Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pronestyl Injection 100 mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml vial contains 1000 mg Procainamide Hydrochloride (100 mg/ml).

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion
Pronestyl is a colourless, mobile liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Atrial arrhythmias: Atrial tachycardia: atrial flutter/fibrillation.

Ventricular arrhythmias: Ventricular extrasystoles; ventricular tachycardia.

4.2 Posology and method of administration

Children:
Pronestyl is not recommended.

Adults:
Intravenous therapy should be reserved for more serious tachyarrhythmias, in which case administration should be under continuous ECG monitoring.

Plasma concentrations correlate well with therapeutic and toxic effects; consequently plasma level assays should be carried out if facilities are available. The usual effective antiarrhythmic serum concentration is 4 to 8 mcg/ml. Toxic manifestations are rare in concentrations less than 12 mcg/ml.

Administration:
To initiate therapy, the dose should be diluted in 5% Glucose Injection BP immediately prior to administration to facilitate control of dosage rate; the dose should be given at a rate no greater than 50 mg per minute under ECG control, and blood pressure must be taken before each dose (see Precautions). Slow administration allows for some initial tissue distribution.

Acute Control of a Tachyarrhythmia:
100 mg may be given every 5 minutes by slow injection, at a rate not exceeding 50 mg in any one minute, until the arrhythmia is suppressed or a maximum dosage of 1 gram has been administered.
Some effects may be seen after the first 100 or 200 mg and it is unusual to require more than 500 to 600 mg to achieve satisfactory antiarrhythmic effects.

Chronic Suppression of Arrhythmias:
An alternative approach to achieving and then maintaining a therapeutic plasma concentration is to infuse 500 to 600

mg of procainamide at a constant rate over a period of 25 to 30 minutes and then change to another infusion for maintenance at a rate of 2 to 6 mg/min (see Table below).

Intravenous therapy should be terminated as soon as the patient's basic cardiac rhythm appears to be stabilized and, if indicated, the patient should be placed on oral antiarrhythmic maintenance therapy. A period of 3 to 4 hours (one half-life) should elapse after the last intravenous dose of procainamide before administering the first oral dose of an antiarrhythmic.

Dilutions And Rates For Intravenous Infusions*

Approximate Final Concentration	Infusion Bottle Size (ml)	ml of Pronestyl (100mg/ml) to be added	Infusion Rate
0.2% (2mg/ml)	500 250	10 5	1-3 ml/min
0.4% (4mg/ml)	500 250	20 10	0.5-1.5 ml/min

* **Caution:** The flow rate of all intravenous infusion solutions must be closely monitored. These dilutions are calculated to deliver 2-6 mg per minute at the infusion rates listed.

Elderly:
Reduction in dose or increase in dosage interval may be necessary to maintain constant blood levels without accumulation (see Dosage and Administration).

4.3 Contraindications

Hypersensitivity to the drug is an absolute contra-indication. In this connection, cross sensitivity to procaine and related drugs must be borne in mind.

Procainamide should not be administered to patients with complete atrioventricular heart block or a high degree of A-V block unless an electrical pacemaker is operative.

"Torsade de Pointes", a variant form of ventricular tachycardia associated with a prolonged QT interval, should not be treated with Pronestyl which may aggravate rather than suppress this arrhythmia.

4.4 Special warnings and precautions for use

Myasthenia gravis: Patients with myasthenia gravis may show worsening of symptoms from procainamide due to its procaine-like effect on diminishing acetylcholine release at skeletal muscle motor nerve endings, so that procainamide administration may be hazardous without optimal adjustment of anticholinesterase medications and other precautions.

Digitalis intoxication: Procainamide may further depress conduction and ventricular asystole or fibrillation may result.

If the patient develops first degree heart block, dosage reduction and/or discontinuation of procainamide should be considered.
Patients with atrial flutter or fibrillation should be cardioverted or digitalised prior to procainamide use.
Caution in patients with congestive heart failure, acute ischaemic heart disease, cardiogenic shock or cardiomyopathy as even slight depression in myocardial contractility may reduce the cardiac output of the damaged heart.

Hypotension may occur when Pronestyl is administered intravenously Patients should be kept in a supine position and blood pressure readings made frequently. If hypotension occurs, the rate of injection should be reduced or temporarily discontinued and, if necessary, a vasopressor agent administered cautiously.

Intravenous administration should be monitored by ECG. Excessive widening of the QRS complex or prolongation of the P-R interval suggests the occurrence of myocardial toxicity and Pronestyl administration should be stopped.

Cardiotoxicity may also be reflected by the appearance of proarrhythmic effects.

In patients with significant impairment of renal or hepatic function, accumulation of Pronestyl may occur, leading to drug toxicity.

