Propranolol 40 mg Tablets
(propranolol hydrochloride)

PL 20395/0082

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted RelonChem Limited a Marketing Authorisation (licence) for the medicinal product Propranolol 40 mg Tablets (PL 20395/0082) on 25 January 2012. This is a prescription-only medicine (POM).

Propranolol is one of a group of medicines called beta-blockers. Beta-blockers slow the heart and circulation and can affect other parts of the body, e.g. liver.

Propranolol can be used for many conditions including:

- high blood pressure, angina (chest pains), some arrhythmias (disorders of heart rhythm), protection of the heart after a heart attack.
- Hypertrophic cardiomyopathy (thickening of the heart muscle).
- Prevention of migraine, essential tremor and anxiety.
- Thyrotoxicosis – a thyroid condition caused by an overactive thyroid gland.
- Phaeochromocytoma (high blood pressure due to a tumour usually near the kidney).
- Prophylaxis of bleeding in the oesophagus due to high blood pressure in the liver.

This Marketing Authorisation for Propranolol 40 mg Tablets is considered to be identical to the previously granted licence for Propranolol 40 mg Tablets BP (PL 20395/0034), authorised to RelonChem Limited on 19 March 2004.

No new or unexpected safety concerns arose from this application. It was judged that the benefits of Propranolol 40 mg Tablets outweigh the risk; hence a Marketing Authorisation has been granted.
Propranolol 40 mg Tablets
(propranolol hydrochloride)

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SCIENTIFIC DISCUSSION

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**INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the MHRA granted RelonChem Limited a Marketing Authorisation for the medicinal product Propranolol 40 mg Tablets (PL 20395/0082) on 25 January 2012. The product is a prescription-only medicine (POM).

This is a simple, abridged, ‘informed consent’ application submitted according to Article 10(c) of EC Directive 2001/83 (as amended), cross-referencing the Marketing Authorisation for Propranolol 40 mg Tablets BP (PL 20395/0034), authorised to RelonChem Limited on 19 March 2004. The cross-referenced product was originally licensed to Dimom Limited (PL 17946/0004) on 16 August 2002; this MA underwent Change of Ownership (CoA) to the current RelonChem Limited licence.

Propranolol 40 mg Tablets are indicated for the following:

- control of hypertension.
- management of angina pectoris.
- long term prophylaxis after recovery from acute myocardial infarction.
- control of most forms of cardiac dysrhythmias.
- prophylaxis of migraine.
- management of essential tremor.
- relief of situational anxiety and generalised anxiety symptoms, particularly those of somatic type.
- prophylaxis of upper gastro-intestinal bleeding in patients with portal hypertension and oesophageal varices.
- adjunctive management of thyrotoxicosis and thyrotoxic crisis.
- management of hypertrophic obstructive cardiomyopathy.
- management of phaeochromocytoma perioperatively (with alpha blocker).

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-adrenoceptor 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-adrenoceptor blocking drugs, 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.
The MHRA considers that the pharmacovigilance system described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

As the application is for a product that is identical to an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment. There is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. The availability of this medicinal product, which is identical to the cited reference product, will not lead to any increase in environmental exposure concentrations of the active ingredient.

No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was first granted prior to the introduction of current legislation, no Public Assessment Report (PAR) was generated for it.
PHARMACEUTICAL ASSESSMENT

LICENCE NUMBER: PL 20395/0082

PROPRIETARY NAME: Propranolol 40 mg Tablets

ACTIVE INGREDIENTS: Propranolol hydrochloride

COMPANY NAME: RelonChem Limited

E.C. ARTICLE: Article 10(c) of Directive 2001/83/EC (as amended)

LEGAL STATUS: POM

1. INTRODUCTION

This is a simple abridged application, submitted under Article 10(c) of Directive 2001/83/EC (as amended) for Propranolol 40 mg Tablets. The proposed Marketing Authorisation Holder (MAH) is RelonChem Limited.

The reference product is Propranolol 40 mg Tablets BP (PL 20395/0034), authorised to RelonChem Limited on 19 March 2004. The proposed and reference products are identical.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The approved name of the product is Propranolol 40 mg Tablets. The product has been named in line with current requirements and the product name is acceptable.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

Each Propranolol 40 mg Tablet contains the active ingredient, propranolol hydrochloride 40 mg. The tablets are licensed for marketing in polyvinylchloride (PVC)-polyvinylidene chloride (PVC)-aluminium foil blister strips in a pack size of 28 tablets. The tablets are also licensed in High Density Polyethylene (HDPE) securitainers with Low Density Polyethylene (LDPE) caps in pack sizes of 20, 50 and 1000, however these packs will not be marketed until mock-up labelling has been approved by the MHRA. The securitainer/blister strips are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons.

