SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bedranol*(Propranolol Hydrochloride) SR Capsules 80mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains propranolol hydrochloride 80mg.
Also contains sucrose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release capsule, hard.
Hard gelatin capsule with a blue transparent cap and body containing white and whitish/cream pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

a) Control of hypertension.

b) Management of angina.

c) Prophylaxis of migraine.

d) Management of essential tremor.

e) Management of anxiety.

f) Adjunctive management of thyrotoxicosis.

g) Prophylaxis of upper gastro-intestinal bleeding in patients with portal hypertension and oesophageal varices.

4.2 Posology and method of administration

Posology

Adults

(i) Hypertension

The initial dose is usually 160mg daily taken orally in the morning or evening. An adequate response is seen by most patients at this dosage. If necessary, it can be increased in 80 mg increments until the desired response is achieved (up to a maximum of 320 mg daily),. A further reduction in blood pressure may be achieved by combining Bedranol* SR with other anti-hypertensive agents or a diuretic.

(ii) Angina, essential tremor, thyrotoxicosis, and the prophylaxsis of migraine

The usual dose is 80 mg daily, taken orally in the morning or evening, may be sufficient to give adequate control to most patients. The dose may be increased to 160 mg, and then if necessary further increased to 240 mg per day

(iii) Situational and generalised anxiety

A daily dose of 80 mg propranolol of should be sufficient to provide short-term relief of acute situational anxiety. Generalised anxiety, requiring longer term therapy, usually responds adequately at the same dosage. In some cases the dosage may be increased to 160 mg. Patients should be reviewed after 6 – 12 months of treatment. Treatment should be continued in accordance with the patient's response.

(iv) Portal hypertension

Dosage should be aimed to achieve approximately 25% reduction in resting heart rate. Dosing should be initiated at one Bedranol* SR 80 mg Capsule increasing to 160 mg depending on heart rate response. Further 80 mg increments may be added up to a maximum dose of 320 mg once daily.

Patients who are already established on 160mg propranolol daily, one capsule of Bedranol* SR Capsules 160mg may be given, taken either in the morning or evening.

Older people

The evidence concerning the relationship between blood level and age is conflicting.

It is suggested that older people being started off on propranolol treatment may need smaller initial doses and in these circumstances Bedranol* SR Capsules 80mg or an alternative preparation should be used.

Paediatric population

Bedranol* SR is not suitable for use in children.

Method of administration

For oral use.

4.3 Contraindications

Bedranol* SR must not be used if any of the following conditions are present and hypersensitivity to the propranolol or to any of the excipients listed in section 6.1:

- hypersensitivity to propranolol or any of the other ingredients
- a history of bronchospasm or asthma.
- bradycardia
- second or third degree heart block
- sick sinus syndrome
- cardiogenic shock
- uncontrolled heart failure
- hypotension
- severe peripheral arterial disease
- Prinzmetal's angina
- untreated phaeochromocytoma
- prolonged fasting, or prone to hypoglycaemia
- metabolic acidosis.

4.4 Special warnings and precautions for use

Patients with a history of wheezing or asthma should not take propranolol unless it is considered essential. The label will carry the following warning: "Do not take this medicine if you have a history of wheezing or asthma.". The patient information leaflet will state "Do not take this medicine if you have a history of wheezing or asthma. Consult your doctor or pharmacist first.".

In patients with ischaemic heart disease treatment must not be discontinued abruptly. Either the equivalent dose of another beta-blocker may be substituted, or the withdrawal of Bedranol* SR should be gradual. This can be carried out by substituting the equivalent dose in propranolol 40mg tablets and then reducing the dose.

Bedranol* SR may aggravate peripheral arterial circulatory disturbances.

Although contraindicated in patients with uncontrolled heart failure (see Section 4.3) Bedranol* SR can be given to patients whose signs of heart failure have been controlled. Caution should be taken in patients with a poor cardiac reserve.

As propranolol has a negative effect on conduction time, care must be taken when giving it to patients with first degree heart block.

Bedranol* SR will reduce the heart rate due to its pharmacological action. Rarely a patient taking this medicine may develop symptoms that may be attributed to a slower heart rate then the dose may be reduced.

Should not be used in patients with Prinzmetal's angina and beta-1 selective agents should be used with care (see section 4.3).