This product contains Sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm. (See Undesirable Effects).

This product contains 9.9 mg Benzyl alcohol and must not be given to premature babies or neonates. Benzyl Alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

This medicinal product contain less than 1mmol sodium per dose i.e. essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Amiodarone: Concomitant use of amiodarone may result in increased plasma procainamide concentrations and subsequent toxicity.

Other antiarrhythmic drugs: Additive effects can occur and dosage reduction may be necessary.

Antihypertensive agents: Procainamide may produce an additive effect and dosage adjustment may be necessary.

Anticholinergic drugs: Additive antivagal effects on A-V nodal conduction may occur.

Neuromuscular blocking agents: Possibly reduce dosage of neuromuscular blocking drugs as procainamide may reduce acetylcholine release.

Captopril: There have been reports of neutropenia and/or Stevens Johnson syndrome in patients on procainamide plus captopril. Although a causal relationship has not been established, this combination should only be used with caution, especially in patients with impaired renal function.

Sulphonamides: p-amino benzoic acid is a metabolite of procainamide and can inhibit the action of sulphonamides.

Trimethoprim: The renal clearance of procainamide is reduced by trimethoprim resulting in increased pharmacodynamic response.

Pharmacokinetic interactions: The elimination of procainamide may be decreased by cimetidine or propranolol, and increased by alcohol.

4.6 Pregnancy and lactation

Safety has not been established: therefore, Pronestyl should be used during pregnancy only if the possible benefits outweigh the potential risks involved. Procainamide is excreted in breast milk; therefore, it should not be given to nursing mothers because of the potential risk of adverse reactions in the infant.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Nausea, vomiting, diarrhoea, abdominal pain, anorexia, mental depression, psychosis, visual hallucinations, headache, pruritus, chills, fever and allergic reactions are usually not sufficiently severe to discontinue treatment. Neutropenia, thrombocytopenia or haemolytic anaemia may rarely be encountered.

Agranulocytosis and a Lupus-like syndrome has been reported after prolonged courses of Pronestyl. The Lupus-like syndrome seldom appears in less than two months, but is very common after six months. It is virtually completely reversible and tests for antinuclear factors are usually positive before clinical signs appear. If long-term treatment is considered desirable, it is advisable to undertake serological tests at no less than monthly intervals and to continue treatment for no longer than absolutely necessary. The patients should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these should occur, and leucocyte counts indicate cellular depression, Pronestyl therapy should be discontinued, and appropriate treatment should be instituted immediately.

Hypotension may occur particularly in conscious patients (see Precautions).

This product contains Sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.9 Overdose

After intravenous administration, but seldom after oral, hypotension may occur. Progressive widening of the QRS or AV conduction block may be seen as may increased ventricular extrasystoles or even ventricular tachycardia or fibrillation. Procainamide and N-acetyl procainamide are removed by haemodialysis but not by peritoneal dialysis. No specific antidote is known.

Overdosage should be managed by general supportive measures and close observation. Fluid expansion and the infusion of noradrenaline (8mcg/ml in sodium chloride injection BP) may be useful for hypotension; insertion of a temporary ventricular pacing system may be beneficial.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Procainamide is a class I anti-arrhythmic agent (Vaughan Williams classification). Abnormal automaticity and excitability are reduced: the former by a slowing of the rate of diastolic phase 4 depolarisation; the latter by a reduction of the rate of rise of phase 0 depolarisation.

Action potention duration is prolonged but the effect on refractory period is greater.

These actions are apparent throughout the myocardium, and are most pronounced within the atria. Abnormal ectopic foci may be suppressed by the slowing of phase 4 depolarisation, while re-entrant tachyarrhythmias may be inhibited both by the reduced excitability of the myocardium and by the prolongation of the refractory period. In those arrhythmias not fully suppressed, procainamide is likely to slow the tachycardia.

5.2 Pharmacokinetic properties

The action of procainamide begins almost immediately after intravenous administration with maximal effects being observed at 30 minutes.

Procainamide is less readily hydrolysed than procaine and plasma levels decline slowly - about 10-20% per hour. The drug is excreted primarily in the urine, about 10% as free and conjugated p-aminobenzoic acid and about 60% in the unchanged form. The remainder is mainly excreted as n-acetyl procainamide.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Sodium hydroxide
Sodium metabisulphite
Water for injections

6.2 Incompatibilities

None.

6.3 Shelf Life

2 years unopened.
Discard remaining contents of the injection 28 days after first use.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Multidose vials of USP Type I clear glass with siliconised rubber stoppers and aluminium seals, containing 10 ml colourless liquid.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharmaceuticals Ltd.
Swords
Dublin

8 MARKETING AUTHORISATION NUMBER

PA 2/34/2

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