The container closure systems are identical to those stated for the reference product.

The approved shelf-lives (5 years for securitainer packs, 3 years for blister packs) and storage conditions (‘Do not store above 25°C. Store in the original container’) are identical to the details registered for the reference product.

2.3 Legal status

POM - The product is available by supply through pharmacies, subject to a medical prescription.
2.4 Marketing Authorisation Holder / Contact Persons / Company
The proposed Marketing Authorisation Holder is ‘RelonChem Limited, 27 Old Gloucester Road, London WC1 3XX, UK’.

The Qualified Person (QP) responsible for pharmacovigilance was stated and their CV included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product / shelf-life specification
The proposed finished product specifications are consistent with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specifications are consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

3. EXPERT REPORT
A satisfactory quality overall summary has been prepared by an appropriately qualified expert. The CV of the expert was provided.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product (pink, biconvex, film-coated tablets with a scoreline on one face and embossed ‘40’ on the other face) is identical to that of the cross-reference product. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The approved SmPC is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET (PIL) / LABELLING

PIL
The approved PIL is satisfactory and in line with the approved SmPC. The patient information leaflet has been prepared in the user-tested format and in line with the details registered for the cross-reference product.

PIL user-testing has been accepted based on bridging to the successful user-testing of the PIL for the reference product, Propranolol 40 mg Tablets BP (PL 20395/0034). The text, content and layout of the proposed PIL are essentially identical to the approved PIL for the reference product. The bridging is accepted.

Labelling
Mock-ups of the labelling for the blister packs have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. Securitainer packaging can not be marketed until satisfactory mocks up are approved by the MHRA.

7. CONCLUSIONS
The grounds for this application are considered adequate. A Marketing Authorisation was, therefore, granted.
NON-CLINICAL ASSESSMENT

This is a simple, abridged, ‘informed consent’ application made under Article 10(c) of EC Directive 2001/83 (as amended).

No new non-clinical data have been supplied with this application and none are required for an application of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the non-clinical expert has been supplied.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).
**CLINICAL ASSESSMENT**

This is a simple, abridged, ‘informed consent’ application made under Article 10(c) of EC Directive 2001/83 (as amended), cross-referring to the Marketing Authorisation for Propranolol 40 mg Tablets BP (PL 20395/0034, RelonChem Limited).

No new clinical data have been supplied with the application, and none are required for applications of this type. A clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the clinical expert has been supplied.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The data for this application are consistent with those previously assessed for the cross-reference product and as such have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL
This application is considered identical to the previously granted licence for Propranolol 40 mg Tablets BP (PL 20395/0034, RelonChem Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC, PIL and labelling are satisfactory and consistent with the details registered for the cross-reference product.

PIL user-testing has been accepted based on bridging to the successful user-testing of the PIL for Propranolol 40 mg Tablets BP (PL 20395/0034). The results show that the leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork for the blister packs complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging. Securitainer packaging can not be marketed until satisfactory mocks up are approved by the MHRA.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. The benefit: risk ratio is considered to be positive.
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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 01 October 2010.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 05 November 2010.

3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 30 December 2010, 13 May 2011 and 10 October 2011.

4 The applicant responded to the MHRA’s request, providing further information for the quality sections on 24 March 2011, 02 August 2011 and 12 December 2011.

5 The application was approved on 25 January 2012.
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STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Propranolol 40 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 40 mg of propranolol hydrochloride.
‘Also contains lactose. For a full list of excipients, see 6.1’

3 PHARMACEUTICAL FORM
Film coated tablets.

The tablets are pink, film coated, bi-convex tablets with a Scoreline on one face and embossed ‘40’ on the other face.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
The control of hypertension.
The management of angina pectoris.
The long term prophylaxis after recovery from acute myocardial infarction.
The control of most forms of cardiac dysrhythmias.
The prophylaxis of migraine.
The management of essential tremor.
The relief of situational anxiety and generalised anxiety symptoms, particularly those of somatic type.
Prophylaxis of upper gastro-intestinal bleeding in patients with portal hypertension and oesophageal varices.
The adjunctive management of thyrotoxicosis and thyrotoxic crisis.
Management of hypertrophic obstructive cardiomyopathy.
Management of phaeochromocytoma perioperatively (with alpha blocker).