Bedranol* SR should not be used concomitantly with calcium channel blockers with negative inotropic effects (e.g. verapamil, diltiazem) as it can lead to an

exaggeration of these effects particularly in patients with impaired ventricular function and/or SA or AV conduction abnormalities. This could result in severe hypotension, bradycardia and cardiac failure. Neither the beta blocker nor the calcium channel blocker should be given intravenously within 48 hours of discontinuing the other.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Intolerance to propranolol, shown as bradycardia and hypotension may occur, in which case propranolol should be withdrawn. If necessary, treatment for overdose should be started.

Beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions, they also may make patients less responsive to doses of adrenaline used to treat the allergic reactions.

Bedranol* SR may mask the signs of thyrotoxicosis.

Bedranol* SR should not be used in untreated phaeochromocytoma, but in patients with phaeochromocytoma an alpha blocker may be administered concomitantly.

Bedranol* SR should not be used to treat the elderly with cautions and start on the lowest possible dose (see section 4.2).

Care must be taken in patients with renal or hepatic dysfunction when beginning treatment and choosing the initial dose.

Bedranol* SR should be used with care in patients with decompensated cirrhosis.

In patients with portal hypertension, liver function may deteriorate. There have been reports that treatment with propranolol may increase the risk of developing hepatic encephalopathy.

Since the half life may be increased in patients with a significant hepatic or renal impairment, cautions should be taken especially at the start of treatment and the initial dosage.

Propranolol, as with other beta-blocking drugs may block the symptoms of hypoglycaemia (especially tachycardia). It may even cause hypoglycaemia in non-diabetic patients e.g. neonates, infants, children, elderly patients, patients on haemodialysis or patients suffering from chronic liver disease and patients suffering from overdose. It has rarely caused seizures and/or coma in isolated patients. Caution should be exercised in the concurrent use of propranolol therapy in diabetic patients as it may prolong the hypoglycaemic response to insulin.

Bronchospasms can usually be reversed by beta $_2$ agonist bronchodilators such as salbutamol. Large doses beta $_2$ agonist bronchodilators may be needed to overcome the beta blockade produced by propranolol and the dose should be titrated according to the clinical response; both intravenous and inhalation administration should be considered. The use of intravenous aminophylline and / or ipratropium (given via a nebuliser) should be considered. Glucagon (1 to 2 mg given intravenously) has also been reported to produce a bronchodilator effect in asthmatic patients. Oxygen or artificial ventilation may be necessary in severe cases.

When a patient is going to have surgery and a decision made to discontinue the beta-blocker therapy, this should be done at least 24 hours prior to the procedure. The risk/benefit of stopping beta blockade should be made for each patient.

Withdrawal of the drug for any reason should be gradual.

Interference with laboratory tests: Bedranol* SR has been reported to interfere with the estimation of serum bilirubin using the diazo method and with the determination of catecholamines by methods when using fluorescence.

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken when prescribing beta-adrenoceptor blocking drugs with Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone, as they may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Digitalis glycosides, in association with beta-blockers could increase the atrio-ventricular conduction time.

There is an increased risk of myocardial depression and bradycardia, there is also an increased risk of lidocaine toxicity. The antidysrhythmic propafenone increases plasma concentration of propranolol.

Beta-adrenoceptor blocking drugs should be used with caution in combination with calcium channel blockers such as verapamil or diltiazem in patients with impaired ventricular function and /or sino-atrial or atrio-ventricular conduction abnormalities. This could result in severe hypotension, bradycardia and cardiac failure. These should not be given to patients with conduction abnormalities. Beta-blockers or calcium channel blockers should not be given intravenously within 48 hours of discontinuing either one or the other.

Use with nifedipine or other dihydropyridines may cause an increased risk of hypotension, and heart failure may occur in patients with undiscovered cardiac insufficiency.

Propranolol modifies the tachycardia of hypoglycaemia and care should be taken when treating diabetic patients with Bedranol* SR whether or not they are also taking hypoglycaemic agents. Propranolol may prolong the hypoglycaemic response to insulin.

Use of adrenaline or other sympathomimetics with propranolol may counteract the effect of propranolol. Care should be taken in giving parenteral administration of adrenaline to patients taking beta-blocking drugs as, rarely, vasoconstriction, hypertension and bradycardia may result.

Rebound hypertension which can follow after withdrawal of clonidine may be exacerbated by beta-blockers. Therefore, if the patient is transferring from clonidine to propranolol, the latter treatment should be started several days after clonidine has been stopped. If Bedranol* SR and clonidine are given together, clonidine should be discontinued several days after stopping treatment with Bedranol* SR.

