SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Angilol® 160 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 160 mg propranolol hydrochloride.

Excipients with known effect:
Lactose - each film-coated tablet contains 298 mg lactose.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet. Pink, round, engraved on one side with ANGILOL 160. Diameter of each film-coated tablet is approximately 11 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated in the management of angina pectoris.
Control of essential and renal hypertension.
Long term management against re-infarction after recovery from acute myocardial infarction
Control of essential tremor.
Control of situational anxiety and generalised anxiety, and anxiety tachycardia.
Control of most forms of cardiac dysrhythmias.
Management of hypertrophic obstructive cardiomyopathy.
Management of phaeochromocytoma peri-operatively (with an alpha blocker).
An adjunct in the management of thyrotoxicosis and thyrotoxic crises.
Prophylaxis of migraine
Prophylaxis of upper gastro-intestinal bleeding in patients with portal hypertension and oesophageal varices.

4.2 Posology and method of administration

Posology

Adults
Hypertension
The starting dose of Angilol should be 80mg twice a day, to be increased by the same amount at weekly intervals, according to patient response. Usually a response is seen within the dose range 160 - 320mg per day. A further reduction of blood pressure may be achieved when a diuretic and/or anti-hypertensive therapy is given in addition to Angilol.

Angina, migraine and essential tremor
The starting dose is 40mg two or three times daily, increasing by the same amount at weekly intervals, according to patient response. An adequate response in migraine and essential tremor is usually seen in the range of 80 - l60mg daily in divided doses. In angina the dose to achieve adequate response will usually be l20 - 240mg/day (in divided doses).

Situational and generalised anxiety
A dose of 40 mg daily may provide short term relief of acute situational anxiety. Generalised anxiety, requiring longer term therapy, usually responds adequately to 40 mg twice daily which, in individual cases, may be increased to 40 mg three times daily. Treatment should be continued according to response. Patients should be reviewed after 6 to 12 months treatment.

Arrhythmias, anxiety tachycardia, hypertrophic obstructive cardiomyopathy and thyrotoxicosis,
Most patients respond within the dosage range of 10 - 40mg three or four times a day.

Post myocardial infarction
Treatment should start between days 5 and 21 after myocardial infarction, with an initial dose of 40 mg four times a day for 2 or 3 days. In order to improve compliance the total daily dosage may thereafter be given as 80 mg twice a day.

Portal hypertension
Dosage should be titrated to achieve approximately 25% reduction in resting heart rate. Dosage should begin with 40 mg twice daily, increasing to 80 mg twice daily depending on heart rate response. If necessary, the dose may be increased incrementally to a maximum of 160 mg twice daily.

Phaeochromocytoma
(Used only in conjunction with an alpha-receptor blocking drug)
Pre-operatively: 60mg daily for three days is recommended - malignant cases (non-operable): 30mg daily.

Paediatric population:

Dysrhythmias, phaeochromocytoma, thyrotoxicosis
The dose of Angilol should be determined according to the cardiac status of the patient and the circumstances necessitating treatment. The doses given are intended only as a guide: Oral: 0.25 - 0.5mg/kg three or four times daily as required.

Migraine
Oral: under the age of 12: 20 mg two to three times daily
Over the age of 12: the adult dose

Fallot's Tetralogy
The value of Angilol in this condition is confined mainly to the relief of the right-ventricular outflow tract shut-down. It is also useful for treatment of associated dysrhythmias and angina. Dosage should be individually determined according to circumstances and is usually up to 1 mg/kg repeated three or four times daily as required.

Elderly:
Evidence concerning the relation between blood level and age is conflicting. Angilol should be used to treat older people with caution. It is suggested that treatment should start with the lowest dose. The optimum dose should be individually determined according to the clinical response.

Method of administration

For oral administration.

4.3 Contraindications

1. Hypersensitivity to Propranolol or to any of the excipients listed in section 6.1
2. In the presence of 2^{nd} and 3^{rd} degree heart block
3. Sick Sinus syndrome
4. Bradycardia
5. Untreated phaeochromocytoma
6. Uncontrolled heart failure
7. Cardiogenic shock
8. Hypotension
9. Asthma
10. Intermittent claudication
11. Severe peripheral circulatory disturbances;
12. Prinzmetals angina;
13. If there is a history of bronchial asthma or bronchospasm. The text on the label for this product will carry this following warning. **'Do not take this medicine if you have wheezing or asthma** A similar warning appears in the patient information leaflet.
    Bronchospasm can usually be reversed by beta-$_2$ agonist bronchodilators such as salbutamol. Large doses of the beta-$_2$ agonist bronchodilator may be required to overcome the beta blockade produced by propranolol and the dose should be titrated according to the clinical response; both intravenous and inhalational administration should be considered. The use of intravenous aminophylline and/or the use of ipratropium (given by nebuliser) may also 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 required in severe cases.
14. After prolonged fasting, patients with restricted counter-regulatory reserves or in patients prone to hypoglycaemia. Patients with restricted counter regulatory reserves may have reduced autonomic and hormonal responses to hypoglycaemia which includes glycogenolysis, gluconeogenesis and /or impaired modulation of insulin secretion. Patients at risk for an inadequate response to hypoglycaemia includes individuals with malnutrition, prolonged fasting, starvation, chronic liver disease, diabetes and concomitant use of drugs which block the full response to catecholamine
15. In metabolic acidosis (e.g. in diabetes).

