Phenylbutazone *(BAN, rINN)*

Butadione; Fenilbutazon; Fenilbutazona; Fenilbutazonas; Fenylbutazon; Fenylobutazon; Fenyylibutatsoni; Phénylbutazone; Phenylbutazonum. 4-Butyl-1,2-diphenylpyrazolidine-3,5-dione.

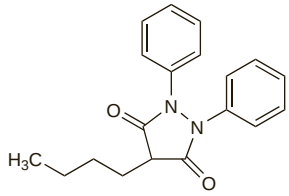
Фенилбутазон

$C_{19}H_{20}N_2O_2$ = 308.4.

CAS — 50-33-9 (phenylbutazone); 129-18-0 (phenylbutazone sodium); 4985-25-5 (phenylbutazone piperazine).

ATC — M01AA01; M02AA01.

ATC Vet — QM01AA01; QM02AA01.



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

Ph. Eur. 6.2 (Phenylbutazone). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; it dissolves in alkaline solutions. Protect from light.

USP 31 (Phenylbutazone). A white to off-white, odourless, crystalline powder. Very slightly soluble in water; soluble in alcohol; freely soluble in acetone and in ether. Store in airtight containers.

Profile

Phenylbutazone, a pyrazolone derivative, is an NSAID (p.96). However, because of its toxicity and in particular its adverse haematological reactions (see Effects on the Blood, below), it is not used as a general analgesic or antipyretic. Although phenylbutazone is effective in almost all musculoskeletal and joint disorders including ankylosing spondylitis, acute gout, osteoarthritis, and rheumatoid arthritis, it should only be used in acute conditions where less toxic drugs have failed. Initial oral doses of up to 600 mg daily in divided doses have been used in the treatment of rheumatic disorders although up to 800 mg daily may be required in acute gout. After 1 to 3 days, the dose should be reduced to the minimum effective amount, which may be as little as 200 mg daily; treatment should be given for the shortest period possible, up to a usual maximum of 1 week. Reduced doses are recommended in elderly patients.

In some countries phenylbutazone has also been given as a rectal suppository and applied topically for musculoskeletal pain and in soft-tissue injury. It has also been given intramuscularly as the sodium salt. Other salts of phenylbutazone that have been used in musculoskeletal, joint, and soft-tissue disorders include the calcium, megallate, and piperazine salts.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given phenylbutazone, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. However, when phenylbutazone had been available in the UK the *BNF* had advised that phenylbutazone should be avoided during breast feeding as small amounts are distributed into breast milk.

1. 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 08/11/07)

Effects on the blood. Both phenylbutazone[1-3] and oxyphenbutazone[1,3] are well known for their adverse effects on the blood and especially for fatal agranulocytosis and aplastic anaemia. Leucopenia, pancytopenia, haemolytic anaemia, and thrombocytopenia may also occur. The UK CSM[4] noted that between July 1963 and January 1993 it had received 74 reports of agranulocytosis (39 fatal) associated with phenylbutazone and 40 reports of neutropenia (4 fatal). Up-to-date figures were not provided on oxyphenbutazone, but it is considered to be more toxic to the bone marrow than phenylbutazone.[1]

1. Anonymous. Phenylbutazone and oxyphenbutazone: time to call a halt. *Drug Ther Bull* 1984; **22:** 5–6.
2. Böttiger LE, Westerholm B. Drug-induced blood dyscrasias in Sweden. *BMJ* 1973; **3:** 339–43.
3. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
4. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)

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

Preparations

Proprietary Preparations (details are given in Part 3)

