

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Cosaldon†.

Multi-ingredient: **S.Afr.:** Cosaldon†.

Pentosan Polysulfate Sodium (BAN, USAN, rINN)

Natrii pentosani polysulfas; Natrii Pentosani Polysulfas; Natriumpentosanipolysulfat; Natriumpentosanpolysulfat; Pentosan Polysulfate Sodium; Pentosane polysulfate sodique; Pentosano polisulfato de sodio; PZ-68; Sodium Pentosan Polysulfate; Sodium Xylanpolysulfate; SP-54.

Натрия Пентозана Полисульфат

CAS — 37319-17-8; 116001-96-8.

ATC — C05BA04.

ATC Vet — QC05BA04.

Description. Pentosan polysulfate sodium is a mixture of linear polymers of β -1 \rightarrow 4-linked xylose, usually sulfated at the 2- and 3-positions and occasionally (approximately 1 in every 4 residues) substituted at the 2-position with 4-O-methyl- α -D-glucuronic acid 2,3-O-sulfate. The average molecular weight lies between 4000 and 6000 with a total molecular weight range of 1000 to 40 000.

Adverse Effects and Precautions

As for Heparin, p.1301. Gastrointestinal disturbances may also occur.

Uses and Administration

Pentosan polysulfate sodium is a heparinoid with anticoagulant and fibrinolytic properties; it may also have hypolipidaemic and anti-inflammatory effects. It is used in thromboembolic disorders, although its anticoagulant effect is less than that of heparin. It is also used in the management of interstitial cystitis (see below) and has been tried in a number of other conditions, including variant Creutzfeldt-Jakob disease (see below). Pentosan polysulfate sodium has been used orally, parenterally, and topically.

In the management of interstitial cystitis, pentosan polysulfate sodium is given orally in a dose of 100 mg three times daily.

Cystitis. Pentosan polysulfate sodium has been used in inflammatory conditions of the bladder, including interstitial cystitis (p.2179) and is thought to act by enhancing the protective effect of mucins at the bladder surface.¹ Studies have differed concerning its efficacy in the treatment of interstitial cystitis and an analysis² of placebo-controlled trials concluded that pentosan polysulfate sodium was more effective in treating pain, urgency, and frequency, but that the difference was small. Any benefit is usually apparent within 3 to 6 months and only occurs in a minority of patients.³ Pentosan polysulfate sodium was reported⁴ to have minimal long-term efficacy in a group of patients with severe or refractory interstitial cystitis.

Pentosan polysulfate sodium has also been reported⁵⁻⁷ to be useful in the control of radiation-induced haemorrhagic cystitis (p.2178).

- Anderson VR, Perry CM. Pentosan polysulfate: a review of its use in the relief of bladder pain or discomfort in interstitial cystitis. *Drugs* 2006; **66**: 821–35.
- Hwang P, et al. Efficacy of pentosan polysulfate in the treatment of interstitial cystitis: a meta-analysis. *Urology* 1997; **50**: 39–43.
- Anonymous. Pentosan for interstitial cystitis. *Med Lett Drugs Ther* 1997; **39**: 56.
- Jepsen JV, et al. Long-term experience with pentosanpolysulfate in interstitial cystitis. *Urology* 1998; **51**: 381–7.
- Parsons CL. Successful management of radiation cystitis with sodium pentosanpolysulfate. *J Urol (Baltimore)* 1986; **136**: 813–14.
- Hampson SJ, Woodhouse CRJ. Sodium pentosanpolysulfate in the management of haemorrhagic cystitis: experience with 14 patients. *Eur Urol* 1994; **25**: 40–2.
- Sandhu SS, et al. The management of haemorrhagic cystitis with sodium pentosan polysulfate. *BJU Int* 2004; **94**: 845–7.

Prostatitis. Pentosan polysulfate sodium is one of a number of drugs that have been tried in the management of prostatitis (p.2181). An improvement in symptoms was reported¹ in an uncontrolled study of oral pentosan polysulfate sodium in men with chronic prostatitis/chronic pelvic pain syndrome. A randomised study² using pentosan polysulfate sodium 300 mg three times daily found that symptoms were moderately or markedly improved at the end of the 16-week treatment period in more members of the active treatment group than in the group given placebo.

- Nickel JC, et al. Pentosan polysulfate therapy for chronic non-bacterial prostatitis (chronic pelvic pain syndrome category II-A): a prospective multicenter clinical trial. *Urology* 2000; **56**: 413–17.
- Nickel JC, et al. Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. *J Urol (Baltimore)* 2005; **173**: 1252–5.