4.4 Special warnings and precautions for use

Although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3), Angilol should be given with caution to patients with less severe peripheral circulatory disturbances as these may be aggravated.

Although contraindicated in uncontrolled heart failure (see section 4.3), may be used in patients whose signs of heart failure have been controlled. Special care should be taken with patients whose cardiac reserve is poor.

Due to a negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Angilol may block/modify the signs and symptoms of the hypoglycaemia (especially tachycardia). Angilol occasionally causes hypoglycaemia, even 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. Severe hypoglycaemia associated with Angilol has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of Angilol and hypoglycaemic therapy in diabetic patients. Angilol may prolong the hypoglycaemic response to insulin (see section 4.3).

Heart failure due to thyrotoxicosis often responds to Angilol alone, but if other adverse factors co-exist myocardial contractility must be maintained and signs of failure controlled with digitalis and diuretics. Angilol may mask the important signs of thyrotoxicosis.

Angilol should not be used in untreated phaeochromocytoma. However, in patients with phaeochromocytoma, an alpha-blocker may be given concomitantly.

Beta-blockers may induce bradycardia as a result of its pharmacological action. In the rare instance that a treated patient develops symptoms which may be attributable to a slow heart rate a reduction in dose may be necessary.

Beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.

It is important that treatment with a beta-blocking agent is not discontinued abruptly. Either the equivalent dosage of another beta-blocker may be substituted or the withdrawal of Angilol should be gradual over a period of 7 to 14 days. Patients should be followed during withdrawal especially those with ischaemic heart disease.

Anaesthesia: Angilol can cause an altered response to stress and therefore it may be necessary to withdraw the drug before surgery. The risk/benefit of stopping beta blockade should be made for each patient. If it is decided to withdraw Angilol it should be done 24 hours before elective surgery. In emergency, or when interruption of treatment might expose the patient to severe uncontrolled angina or dysrhythmia, such withdrawal may be impracticable. Anaesthesia may still proceed, however, provided that the patient is protected against vagal dominance by the intravenous administration of atropine l - 2mg and that agents such as ether, chloroform, cyclopropane and trichloroethylene are avoided.

Since the half-life may be increased in patients with significant hepatic or renal impairment, caution must be exercised when starting treatment and selecting the initial dose.

Angilol must be used with caution in patients with decompensated cirrhosis (see section 4.2).

In patients with portal hypertension, liver function may deteriorate and hepatic encephalopathy may develop. There have been reports suggesting that treatment with propranolol may increase the risk of developing hepatic encephalopathy (see section 4.2).

Psoriasis may be aggravated by the use of beta adrenoceptor blocking drugs. Patients with psoriasis should take beta-blockers only after careful consideration.

Interference with laboratory tests: Angilol 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Propranolol modifies the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of propranolol and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin (see section 4.3 and 4.4).

Simultaneous administration of rizatriptan and propranolol can cause an increased rizatriptan AUC and Cmax by approximately 70-80%. The increased rizatriptan exposure is presumed to be caused by inhibition of first-passage metabolism of rizatriptan through inhibition of monoamine oxidase-A. If both drugs are to be used, a rizatriptan dose of 5 mg has been recommended.

Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Digitalis glycosides in association with beta-blockers may increase atrioventricular conduction time.

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects (e.g., verapamil, diltiazem) can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or SA or AV conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridine calcium channel blockers, e.g., nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Concomitant use of sympathomimetic agents e.g., adrenaline, may counteract the effect of beta-blockers. Caution must be exercised in the parenteral administration of

preparations containing adrenaline to patients taking beta-blockers as, in rare cases, vasoconstriction, hypertension and bradycardia may result.

Administration of propranolol during infusion of lidocaine may increase the plasma concentration of lidocaine by approximately 30%. Patients already receiving propranolol tend to have higher lidocaine levels than controls. The combination should be avoided.

Concomitant use of cimetidine or hydralazine will increase plasma levels of propranolol, and concomitant use of alcohol may increase the plasma levels of propranolol.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the betablocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of betablockers should be delayed for several days after clonidine administration has stopped.

Caution must be exercised if ergotamine, dihydroergotamine or related compounds are given in combination with propranolol since vasospastic reactions have been reported in a few patients.

Concomitant use of prostaglandin synthetase inhibiting drugs eg, ibuprofen and indometacin, may decrease the hypotensive effects of propranolol.

Concomitant administration of propranolol and chlorpromazine may result in an increase in plasma levels of both drugs. This may lead to an enhanced antipsychotic effect for chlorpromazine and an increased antihypertensive effect for propranolol.