4.2 Posology and method of administration
Tablets are to be taken orally with a drink of water.

The lowest possible dose should be used initially in all patient groups, but this is particularly important in elderly patients. Subsequent increases in dose should be gradual.

Posology:
Adults:

Hypertension:
A starting dose of 80mg twice a day may be increased at weekly intervals according to response. The usual dose range is 160-320mg per day. Lower doses may be effective when a diuretic or other antihypertensive drugs are given concurrently.

Angina, Migraine and Essential Tremor:
Initially, 40mg two or three times daily, increased 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 80-160mg/day and in angina in the range 120-240mg/day.

Situational and Generalised Anxiety:
In acute situational anxiety, a dose of 40mg daily may provide short term relief. In generalised anxiety requiring longer term therapy, an adequate response may be expected with 40mg twice daily which, in individual cases, may be increased to 40mg three times daily. Treatment
should be continued according to response and patients should be reviewed after six to twelve months’ treatment.

**Dysrhythmias, Anxiety Tachycardia, Hypertrophic Obstructive Cardiomyopathy and Thyrotoxicosis:**
10–40mg three or four times a day.

**Post Myocardial Infarction:**
For long-term prevention of sudden cardiac death in patients who have survived the acute phase of myocardial infarct, treatment should start between days 5 and 21 after myocardial infarction, with an initial dose of 40mg four times a day for 2 to 3 days. In order to improve compliance the total daily dosage may thereafter be given as 80mg twice a day.

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

**Phaeochromocytoma:**
Propranolol should be used only with an alpha-receptor blocking drug.

**Pre-operative:**
60mg daily for three days.

**Non-Operable Malignant Cases:**
30mg daily.

**Children:**

**Dysrhythmias, Phaeochromocytoma, Thyrotoxicosis:**
Dosage should be determined individually. The following dosages are intended only as a guide.

0.25 – 0.50mg/kg three or four times daily as required. Adjusted according to response. Max 1mg/kg 4 times daily, total daily dose not to exceed 160 mg daily.

**Migraine**
Under the age of 12: 20mg two or three times daily.
Over the age of 12: Similar to adult dose.

**Fallot’s Tetralogy:**
Propranolol is used mainly to relieve right-ventricular outflow tract shutdown. It is also useful for treatment of associated dysrhythmias and angina. Dosage should be individually determined and the following is only a guide:

Up to 1mg/kg repeated three or four times daily as required.

**Elderly Patients:**
The optimum, dose should be individually determined according to clinical response.

### 4.3 Contraindications

In patients with cardiogenic shock.
Uncontrolled heart failure
Sick sinus syndrome (including sino-atrial block)
In patients with second or third degree heart block.
Prinzmetal’s angina (in case of non-selective beta-blockers)
If there is a history of bronchospasm and bronchial asthma or wheezing.
Untreated phaeochromocytoma
In metabolic acidosis (e.g. in some diabetics).
Bradycardia (<45 - 50 bpm)
Hypotension
Hypersensitivity to the substance
Severe peripheral arterial circulatory disturbances
After prolonged fasting.
In patients prone to hypoglycaemia ie, patients after prolonged fasting or patients with restricted counter-regulatory reserves.

4.4 Special warnings and precautions for use

In patients with ischaemic heart disease, sudden withdrawal of beta-adrenoceptor blocking drugs may result in anginal attacks of increased frequency or severity. Therefore, withdrawal of Propranolol in patients with ischaemic heart disease should be gradual, i.e. over 1-2 weeks. If necessary at the same time initiating replacement therapy, to prevent exacerbation of angina pectoris.

In addition, hypertension and arrhythmias may develop. When it has been decided to interrupt a beta-blockade in preparation for surgery, therapy should be discontinued for at least 24-hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation; however, the risk of hypertension may be increased as well. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. The patient may be protected against vagal reactions by intravenous administration of atropine.

Propranolol should not be used in combination 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 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.

A reduction in heart rate is a pharmacological effect of Propranolol. In rare cases where symptoms may be attributable to the slow heart rate, the dose may be reduced. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dosage should be reduced.

Propranolol is contraindicated in patients with severe peripheral arterial circulatory disorders. In patients with less severe peripheral arterial circulatory disorders (Raynaud’s disease or syndrome, intermittent claudication), beta-blockers should be used with great caution as aggravation of these disorders may occur.