Variant Creutzfeldt-Jakob disease. Variant Creutzfeldt-Jakob disease (vCJD) is a transmissible spongiform encephalopathy believed to be caused by infection of the nervous system with prions. Pentosan polysulfate sodium has been tried in small

numbers of patients with vCJD, although there is little published research data. In 2003 the UK Department of Health¹ took advice from the CJD Therapy Advisory Group and the CSM; both groups considered that there was insufficient information on which to base prescribing regimens, and further work was needed.

- UK Department of Health. Use of pentosan polysulfate in the treatment of, or prevention of, vCJD. Available at: http://www.dh.gov.uk/en/PublicHealth/CommunicableDiseases/CJD/CJDgeneralinformation/DH_4031039 (accessed 19/08/08)

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Elmiron; **Austral.:** Elmiron†; **Austria:** Polyanyon; **Canad.:** Elmiron; **Fr.:** Hemoclar; **Ger.:** Fibrezym; **Hong Kong:** Elmiron; SP 54†; **Hung.:** SP 54; **Ital.:** Fibrase; **Malaysia:** SP 54; **Port.:** Fibrocid; **S.Afr.:** Tavan-SP 54; **Spain:** Thrombicid; **USA:** Elmiron.

Multi-ingredient: **Austria:** Thrombicid; **Cz.:** Thrombicid; **Ger.:** Thrombicid; **Hong Kong:** Anso; **Thrombicid**; **Port.:** Thrombicid; **Spain:** Anso; **Switz.:** Thrombicid.

Pentoxifylline (BAN, USAN, rINN)

BL-191; Okspentifilin; Oxpentifilina; Pentoksifilin; Pentoksifilinas; Pentoksifilini; Pentoksifilina; Pentoksifilin; Pentoksifilin; Pentoksifilin; Pentoksifilinum. 3,7-Dimethyl-1-(5-oxohexyl)xanthine.

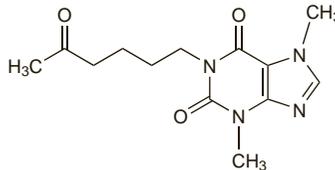
Пентоксифилин

C₁₃H₁₈N₄O₃ = 278.3.

CAS — 6493-05-6.

ATC — C04AD03.

ATC Vet — QC04AD03.



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

Ph. Eur. 6.2 (Pentoxifylline). A white or almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 31 (Pentoxifylline). A white to almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in chloroform and in methyl alcohol; slightly soluble in ether.

Adverse Effects

Pentoxifylline can cause nausea, gastrointestinal disturbances, dizziness, and headache. Flushing, angina, palpitations, cardiac arrhythmias, and hypersensitivity reactions may also occur. Bleeding events have been reported rarely, usually in association with bleeding risk factors.

Overdose with pentoxifylline may be associated with fever, faintness, flushing, hypotension, drowsiness, agitation, and seizures.

Haemorrhage. Three major bleeding episodes including 2 fatal cerebral haemorrhages were reported in a group of patients receiving pentoxifylline 400 mg three times daily together with acenocoumarol for intermittent claudication.¹ Gastrointestinal bleeding occurred in a 67-year-old patient with a history of duodenal ulcer after a single dose of pentoxifylline for optic neuropathy.²

- APIC Study Group. Acenocoumarol and pentoxifylline in intermittent claudication: a controlled clinical study. *Angiology* 1989; **40**: 237–48.
- Oren R, et al. Pentoxifylline-induced gastrointestinal bleeding. *DICP Ann Pharmacother* 1991; **25**: 315–16.

Overdose. A 22-year-old woman who took pentoxifylline 4 to 6 g with suicidal intent experienced severe bradycardia and first- and second-degree AV block; other effects included nausea, vomiting, abdominal cramps, hypokalaemia, excitation, and insomnia.¹ She recovered after intensive supportive and symptomatic treatment.

- Sznajder JJ, et al. First and second degree atrioventricular block in oxpentifilina overdose. *BMJ* 1984; **288**: 26.

Precautions

Pentoxifylline should be avoided in cerebral haemorrhage, extensive retinal haemorrhage, severe cardiac arrhythmias, and acute myocardial infarction. It should be used with caution in patients with ischaemic heart disease or hypotension. The dose of pentoxifylline may need to be reduced in patients with hepatic or renal impairment (see under Uses and Administration, below).

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

Interactions

Pentoxifylline may potentiate the effect of antihypertensives. High parental doses of pentoxifylline may enhance the action of insulin and oral hypoglycaemics in diabetic patients. Pentoxifylline should not be given with ketorolac as there is reported to be an increased risk of bleeding and/or prolongation of the prothrombin time. There may also be an increased risk of bleeding during use with meloxicam. Serum levels of theophylline may be raised by pentoxifylline.

