Prolonged use of large doses of analgesic mixtures containing phenacetin has been associated with the development of renal papillary necrosis (see Effects on the Kidneys, p.98) and transitional-cell carcinoma of the renal pelvis.

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

Uses and Administration

Phenacetin, a para-aminophenol derivative, has analgesic and antipyretic properties. It was usually given with aspirin, caffeine, or codeine but is now little used because of adverse haematological effects and nephrotoxicity.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Dinyl†; Mironal†; ***Hung.:*** Antineuralgica; Dolor.

Phenazone *(BAN, rINN)*

Analgésine; Antipyrin; Antipyrine; Azophenum; Fenatsoni; Fenazon; Fenazona; Fenazonas; Phénazone; Phenazonum; Phenyldimethylpyrazolone. 1,5-Dimethyl-2-phenyl-4-pyrazolin-3-one.

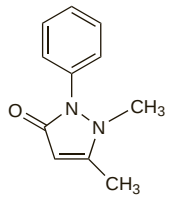
Феназон

$C_{11}H_{12}N_2O$ = 188.2.

CAS — 60-80-0.

ATC — N02BB01.

ATC Vet — QN02BB01.



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

Ph. Eur. 6.2 (Phenazone). White or almost white crystalline powder or colourless crystals. Very soluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 31 (Antipyrine). Colourless crystals or white crystalline powder. Is odourless. Very soluble in water; freely soluble in alcohol and in chloroform; sparingly soluble in ether. Solutions are neutral to litmus. Store in airtight containers.

Phenazone and Caffeine Citrate

Antipyrino-Coffeinum Citricum; Fenazona y citrato de cafeína; Migrenin; Phenzone and Caffeine Citrate.

Феназон и Кофеина Цитрат

Description. Phenazone and caffeine citrate is a powder usually containing phenazone 90%, caffeine 9%, and citric acid monohydrate 1%.

Pharmacopoeias. In *Jpn*.

Phenazone Salicylate

Antipyrin Salicylate; Fenatsonisalisylaatti; Fenazona salicilato; Fenazonsalicylat; Phenazoni Salicylas; Salipyrin.

Феназона Салицилат

$C_{11}H_{12}N_2O,C_7H_6O_3$ = 326.3.

CAS — 520-07-0.

Pharmacopoeias. In *Fr.*

Adverse Effects and Precautions

Phenazone is liable to give rise to skin eruptions and in susceptible individuals even small doses may have this effect. Hypersensitivity reactions and nephrotoxicity have been reported. Large oral doses may cause nausea, drowsiness, coma, and convulsions.

Effects on the blood. Phenazone can cause haemolytic anaemia in certain individuals with a deficiency of G6PD.[1] Episodes of agranulocytosis were reported[2] in 6 women using a cream containing phenazone; all recovered on withdrawal.

1. Prankerd TAJ. Hemolytic effects of drugs and chemical agents. *Clin Pharmacol Ther* 1963; **4:** 334–50.
2. Delannoy A, Schmit J-C. Agranulocytosis after cutaneous contact with phenazone. *Eur J Haematol* 1993; **50:** 124.

Effects on the kidneys. Phenazone is considered nephrotoxic but only limited clinical information on phenazone is available because it has been mainly used with phenacetin.[1]

1. Prescott LF. Analgesic nephropathy: a reassessment of the role of phenacetin and other analgesics. *Drugs* 1982; **23:** 75–149.

Effects on the skin. In a summary[1] of 77 cases of fixed drug eruption phenazone derivatives were considered to be the causative agent in 9 of the 14 cases that were severe generalised reactions.

1. Stubb S, *et al*. Fixed drug eruptions: 77 cases from 1981 to 1985. *Br J Dermatol* 1989; **120:** 583.

Hypersensitivity. Immediate allergic reactions to phenazone have been reported.[1,2] In one patient leucopenia was detected 8 weeks later.[1]

1. Kadar D, Kalow W. Acute and latent leukopenic reaction to antipyrine. *Clin Pharmacol Ther* 1980; **28:** 820–22.
2. McCrea JB, *et al*. Allergic reaction to antipyrine, a marker of hepatic enzyme activity. *DICP Ann Pharmacother* 1989; **23:** 38–40.

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

Interactions

Phenazone affects the metabolism of some other drugs and its own metabolism is affected by other drugs that increase or reduce the activity of liver enzymes.

Pharmacokinetics

Phenazone is absorbed from the gastrointestinal tract and peak plasma concentrations are obtained within 1 to 2 hours of ingestion. It is distributed throughout the body fluids with concentrations in the saliva and breast milk reaching about the same levels as those in plasma. Less than 10% is bound to plasma proteins and it has an elimination half-life of about 12 hours. Phenazone is metabolised in the liver to 3 major metabolites 3-hydroxymethylphenazone, 4-hydroxyphenazone, and norphenazone. Phenazone, 3-hydroxymethylphenazone, and glucuronidated metabolites are all excreted in the urine. A small portion may be eliminated via the bile.