In patients with chronic obstructive pulmonary disorders, airway obstructions may be aggravated. Therefore, non-selective beta-blockers should not be used for these patients, and beta-1 selective blockers only with the utmost care.

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

Patients with liver or kidney insufficiency may need a lower dosage, depending on the pharmacokinetic profile of the compound.

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.

The elderly should be treated with caution, starting with a lower dosage but tolerance is usually good in the elderly.

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

Propranolol should be used with caution in patients with decompensated cirrhosis.
Beta-blockers may increase the number and the duration of anginal attacks in patients with Prinzmetal’s angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Non-selective beta-blockers should not be used for these patients, and beta-1 selective blockers only with the utmost care.

Patients with anamnestically known psoriasis should take beta-blockers only after careful consideration.

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.

Particular care is required with patients whose cardiac reserve is poor. Beta-adrenoceptor blocking drugs should be avoided in overt heart failure, although they may be used when signs of failure have been controlled.

Cardiac failure due to thyrotoxicosis may respond to Propranolol alone but if other adverse factors are also present, it is important to control signs of failure with digitalis and diuretics. Propranolol may mask the signs of thyrotoxicosis.

Propranolol may block/modify the signs and symptoms of the hypoglycaemia (especially tachycardia). Propranolol 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 propranolol has rarely presented with seizures and/or coma in isolated patients. 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).

Hepatic function will deteriorate in patients with portal hypertension and hepatic encephalopathy may develop. It has been suggested that treatment with Propranolol may increase the risk of developing hepatic encephalopathy.

Care is required when transferring patients from Clonidine to a beta-adrenoceptor blocking drug. If the two drugs are given concurrently, Clonidine should not be discontinued until several days after the withdrawal of the beta-adrenoceptor blocking drug. Care is required with prescribing a beta-adrenoceptor blocking drug with class I antidysrhythmic agent such as Disopyramide. Beta-adrenoceptor blocking drugs should be used with caution in combination with Verapamil where ventricular function is impaired. The combination should not be given to patients with conduction abnormalities, nor should either drug be administered intravenously within 48 hours of discontinuing the other. Care is required during parenteral administration of preparations containing adrenaline to patients receiving beta-adrenoceptor blocking drugs, as in rare instances vasoconstriction, hypertension and bradycardia may occur.

Care is required when administering anaesthetic agents to patients receiving Propranolol. The anaesthetist should always be informed of the use of beta-adrenoceptor blocking drug and the chosen anaesthetic should have as little negative inotropic activity as possible.

Abrupt withdrawal of beta-blockers is to be avoided. The dosage should be withdrawn gradually over a period of 7 to 14 days.

When a patient is scheduled for surgery and a decision is made to discontinue 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.

Propranolol has been reported to interfere with some laboratory tests, viz estimation of serum bilirubin by the diazo method and determination of catecholamines by fluorescence methods.

Due to the excipient lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine
The product label will carry the following warning:
Do not take this medicine if you have a history of wheezing or asthma.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended association:

**Calcium antagonists:**
Combined use of beta-adrenoceptor blocking drugs and calcium channel blockers with negative inotropic effects eg, verapamil, diltiazem, can lead to an exaggeration of these effects, particularly in patients with impaired ventricular function and/or sino-atrial or atrio-ventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-adrenoceptor blocking drug nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

**Digitalis glycosides:**
Association with beta-blockers may increase atrio-ventricular conduction time.

**Clonidine:**
Beta-Blockers increase the risk of “rebound hypertension”. When clonidine is used in conjunction with non-selective beta-blockers, such as propranolol, treatment with clonidine should be continued for some time after treatment with the beta-blocker has been discontinued.

**Precautions for use:**

**Class 1 anti-arrhythmic drugs (e.g. disopyramide, quinidine) and amiodarone:**
May have potentiating effect on atrial-conduction time and induce negative inotropic effect.

**Insulin and oral antidiabetic drugs:**
May intensify the blood sugar lowering effect (especially non-selective beta-blockers).

Beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).

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

Caution must be exercised when using anaesthetic agents with propranolol tablets. 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-adrenoceptor blocking drugs 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.

**Cimetidine, hydralazine:**
Induce increased plasma levels of hepatically metabolised beta-blockers.

**Alcohol**
May decrease the plasma levels of Propranolol.

**Take into account:**

**Calcium antagonists:**
The risk of hypotension may be increased with dihydropyridine derivates such as nifedipine. In patients with latent cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure.