Concomitant administration of antidepressants such as fluvoxamine increases plasma concentration of propranolol. Hypotensive effect enhanced with tricyclic antidepressants.

Concomitant administration of barbiturates with propranolol may result in an enhanced hypotensive effect.

Caution must be exercised when using anaesthetic agents with propranolol. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of betablockers 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.

Pharmacokinetic studies have shown that the following agents may interact with propranolol due to effects on enzyme systems in the liver which metabolise propranolol and these agents: quinidine, propafenone, rifampicin, theophylline, warfarin, thioridazine and dihydropyridine calcium channel blockers such as nifedipine, nisoldipine, nicardipine, isradipine and lacidipine. Owing 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 the concomitant therapy with dihydropyridine calcium channel blockers).

4.6 Fertility, pregnancy and lactation

Pregnancy

Angilol should not be given in pregnancy unless its use is essential. There is no evidence of teratogenicity with Angilol. Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycemia and bradycardia in the neonate and bradycardia in the foetus) may occur. There is an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period.

Breast-feeding

Most beta-blockers, particularly lipophilic compounds, will pass into breast milk although to a variable extent. Breast-feeding is not recommended following administration of these compounds.

4.7 Effects on ability to drive and use machines

Angilol has no or negligible influence on the ability to drive and use machines. The side effects of bradycardia and hypotension may occur. Patients should be warned that dizziness or fatigue may occasionally occur and they should not drive or operate machinery if they feel affected.

4.8 Undesirable effects

Angilol 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. The following definitions of frequencies are used: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ class	**Frequency**	**Undesirable Effect**
Blood and lymphatic system disorders	Rare	Thrombocytopaenia
Endocrine disorders	Not known	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
Nervous system disorders	Common	Sleep disturbances, nightmares
	Rare	Hallucinations, psychoses, mood changes, confusion, memory loss, paraesthesia
	Very rare	Isolated reports of myasthenia gravis like syndrome or exacerbation of

		myasthenia gravis have been reported
	Not known	Depression
Eye disorders	Rare	Dry eyes, visual disturbances
Cardiovascular disorders	Common	Bradycardia, cold extremities, Raynaud's phenomenon
	Rare	Heart failure deterioration, precipitation of heart block, postural hypotension, which may be associated with syncope, exacerbation of intermittent claudication
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome
Gastrointestinal disorders	Uncommon	Gastrointestinal disturbance, such as nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Rare	Purpura, alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes
Reproductive system and breast disorders	Not known	Impotence
General disorders and administration site conditions	Common	Fatigue and/or lassitude (often transient)
	Rare	Dizziness
Investigations	Very rare	An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear

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 of Angilol manifested by bradycardia and hypotension, the drug should be withdrawn and, if necessary, treatment instituted for overdosage.

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. Website: 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

Pharmacotherapeutic group: Beta blocking agents, non-selective, ATC code: C07AA05

Propranolol is a competitive antagonist at both the $beta_1$- and $beta_2$ adrenoceptors. It 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 other beta-blockers, has negative inotropic effects and is therefore contraindicated in uncontrolled heart failure.

Propranolol is a racemic mixture and the active form is the S (-) isomer of propranolol. 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, will give rise to different therapeutic effects.

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

5.2 Pharmacokinetic properties

Following intravenous administration the plasma half-life of propranolol is about 2 hours and the ratio of metabolites to parent drug in the blood is lower than after oral administration. In particular 4-hydroxypropranolol is not present after intravenous administration. Propranolol is completely absorbed after oral administration and peak plasma concentrations occur 1 to 2 hours after dosing in fasting patients. The liver removes up to 90% of an oral dose with an elimination half-life of 3 to 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 highly protein bound (80 to 95%).

5.3 Preclinical safety data

Propranolol is a drug on which extensive clinical experience has been obtained. All relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Gelatin
Stearic Acid
Magnesium Stearate

Coating:
Ethylcellulose
Hypromellose
Diethylphthalate
Titanium dioxide E171

Carmine E120
Beeswax

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Blister packs: Store below 25°C. Store in the original package in order to protect from light and moisture.
Containers: Store below 25°C. Keep containers tightly closed in order to protect from light and moisture.

6.5 Nature and contents of container

Opaque, high density polystyrene containers, with polythene lids, and/or polypropylene containers with polypropylene or polythene lids, and polyurethane foam sponge wads or polythene wads. Pack sizes: 50, 100, 250, 500 and 1000 tablets.

250 micron PVC glass-clear/bluish rigid PVC (pharmaceutical grade). 25 micron hard-tempered aluminium foil coated on the dull side with 6 – 7 gsm heat seal lacquer and printed on the bright side. Pack size: 28 and 56 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Chelonia Healthcare Limited
Boumpoulinas 11, 3rd Floor
Nicosia
P.C. 1060
Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 33414/0098

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31st December 1980 / 26th August 1998

10 DATE OF REVISION OF THE TEXT

14/04/2020