Belg.: Butazolidin; ***Braz.:*** Butazolidina; Butazolon†; Butazona; Butazonil†; Neo Butazol; Peralgin†; ***Fr.:*** Butazolidine†; ***Ger.:*** Ambene; exrheudon OPT; ***Indon.:*** Akrofen; Berlizon; Irgapan; ***Ital.:*** Kadol; ***Mex.:*** Astrofen; Bloken; Bresal; Butalen; Butazolidina; Delbulasa†; Fezona†; Lorfenil†; Meprosona-F; Rudesol†; ***Neth.:*** Butazolidin; ***Pol.:*** Butapirazol; ***Port.:*** Basireuma†; ***Rus.:*** Butadion (Бутадион); ***S.Afr.:*** Inflazone; ***Spain:*** Butazolidina; ***Switz.:*** Butadion; ***Thai.:*** Buta†; Neo-Pyrazol; ***Venez.:*** Promifen†; Ticinil.

Multi-ingredient: ***Austria:*** Ambene; Ambene N; ***Braz.:*** Butazil†; Dorend†; Mioflex; Reumat†; Reumix†; ***Chile:*** Balsamo Analgesico con Fenilbutazona; ***Fr.:*** Dextrarine Phenylbutazone; ***Ger.:*** Ambene Comp†; ***Hung.:*** Rheosolon; ***Indon.:*** Butamidon; Cetapyrin; Enkapyrin; New Skelan; ***Mex.:*** Butayonacol; Butisel; Dexadutil; Dibutasona; Vengesic†; Zolidime†; ***Rus.:*** Ambene (Амбене); ***Spain:*** Artrodesmol Extra; Doctofril Antiinflamat; ***Switz.:*** Butaparin; Hepabuzone; ***Thai.:*** Alaxan; Asialax; Buta Pee Dee†; Butarion; Myophen; Trabit†.

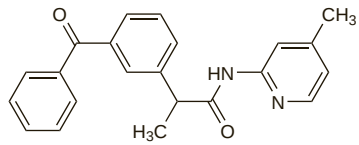
Piketoprofen *(rINN)*

Pikétoprofène; Piketoprofeno; Piketoprofenum. *m*-Benzoyl-*N*-(4-methyl-2-pyridyl)hydratropamide.

Пикетопрофен

$C_{22}H_{20}N_2O_2$ = 344.4.

CAS — 60576-13-8.



Profile

Piketoprofen is an NSAID (p.96) that has been used topically as the hydrochloride in concentrations of about 2% in musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Port.: Picalm; Zemalex; ***Spain:*** Calmatel; Triparsean.

Piritramide *(BAN, rINN)*

Pirinitramide; Piritramid; Piritramida; Piritramidi; Piritramidum; R-3365. 1-(3-Cyano-3,3-diphenylpropyl)-4-piperidinopiperidine-4-carboxamide.

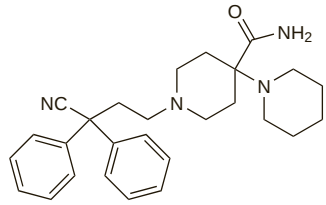
Пиритрамид

$C_{27}H_{34}N_4O$ = 430.6.

CAS — 302-41-0.

ATC — N02AC03.

ATC Vet — QN02AC03.



Profile

Piritramide is an opioid analgesic (p.101).

It is used for the management of severe pain including postoperative pain, for premedication, and to provide analgesia during anaesthesia. It is given by intramuscular, subcutaneous, or slow intravenous injection as the tartrate in doses equivalent of up to about 30 mg of the base.

◊ Reviews.

1. Kumar N, Rowbotham DJ. Piritramide. *Br J Anaesth* 1999; **82:** 3–5.

Porphyria. Piritramide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Dipidolor; ***Belg.:*** Dipidolor; ***Cz.:*** Dipidolor; ***Ger.:*** Dipidolor; ***Neth.:*** Dipidolor.

Piroxicam *(BAN, USAN, rINN)*

CP-16171; Piroksikaami; Piroksikam; Piroksikamas; Piroxicamum; Piroxikám; Piroxikam. 4-Hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

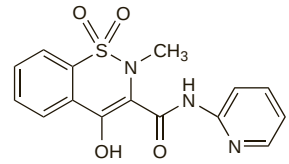
Пироксикам

$C_{15}H_{13}N_3O_4S$ = 331.3.