Digitoxin or digoxin taken at the same time as beta-blockers can increase atrioventricular conduction time.

Ergotamine, dihydroergotamine or related compounds given with propranolol have resulted in reports of vasospastic reactions in some patients.

The hypotensive effects of propranolol may be decreased if the patient also takes prostaglandin synthetase inhibitors, eg ibuprofen or indometacin.

If propranolol is taken with chlorpromazine, plasma levels of both agents may be increased, leading to enhanced antipsychotic and elevated antihypertensive effects.

Concomitant administration of rifampicin with propranolol may result in reduced plasma concentrations of propranolol. Thyroxine taken at the same time as propranolol also has this effect.

Cimetidine taken at the same time as propranolol will increase propranolol plasma levels. Fluvoxamine taken with propranolol also has this effect.

Alcohol enhances hypotensive effect, and may increase the plasma levels of propranolol.

Propranolol may affect lidocaine infusion by increasing the plasma concentration of lidocaine by approximately a third and therefore this should be avoided.

ACE inhibitors and Angiotensin-II Antagonists taken at the same time as propranolol may result in enhanced hypotensive effects. Aldesleukin and Alprostadil also has this effect.

Concomitant administration of corticosteroid may result in antagonism of hypotensive effect.

Propranolol may increase plasma concentration of rizatriptan when taken concomitantly.

Beta blockers including propranolol when taken with moxisylyte may result in severe postural hypotension

Concomitant administration of muscle relaxants may result in enhanced hypotensive effect.

Oestrogen and progestrogens, as used in the contraceptive pill, when taken with propranolol may antagonise the hypotensive effect.

The manufacturer of tropisetron advises caution for the co-administration with propranolol.

The concomitant administration of xamoterol with propranolol may result in a reduction in the beta-blockade.

Parasympathomimetics when used with propranolol increase the possibility of arrhythmias.

Caution must be exercised when using anaesthetic agents with Propranolol. The anaesthetist should be informed and the choice of anaesthetic should be the agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

Interference with laboratory tests: Propranolol has been reported to interfere with the estimation of serum bilirubin by the diazo method and with the determination of catecholamines by methods using fluorescence.

Pharmacodynamic studies have shown the following agents may interact with propranolol due to the effects on enzyme systems in the liver, which metabolise propranolol and the following agents: quinidine, propafenone, rifampicin, theophylline, warfarin, thioridazine, dihydropyridine, calcium channel blockers (e.g. nifedipine, nisoldipine, isradipine and lacidipine). Due to the fact that blood concentrations of either agent may be affected, dosage adjustments may be needed according to clinical judgement. (See also the interaction above concerning concomitant therapy with dihydropyridine calcium channel blockers).

4.6 Fertility, pregnancy and lactation

Pregnancy

Although there is no evidence that propranolol is teratogenic Bedranol* SR should not be used in pregnancy unless absolutely necessary. Beta-blockers reduce placental perfusion which may result in intra-uterine foetal death, immature or premature deliveries. Bradycardia may occur in the foetus and there may be an increased risk of cardiac and pulmonary problems in the post-natal period. Hypoglycaemia or bradycardia may occur in the neonate.

Breast-feeding

Most beta-blockers, particularly lipophilic compounds, will pass into breast milk although to a variable extent.. Breast-feeding is not recommended as beta-blockers taken by the mother will pass into the breast-milk.

4.7 Effects on ability to drive and use machines

Bedranol* SR should not impair ability to drive and use machines. However, sometimes dizziness or tiredness may occur. If so, the patient should not drive or operate machines.

4.8 Undesirable effects

Bedranol* SR is usually well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of propranolol.

The following undesired events, listed by body system, have been reported.

Common may affect up to 1in 10 people
General: Fatigue and/or lassitude (often transient)

Cardiovascular: Bradycardia, cold extremities, Raynaud's phenomenon.

CNS: Sleep disturbances, nightmares.

Uncommon may affect up to 1 in 100 people
GI: Gastrointestinal disturbance, such as nausea, vomiting, diarrhoea.

Rare may affect up to1 in 1,000 people
General: Dizziness.

Blood: Thrombocytopaenia.

Cardiovascular: Heart failure deterioration, precipitation of heart block, postural hypotension, which may be associated with syncope, exacerbation of intermittent claudication.

CNS: Hallucinations, psychoses, mood changes, confusion, memory loss.

Skin: Purpura, alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.

Neurological: Paraesthesia.

Eyes: Dry eyes, visual disturbances.

