Azapropazonum; Mi85; NSC-102824. 5-Dimethylamino-9-methyl-2-propylpyrazolo[1,2-*a*][1,2,4]benzotriazine-1,3(2*H*)-dione.

Азапропазон

$C_{16}H_{20}N_4O_2$ = 300.4.
CAS — 13539-59-8.
ATC — M01AX04.
ATC Vet — QM01AX04.



Pharmacopoeias. *Br.* includes the dihydrate.
BP 2008 (Azapropazone). The dihydrate is a white to pale yellow crystalline powder. Very slightly soluble in water and in chloroform; soluble in alcohol; dissolves in solutions of alkali hydroxides.

Profile
Azapropazone is an NSAID (see p.96), structurally related to phenylbutazone (p.117). It also has uricosuric properties. Because azapropazone appears to be associated with a higher incidence of adverse effects than with some other NSAIDs, its use has been restricted to the treatment of rheumatoid arthritis, ankylosing spondylitis, and acute gout in patients for whom other NSAIDs have been ineffective.

Azapropazone is used as the dihydrate and doses are expressed in terms of this hydrated form. For the treatment of rheumatoid arthritis or ankylosing spondylitis the usual oral dose was up to 1.2 g daily in 2 divided doses. Patients *over 60 years of age* have been given 300 mg twice daily. Reduced doses were also recommended in patients with renal impairment, see below.

Administration in renal impairment. In the treatment of *rheumatoid arthritis* or *ankylosing spondylitis* in patients with reduced renal function the usual dose was reduced according to creatinine clearance (CC) as follows:

- CC 50 to 75 mL/minute: reduce usual dose (see above) by one-third to one-half
- CC less than 50 mL/minute: reduce usual dose by one-half to two-thirds

Breast feeding. Small quantities of azapropazone are excreted into breast milk.[1] However, the American Academy of Pediatrics[2] states that there have been no reports of any clinical effect on the infant associated with the use of azapropazone by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. Bald R, *et al*. Excretion of azapropazone in human breast milk. *Eur J Clin Pharmacol* 1990; **39:** 271–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/11/07)

Effects on the blood. Auto-immune haemolytic anaemia, occasionally fatal, often with pulmonary infiltration, allergic alveolitis, pulmonary fibrosis, or fibrosing alveolitis, has been reported in patients receiving azapropazone.[1-3]

1. Chan-Lam D, *et al*. Red cell antibodies and autoimmune haemolysis after treatment with azapropazone. *BMJ* 1986; **293:** 1474.

2. Albazzaz MK, *et al.* Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1986; **293:** 1537–8.
3. Montgomery RD, Babb RG. Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1987; **294:** 375.

Effects on the gastrointestinal tract. In a review[1] of the relative safety of 7 oral NSAIDs, the UK CSM commented that azapropazone was associated with the highest risk of gastrointestinal reactions in both epidemiological studies and an analysis of spontaneous reporting of adverse reactions. Although it appeared that some patients over 60 years of age had received doses exceeding those recommended for this age group, it was considered that even when this was taken into account a marked difference remained between gastrointestinal reactions for azapropazone compared with other NSAIDs.

The CSM recommended that azapropazone should be restricted to use in rheumatoid arthritis, ankylosing spondylitis, and acute gout and only when other NSAIDs have been ineffective. Its use in patients with a history of peptic ulceration was contra-indicated. It was also recommended that when used in patients over 60 years of age for rheumatoid arthritis or ankylosing spondylitis the dose should be restricted to a maximum of 600 mg daily.

Azapropazone has been withdrawn in many countries including the UK.

1. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Effects on the skin. Of 917 reports of adverse reactions associated with azapropazone forwarded to the WHO Collaborating Centre for International Drug Monitoring[1] before September 1984, 190 (21%) were of photosensitivity. Of 154 reports of photosensitivity evaluated a causal relationship to use of azapropazone was considered certain in 6, probable in 138, and possible in 10. In May 1994 the UK CSM stated[2] that since 1976 they had received 464 reports of photosensitivity reactions associated with azapropazone and commented that, when corrected for prescription volume, reporting of this reaction was 50 times greater than with other commonly prescribed NSAIDs. They recommended that patients should be advised to avoid direct exposure to sunlight or to use sunblock preparations.

1. Olsson S, *et al.* Photosensitivity during treatment with azapropazone. *BMJ* 1985; **291:** 939.
2. CSM/MCA. Photosensitivity associated with azapropazone (Rheumox). *Current Problems* 1994; **20:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Porphyria. Azapropazone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Preparations

BP 2008: Azapropazone Capsules; Azapropazone Tablets.