Pharmacokinetics

Pentoxifylline is readily absorbed from the gastrointestinal tract but undergoes first-pass hepatic metabolism. Some metabolites are active. The apparent plasma half-life of pentoxifylline is reported to be 0.4 to 0.8 hours; that of the metabolites varies from 1.0 to 1.6 hours. In 24 hours most of a dose is excreted in the urine, mainly as metabolites, and less than 4% is recovered in the faeces. Elimination of pentoxifylline is decreased in elderly patients and patients with hepatic disease. Pentoxifylline and its metabolites are distributed into breast milk.

References

- Beertram B, et al. Kinetics of intravenous and oral pentoxifylline in healthy subjects. *Clin Pharmacol Ther* 1985; **37**: 25–8.
- Witter FR, Smith RV. The excretion of pentoxifylline and its metabolites into human breast milk. *Am J Obstet Gynecol* 1985; **151**: 1094–7.
- Smith RV, et al. Pharmacokinetics of orally administered pentoxifylline in humans. *J Pharm Sci* 1986; **75**: 47–52.
- Rames A, et al. Pharmacokinetics of intravenous and oral pentoxifylline in healthy volunteers and in cirrhotic patients. *Clin Pharmacol Ther* 1990; **47**: 354–9.
- Paap CM, et al. Multiple-dose pharmacokinetics of pentoxifylline and its metabolites during renal insufficiency. *Ann Pharmacother* 1996; **30**: 724–9.

Uses and Administration

Pentoxifylline is a xanthine derivative used in the treatment of peripheral vascular disease (p.1178). Although often classified as a vasodilator, its primary action seems to be a reduction in blood viscosity, probably by effects on erythrocyte deformability and platelet adhesion and aggregation. It is reported to increase blood flow to ischaemic tissues and improve tissue oxygenation in patients with peripheral vascular disease and to increase oxygen tension in the cerebral cortex and in the cerebrospinal fluid; it has been used in cerebrovascular disorders. Pentoxifylline also inhibits production of the cytokine, tumour necrosis factor alpha (TNF α), and this property is under investigation in a number of diseases (see below).

In the treatment of peripheral vascular disease the usual oral dose is 400 mg three times daily in a modified-release formulation; this may be reduced to 400 mg twice daily for maintenance or if adverse effects are troublesome. Doses should be taken with meals to reduce gastrointestinal disturbances. In severe hepatic or renal impairment, doses may need to be reduced (see below). Beneficial effects may not be evident until after 2 to 8 weeks of treatment. Pentoxifylline may also be given parenterally.

General references

- Ward A, Clissold SP. Pentoxifylline: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. *Drugs* 1987; **34**: 50–97.
- Samlaska CP, Winfield EA. Pentoxifylline. *J Am Acad Dermatol* 1994; **30**: 603–21.

Administration in hepatic and renal impairment. The elimination half-life of pentoxifylline and its metabolites is significantly prolonged in patients with hepatic cirrhosis,¹ and some metabolites have a prolonged half-life in renal impairment.² The UK manufacturers state that in patients with severely impaired hepatic function the dose of pentoxifylline may need to be reduced, while accumulation may occur in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) who receive more than 400 mg once or twice daily.

References

- Rames A, et al. Pharmacokinetics of intravenous and oral pentoxifylline in healthy volunteers and in cirrhotic patients. *Clin Pharmacol Ther* 1990; **47**: 354–9.
- Paap CM, et al. Multiple-dose pharmacokinetics of pentoxifylline and its metabolites during renal insufficiency. *Ann Pharmacother* 1996; **30**: 724–9.

Inhibition of tumour necrosis factor alpha. Pentoxifylline inhibits production of tumour necrosis factor alpha (TNF α), a cytokine that is implicated in the pathogenesis of many diseases, and investigative work with pentoxifylline is being, or has been, carried out in many such disorders. Studies have been performed in patients with alcoholic hepatitis,¹ cardiomyopathy,² cerebral malaria,^{3,4} diabetic nephropathy,⁵ leishmaniasis,^{6,7} leprosy,^{8,9} membranous nephropathy,¹⁰ radiation-induced damage,¹¹⁻¹³ severe sepsis or septic shock,¹⁴ recurrent aphthous stomatitis,¹⁵⁻¹⁷ and various vasculitic syndromes, including Behçet's syndrome.¹⁸ Pentoxifylline has also been tried for improving graft survival in kidney transplantation.^{19,20} For mention of a possible benefit in sarcoidosis, see p.1512. Although promising results