Respiratory: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome.

Very rare may affect up to 1 in 10,000 people

Investigations: an increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear.

Nervous system: Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported.

Not known (frequency **cannot be estimated from the available data)**

Endocrine system: Hypoglycaemia in neonates, infants, children, elderly patients, patients on haemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported.

Seizure linked to hypoglycaemia

Discontinuance of the drug should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions. Cessation of therapy with a beta-blocker should be gradual. In the rare event of intolerance manifested as bradycardia and hypotension, the drug should be withdrawn and, if necessary, treatment for overdosage instituted.

Cases of abnormal weight gain have also been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

4.9 Overdose

Propranolol is known to cause severe toxicity when used in overdose. Patients should be informed of the signs of overdose and advised to seek urgent medical assistance if an overdose of propranolol has been taken.

Clinical features

- Cardiac

Bradycardia, hypotension, pulmonary oedema, syncope and cardiogenic shock may develop. QRS complex prolongation, ventricular tachycardia, first to third degree AV block, ventricular fibrillation or asystole may also occur. Development of cardiovascular complications is more likely if other cardioactive drugs, especially calcium channel blockers, digoxin, cyclic antidepressants or neuroleptics have also been ingested. Older patients and those with underlying ischaemic heart disease are at risk of developing severe cardiovascular compromise.

- CNS

Drowsiness, confusion, seizures, hallucinations, dilated pupils and in severe cases coma may occur. Neurological signs such as coma or absence of pupil reactivity are unreliable prognostic indicators during resuscitation.

- Other features
  Bronchospasm, hyperkalaemia and occasionally CNS-mediated respiratory depression may occur.

Management

In cases of overdose or extreme falls in heart rate or blood pressure, treatment with propranolol must be stopped. Management should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. In symptomatic patients, or patients with an abnormal ECG, early discussion with critical care should be considered. Consult national clinical guidance for further information on the management of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C07AA05

Propranolol is a competitive antagonist at both the $beta_1$ and $beta_2$-adrenoceptors, has no agonist activity at the beta adrenoceptor, but has membrane stabilising activity at concentrations exceeding 1 to 3 mg/litre, though such concentrations are rarely achieved during oral therapy. Competitive beta blockade has been demonstrated in man by a parallel shift to the right in the dose-heart rate response curve to beta agonists such as isoprenaline.

Propranolol as with all other beta-blockers, has a negative inotropic effects and is therefore, contra-indicated in uncontrolled heart failure.

Propranolol is a racemic mixture and the active form is the S (-) isomer. With the exception of inhibition of the conversion of thyroxine to triiodothyronine it is unlikely that any additional ancillary properties possessed by R (+) propranolol, in comparison with the racemic mixture this will give rise to different therapeutic effects.

Propranolol is effective and well tolerated in most ethnic populations although the response may be a bit less in black patients.

The sustained release preparations of propranolol maintains a higher degree of $beta_1$-blockade 24 hours after dosing compared with conventional propranolol.

5.2 Pharmacokinetic properties

Propranolol is completely absorbed after oral administration and the peak plasma concentrations occur 1-2 hours after dosing in fasting patients. Following oral dosing with the sustained release preparation of propranolol, the blood profile is flatter than after conventional propranolol but the half-life is increased to between 10 and 20 hours. The liver removes up to 90% of an

oral dose and an elimination half-life of 3- 6 hours. Propranolol is widely and rapidly distributed throughout the body with highest levels occurring in the lungs, liver, kidney, brain and heart. Propranolol is a highly protein bound (80 to 95%).

5.3 Preclinical safety data

Propranolol is a drug where there is an extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in this Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Sucrose
Maize starch
Shellac
Talc

Capsule shells:
Gelatin,
Indigotine (E132)

Printing Ink:
Shellac
Black iron oxide (E172)
Propylene glycol
Ammonium hydroxide 28%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

No special temperature precautions for storage.

6.5 Nature and contents of container

Blister strips composed of: White opaque PVC/PVdC laminate (PVC 250µm coated with PVdC 40gsm), Aluminium foil (20µm). Blister strips will be packed into cartons.

Pack sizes: 28, 30, 56, 60 and 100. Not all pack sizes are marketed.

6.6 Instructions for use/handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Sandoz Ltd
Maxis 1
Western Road,
Bracknell,
Berkshire,
RG12 1RF
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04416/0320

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4th September 2001

10 DATE OF REVISION OF THE TEXT

01/12/2025