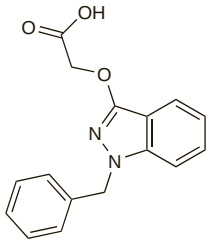
Proprietary Preparations (details are given in Part 3)
Arg.: Debelex†; ***Austria:*** Prolixan†; ***Gr.:*** Prolixan†; ***Hung.:*** Prolixan†; ***Irl.:*** Rheumox†; ***Port.:*** Prolixan†; ***S.Afr.:*** Rheumox; ***Turk.:*** Prodisan; ***UK:*** Rheumox†.

Bendazac *(BAN, USAN, rINN)*

AF-983; Bendazaco; Bendazacum; Bindazac. (1-Benzyl-1*H*-indazol-3-yloxy)acetic acid.

Бендазак

$C_{16}H_{14}N_2O_3$ = 282.3.
CAS — 20187-55-7.
ATC — M02AA11; S01BC07.
ATC Vet — QM02AA11; QS01BC07.



Bendazac Lysine *(BANM, rINNM)*

AF-1934; Bendazac lisina; Bendazacum Lysinum. L-Lysine-(1-benzyl-1*H*-indazol-3-yloxy)acetic acid.

Бендазак Лизин

$C_{22}H_{28}N_4O_5$ = 428.5.
CAS — 81919-14-4.
ATC — S01BC07.
ATC Vet — QS01BC07.

Pharmacopoeias. In *Chin.*

Profile

Bendazac is an NSAID (p.96) structurally related to indometacin (p.66). It has been used topically in preparations containing 1 or 3% for the treatment of various inflammatory skin disorders.

Bendazac lysine has been used in the management of cataract, eye drops containing 0.5% being instilled three times daily.

Hepatotoxicity has been reported.

◊ References.

1. Balfour JA, Clissold SP. Bendazac lysine: a review of its pharmacological properties and therapeutic potential in the management of cataracts. *Drugs* 1990; **39:** 575–96.
2. Prieto de Paula JM, *et al.* Hepatotoxicidad por bendazaco: análisis de 16 casos. *Rev Clin Esp* 1995; **195:** 387–9.

Preparations

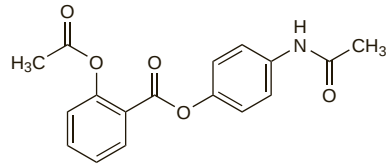
Proprietary Preparations (details are given in Part 3)
Austria: Versus; ***Gr.:*** Versalba; ***Ital.:*** Bendalina; Versus; ***Philipp.:*** Bendalina; ***Port.:*** Bendalina; ***Venez.:*** Bendalina.

Benorilate *(BAN, rINN)*

Benorilaatti; Benorilat; Bénorilate; Benorilato; Benorilatum; Benorylate; FAW-76; Fenasprate; Win-11450. 4-Acetamidophenyl *O*-acetylsalicylate.

Бенорилат

$C_{17}H_{15}NO_5$ = 313.3.
CAS — 5003-48-5.
ATC — N02BA10.
ATC Vet — QN02BA10.



Pharmacopoeias. In *Br.* and *Chin.*
BP 2008 (Benorilate). A white or almost white, odourless or almost odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone and in chloroform.

Profile

Benorilate is an aspirin-paracetamol ester with analgesic, anti-inflammatory, and antipyretic properties. After absorption, it is rapidly metabolised to salicylate and paracetamol. It has been used orally in the treatment of mild to moderate pain (see Choice of Analgesic, p.2) and fever (p.10). It has also been used in osteoarthritis, rheumatoid arthritis, and soft-tissue rheumatism.

When an overdose of benorilate is suspected, it has been suggested that plasma concentrations of both salicylate and paracetamol should be measured since a normal plasma-paracetamol concentration cannot necessarily be assumed from a normal plasma-salicylate measurement.

◊ References.

1. Aylward M. Toxicity of benorylate. *BMJ* 1973; **2:** 118.
2. Symon DNK, *et al.* Fatal paracetamol poisoning from benorylate therapy in child with cystic fibrosis. *Lancet* 1982; **ii:** 1153–4.

Preparations

BP 2008: Benorilate Oral Suspension; Benorilate Tablets.

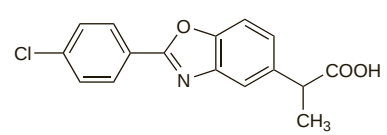
Proprietary Preparations (details are given in Part 3)
Belg.: Duvium†; ***Fr.:*** Salipran†; ***Irl.:*** Benoral†; ***Switz.:*** Duvium†; ***UK:*** Benoral†.

Benoxaprofen *(BAN, USAN, rINN)*

Benoksaprofeeni; Bénoxaprofène; Benoxaprofeno; Benoxaprofenum; Compound 90459; LRCL-3794. 2-[2-(4-Chlorophenyl)benzoxazol-5-yl]propionic acid.