Uses and Administration

Phenazone is an NSAID (p.99) and has been given orally; phenazone and caffeine citrate and phenazone salicylate have similarly been given orally as analgesics.

Solutions containing about 5% of phenazone have been used topically as ear drops in disorders such as acute otitis media (but see below).

Phenazone is used as a test for the activity of drug-metabolising enzymes in the liver.

Diagnosis and testing. A review[1] of normal plasma-phenazone pharmacokinetics, urinary metabolite disposition, and total body clearances of phenazone in the presence of cirrhosis, fatty liver, hepatitis, and cholestatis.

1. St Peter JV, Awni WM. Quantifying hepatic function in the presence of liver disease with phenazone (antipyrine) and its metabolites. *Clin Pharmacokinet* 1991; **20:** 50–65.

Otitis media. There appears to be no justification[1] for the inclusion of phenazone in topical preparations used in treating acute otitis media (p.182). It is presumably included in such preparations because it is believed to have a local anti-inflammatory and, therefore, analgesic action. It would, however, seem unlikely that phenazone would have any action on the skin of the intact tympanic membrane and, therefore, on the pain which is due primarily to the stretching and distention of the membrane.

1. Carlin WV. Is there any justification for using phenazone in a local application prescribed for the treatment of acute otitis media? *BMJ* 1987; **294:** 1333.

Preparations

USP 31: Antipyrine and Benzocaine Otic Solution; Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution.

Proprietary Preparations (details are given in Part 3)

Austral.: Erasol; ***Ger.:*** Aequiton-P†; Migrane-Kranit; Mono Migranin; ***Hong Kong:*** Tropex; ***Irl.:*** Tropex; ***Pol.:*** Antotalgin; ***S.Afr.:*** Aurone; Oto-Phen; ***Venez.:*** Otamina.

Multi-ingredient: ***Arg.:*** Aqua Lent Colirio; Bajumol†; Bideon; Cerosporin GS†; Clarisoft; Coliria; Cristalomicina; Irix; Kalopsis; Leroid†; Otalex G; Otocalmia Biotic; Otocerol; Otocuril; Otonorthia; Sincerum; Usualix; Vislus; ***Austral.:*** Auralgan; ***Austria:*** Asthma Efeum; Coffo Selt; Otalgan; Spalt†; ***Belg.:*** Hemorhinol; Otocalmine; Ouate Hemostatique; Tympalgine†; ***Braz.:*** Anestesiol†; Espasmalgon†; Osmotil†; Otovix†; ***Canad.:*** Auralgan; ***Cz.:*** Otipax; ***Denm.:*** Koffisal; ***Fr.:*** Brulex; HEC; Otipax; ***Ger.:*** Coffeemed N†; Migranin†; Otalgan; ***Hung.:*** Otipax; ***India:*** Tytin; ***Israel:*** Anaesthetic Ear Drops; Otidin; ***Ital.:*** Otalgan; Otomidone; Otopax; ***Neth.:*** Spalt N; ***Norw.:*** Antineuralgica; Fanalgin; ***NZ:*** Auralgan; Degest 2†; ***Philipp.:*** Auralgan; ***Port.:*** Otocalma†; Profrin-A†; ***Rus.:*** Otipax (Отипакс); ***S.Afr.:*** Auralyt; Aurasept; Aurone Forte; Covancaine; Ilvico; Otised; Oto-Phen Forte; Universal Earache Drops; ***Singapore:*** HEC†; Tropex; ***Spain:*** AB FE†; Epistaxol; Otalgan†; Otosedol; Pomada Heridas†; Quimpedor; Tabletas Quimpe; ***Swed.:*** Doleron†; Koffazon; ***Switz.:*** Otalgan; Otipax; Otosan; Otothricinol; Seranex sans codeine†; Spedralgin sans codeine†; ***Thai.:*** Auralgan†; ***USA:*** Allergen; Auralgan; Auroguard Otic; Auroto†; Cy-Gesic; Otocalm†; Tympagesic†; ***Venez.:*** Audocaina†; Otan; Otanol†; Otirilin; Otodon†; Otofrin†.

Phenazopyridine Hydrochloride

(BANM, USAN, rINNM)

Chloridrato de Fenazopiridina; Fenazopiridin Hidroklorür; Fenazopirydyny chlorowodorek; Hidrocloruro de fenazopiridina; NC-150; NSC-1879; Phénazopyridine, Chlorhydrate de; Phenazopyridini Hydrochloridum; W-1655. 3-Phenylazopyridine-2,6-diyldiamine hydrochloride.

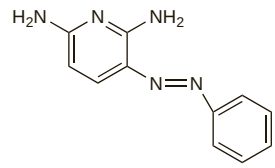
Феназопиридина Гидрохлорид

$C_{11}H_{11}N_5$,HCl = 249.7.

CAS — 94-78-0 (phenazopyridine); 136-40-3 (phenazopyridine hydrochloride).

ATC — G04BX06.

ATC Vet — QG04BX06.



(phenazopyridine)

Pharmacopoeias. In *Pol*. and *US*.