CAS — 36322-90-4.

ATC — M01AC01; M02AA07; S01BC06.

ATC Vet — QM01AC01; QM02AA07; QS01BC06.



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

Ph. Eur. 6.2 (Piroxicam). A white or slightly yellow, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Piroxicam). An off-white to light tan or light yellow, odourless powder. It forms a monohydrate that is yellow. Very slightly soluble in water, in dilute acids, and in most organic solvents; slightly soluble in alcohol and in aqueous alkaline solutions. Store in airtight containers. Protect from light.

Piroxicam Betadex *(USAN, rINNM)*

CHF-1194; Piroxicam Beta Cyclodextrin; Piroxicam Beta Cyclodextrin Complex; Piroxicam Bétadex; Piroxicamum Betadexum.

Пироксикам Бетадекс

$(C_{15}H_{13}N_3O_4S)_2.(C_{42}H_{70}O_{35})_5$ = 6337.6.

CAS — 96684-40-1.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

Local irritation and occasionally bleeding may occur with piroxicam suppositories and there may be pain and occasionally tissue damage at the injection site on intramuscular use. Application site reactions have also occurred with topical preparations of piroxicam.

Piroxicam is considered to be associated with an intermediate risk of gastrointestinal effects although there is some suggestion that the risk may be higher than for other intermediate-risk NSAIDs (p.97).

◊ A report[1] of the adverse reactions associated with piroxicam in South Africa during 1981-86 included two reactions, paraesthesia and hair loss, not previously recorded in the literature.

1. Gerber D. Adverse reactions of piroxicam. *Drug Intell Clin Pharm* 1987; **21:** 707–10.

Effects on the blood. Decreases in haemoglobin and haematocrit not associated with obvious gastrointestinal bleeding, have occurred in patients taking piroxicam. Thrombocytopenia, thrombocytopenic purpura,[1] and aplastic anaemia[2] have been described in patients on piroxicam.

1. Bjørnstad H, Vik Ø. Thrombocytopenic purpura associated with piroxicam. *Br J Clin Pract* 1986; **40:** 42.
2. Lee SH, *et al.* Aplastic anaemia associated with piroxicam. *Lancet* 1982; **i:** 1186.

Effects on electrolytes. Reversible hyperkalaemic hyperchloraemic acidosis has been reported[1,2] in patients receiving piroxicam. Severe hyponatraemia and symptoms resembling the syndrome of inappropriate antidiuretic hormone secretion have also been associated with piroxicam.[3]

See also Effects on the Kidneys, below.

1. Grossman LA, Moss S. Piroxicam and hyperkalemic acidosis. *Ann Intern Med* 1983; **99:** 282.
2. Miller KP, *et al.* Severe hyperkalemia during piroxicam therapy. *Arch Intern Med* 1984; **144:** 2414–15.
3. Petersson I, *et al.* Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221:** 221–3.

Effects on the kidneys. Acute nephropathy with characteristic features of Henoch-Schönlein purpura,[1] acute renal failure,[2] uraemia with hyperkalaemia, and acute interstitial nephritis[3] have been associated with systemic use of piroxicam. Nephrotic syndrome and interstitial nephritis have followed topical use of piroxicam gel.[4]

1. Goebel KM, Mueller-Brodmann W. Reversible overt nephropathy with Henoch-Schönlein purpura due to piroxicam. *BMJ* 1982; **284:** 311–12.
2. Frais MA, *et al.* Piroxicam-induced renal failure and hyperkalemia. *Ann Intern Med* 1983; **99:** 129–30.
3. Mitnick PD, Klein WJ. Piroxicam-induced renal disease. *Arch Intern Med* 1984; **144:** 63–4.
4. O'Callaghan CA, *et al.* Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; **308:** 110–11.