Беноксапрофен

$C_{16}H_{12}ClNO_3$ = 301.7.
CAS — 51234-28-7.
ATC — M01AE06.
ATC Vet — QM01AE06.



Profile

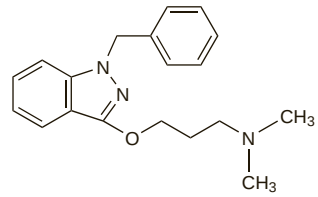
Benoxaprofen is an NSAID (p.96) structurally related to ibuprofen (p.64). It was formerly given orally in rheumatoid arthritis and osteoarthritis but because of reports of adverse reactions and fatalities the manufacturers halted worldwide marketing of the preparation known as *Opren* in the early 1980s. Adverse effects that have occurred with benoxaprofen include skin disorders, notably photosensitivity reactions but also erythema multiforme and the Stevens-Johnson syndrome, onycholysis and other nail disorders, gastrointestinal disturbances including peptic ulceration and bleeding, blood disorders such as thrombocytopenia, cholestatic jaundice and other liver or biliary disorders, and renal failure.

Benzydamine Hydrochloride *(BANM, USAN, rINNM)*

AF-864; Benzidamin Hidroklorür; Benzindamine Hydrochloride; Benzydamine, Chlorhydrate de; Benzydamini Hydrochloridum; Benzydaminy chlorowodorek; Hidrocloruro de bencidamina. 3-(1-Benzyl-1*H*-indazol-3-yloxy)-*NN*-dimethylpropylamine hydrochloride.

Бензидамина Гидрохлорид

$C_{19}H_{23}N_3O$,HCl = 345.9.
CAS — 642-72-8 (benzydamine); 132-69-4 (benzydamine hydrochloride).
ATC — A01AD02; G02CC03; M01AX07; M02AA05.
ATC Vet — QA01AD02; QG02CC03; QM01AX07; QM02AA05.



(benzydamine)

Pharmacopoeias. In *Br.* and *Pol.*
BP 2008 (Benzydamine Hydrochloride). A white crystalline powder. Very soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether. A 10% solution in water has a pH of 4.0 to 5.5.

Adverse Effects

After topical application to the skin local reactions such as erythema or rash may occur and photosensitivity has been reported. After use as mouth and throat preparations, numbness or stinging sensations of the oral mucosa have been reported; hypersensitivity reactions including urticaria, photosensitivity, and bronchospasm may also occur rarely.

Effects on the kidneys. A 57-year-old woman who had used 400 g of a topical cream containing benzydamine hydrochloride 3% over a period of 4 months was found to have raised plasma concentrations of creatinine and urea consistent with a substantial reduction in glomerular filtration rate.[1]

1. O'Callaghan CA, *et al.* Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; **308:** 110–11.

Effects on the skin. Photoallergic contact dermatitis developed on the hands of a 65-year-old woman after the use of a genital wash containing benzydamine 0.1% for several years.[1] The lesions disappeared once the patient stopped using the solution.

1. Lasa Elgezua O, *et al.* Photoallergic hand eczema due to benzydamine. *Eur J Dermatol* 2004; **14:** 69–70.

Overdose. A 6-year old girl had hallucinations[1] after receiving 500 mg of benzydamine orally; it had been intended as a vaginal douche for pruritus vulvae; recovery was spontaneous.

1. Gómez-López L, *et al.* Acute overdose due to benzydamine. *Hum Exp Toxicol* 1999; **18:** 471–3.

Uses and Administration

Benzydamine hydrochloride is an NSAID (p.99). It is used topically on the skin in concentrations of 3 to 5% in painful musculoskeletal and soft-tissue disorders. Benzydamine hydrochloride is also used as a mouthwash or spray in concentrations of 0.15% for the relief of inflammatory conditions of the mouth and throat. It has been given orally or rectally for the relief of painful and inflammatory conditions, and as a topical solution for vaginal irrigation.

Benzydamine salicylate (benzasal) has been used topically on the skin as a 6% cream or spray.

Mouth disorders. Results of a randomised placebo-controlled study in patients undergoing radiotherapy for oropharyngeal cancer indicated that benzydamine as an oral rinse was effective in reducing the area and severity of mucositis.[1] Benzydamine is also used locally for the management of mouth ulcers (p.1700) although an early study[2] found it no more useful than placebo.

1. Epstein JB, *et al.* Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Cancer* 2001; **92:** 875–85.
2. Matthews RW, *et al.* Clinical evaluation of benzydamine, chlorhexidine, and placebo mouthwashes in the management of recurrent aphthous stomatitis. *Oral Surg Oral Med Oral Pathol* 1987; **63:** 189–91.