USP 31 (Phenazopyridine Hydrochloride). A light or dark red to dark violet crystalline powder. Is odourless or with a slight odour. Soluble 1 in 300 of cold water, 1 in 20 of boiling water, 1 in 59 of alcohol, 1 in 331 of chloroform, and 1 in 100 of glycerol; very slightly soluble in ether. Store in airtight containers.

Removal of stains. Phenazopyridine stains may be removed from fabric by soaking in a 0.25% solution of sodium dithionite.

Adverse Effects

Phenazopyridine hydrochloride has caused gastrointestinal adverse effects, headache, and rashes. Hepatotoxicity, haemolytic anaemia, methaemoglobinaemia, and acute renal failure have also been reported, generally associated with overdosage or with therapeutic doses in patients with renal impairment. Crystal deposits of phenazopyridine have formed in the urinary tract.

Abnormal coloration of body tissues or fluids may occur. Urine is tinged either orange or red and underclothes are apt to be stained.

Effects on the CNS. A case of aseptic meningitis, with distinct episodes of fever and confusion, was associated with the use of phenazopyridine.[1]

1. Herlihy TE. Phenazopyridine and aseptic meningitis. *Ann Intern Med* 1987; **106:** 172–3.

Overdosage. Report of a 2-year-old child who developed cyanosis and methaemoglobinaemia after ingesting at most three 200-mg tablets of phenazopyridine hydrochloride.[1]

1. Gold NA, Bithoney WG. Methemoglobinemia due to ingestion of at most three pills of pyridium in a 2-year-old: case report and review. *J Emerg Med* 2003; **25:** 143–8.

Precautions

Phenazopyridine hydrochloride is contra-indicated in patients with renal impairment or severe hepatitis and should be used with caution in those with G6PD deficiency. Treatment should be stopped if the skin or sclerae become discoloured; this may indicate accumulation as a result of impaired renal excretion. Phenazopyridine may interfere with urinalysis based on colour reactions or spectrometry.

Staining of contact lenses may occur.

Pharmacokinetics

Phenazopyridine hydrochloride is absorbed from the gastrointestinal tract. It is excreted mainly in the urine; up to 65% may be excreted as unchanged phenazopyridine and 18% as paracetamol.

Uses and Administration

Phenazopyridine is an azo dye that exerts an analgesic effect on the mucosa of the urinary tract and is used to provide symptomatic relief of pain and irritability in conditions such as cystitis and prostatitis (see p.2178 and p.2181, respectively), and urethritis (p.199). Phenazopyridine hydrochloride has been given in usual oral doses of about 200 mg three times daily after food. If given with an antibacterial for the treatment of urinary-tract infections (p.199), treatment should usually not exceed 2 days, although lower doses have been given as part of a combined preparation for at least a week.

Urinary-tract infections. There is currently no well-substantiated role for phenazopyridine in the treatment of urinary-tract infections and its adverse effects are potentially serious.[1]

1. Zelenitsky SA, Zhanel GG. Phenazopyridine in urinary tract infections. *Ann Pharmacother* 1996; **30:** 866–8.

Preparations

USP 31: Phenazopyridine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cistalgina; ***Belg.:*** Uropyrine; ***Braz.:*** Pyridium; Pyrisept; Urologin; Urotril†; ***Canad.:*** Phenazo; Pyridium†; ***Chile:*** Nazamit; Nordox; Pyridium†; ***Hong Kong:*** CP-Pyridine; Phenadine; Pyridium; ***India:*** Pyridium; ***Indon.:*** Pyridium; Urogetix; ***Israel:*** Sedural; ***Mex.:*** Alvena; Azofur; Bioferina; Pirimir; Urezol; ***Philipp.:*** Azomir; ***Pol.:*** Nefrecil; ***S.Afr.:*** Pyridium; ***Singapore:*** Urogesic; ***Thai.:*** Ammilazo; Anazo; Phendiridine; Sumedium; ***USA:*** Azo-Standard; Baridium; Prodium; Pyridiate†; Pyridium; Re-Azo; Urogesic; ***Venez.:*** Pyridium†.

Multi-ingredient: ***Arg.:*** Bacti-Uril; Nor 2; Priper Plus; Uro-Bactrim†; Urotem Dol; ***Braz.:*** Minazol; Uro-Baxapril†; Urobiotic†; Urocrtin; Urofen†; Uropac; Uropielon; ***Chile:*** Uro-Micinovo; ***Ger.:*** Urospasmon†; ***India:*** Nephrogesic; ***Mex.:*** Azo-Uronalin; Azo-Wintomylon; Azogen; Mictasol; Nalixone; Naxilan-Plus; Pirifur; Urovec; Vodelan; ***Spain:*** Micturol Sedante; ***Turk.:*** Azo Gantrisin; Azosilin; Uriseptin; ***USA:*** Phenazopyridine Plus; Pyridium Plus; Trellium Plus; Urelief Plus; Urobiotic-250; ***Venez.:*** Azo-Mandelamine; Bacteval.