**Prostaglandin synthetase inhibiting drugs e.g. ibuprofen or indomethacin:**
May decrease the hypotensive effects of beta-blockers
**Sympathomimetic agents:**
May counteract the effects of beta blockers.

Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as other antihypertensive agents, may increase the blood pressure lowering effect.

Parenteral administration of preparations containing adrenaline to patients taking beta-adrenoceptor blocking drugs may, in rare cases, result in vasoconstriction, hypertension and bradycardia. Propranolol may prolong the hypoglycaemic response to insulin.

Beta-adrenoceptor blocking drugs may enhance the negative inotropic action of verapamil, class I antidysrhythmic agents such as disopyramide and certain anaesthetic agents.

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.

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 concomitant therapy with dihydropyridine calcium channel blockers).

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.

4.6 **Fertility, pregnancy and lactation**

The safety of Propranolol in pregnancy has not been established and its use should be avoided unless the potential benefits are likely to outweigh the possible risk to the foetus.

Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. In addition, adverse affects (especially hypoglycaemia and bradycardia) may occur in foetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period.

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

4.7 **Effects on ability to drive and use machines**

Propranolol is unlikely to impair the ability of patients to drive or operate machinery. However, it should be noted that occasionally dizziness or fatigue may occur.

4.8 **Undesirable effects**

Propranolol tablets are 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.

*Cardiovascular:* bradycardia, heart failure deterioration, postural hypotension which may be associated with syncope, cold cyanotic extremities. In susceptible patients: precipitation of heart block, exacerbation of intermittent claudication, Raynaud's phenomenon.

*CNS:* confusion, dizziness, mood changes, nightmares, psychoses and hallucinations, sleep disturbances, headache.
Endocrine: 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 (see section 4.3, 4.4 and 4.5). Frequency of hypoglycaemia is not known in children.

Gastrointestinal: gastrointestinal disturbance.

Haematological: purpura, thrombocytopenia.

Integumentary: alopecia, dry eyes, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.

Neurological: paraesthesia. Seizures linked to hypoglycaemia.

Respiratory: bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome (see Section 4.3).

Special senses: visual disturbances.

Others: fatigue and/or lassitude (often transient), an increase in ANA (antinuclear antibodies) has been observed, however the clinical relevance of this is not clear; isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported in patients administered propranolol.

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-adrenoceptor blocking drug 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.

4.9 Overdose

Symptoms of overdose are: bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock.

Excessive bradycardia can be countered with atropine 1 to 2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1 to 10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 microgram/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect, could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Propranolol is a competitive antagonist at both the beta1 and beta2 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-adrenoceptor 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-adrenoceptor blocking drugs, 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 groups, 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 fasted 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
There is no pre-clinical data of relevance to a prescriber, which is additional to that already included in other sections of the Summary of Product Characteristics

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose
Microcrystalline cellulose
Talc
Stearic acid
Magnesium stearate
Hypromellose
Polyethylene glycol
Titanium dioxide (E171)
Carmine (E120)

6.2 Incompatibilities
There are no known major incompatibilities with propranolol tablets.

6.3 Shelf life
Securitainer: 5 years
Blisters: 3 years

6.4 Special precautions for storage
Do not store above 25°C
Store in the original container

6.5 Nature and contents of container
The product is available in:
1) Securitainer. (High Density Polyethylene Container and Low Density Polyethylene Cap).
Pack sizes: 20, 50 and 1000 tablets.
2) Blisters strips (20um aluminium foil / clear 250um PVC / 40gsm PVdC).
Pack sizes: 28 Tablets.

6.6 Special precautions for disposal
No special instructions necessary
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
RelonChem Limited
27 Old Gloucester Road
London
WC1 3XX
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 20395/0082

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/01/2012

10 DATE OF REVISION OF THE TEXT
25/01/2012
UKPAR Propranolol 40 mg Tablets

PRODUCT INFORMATION LEAFLET

Propranolol Tablets
Propranolol hydrochloride

PACKAGE LEAFLET: INFORMATION FOR THE USER

Read all of this leaflet carefully before you start taking these tablets

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- Your doctor has prescribed these tablets for you. Do not pass them on to others. They may harm them even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Propranolol Tablets are and what they are used for
2. Before you take Propranolol Tablets
3. How to take Propranolol Tablets
4. Possible side effects
5. How to store Propranolol Tablets
6. Further information

1. What Propranolol Tablets are and what they are used for

Propranolol is one of a group of drugs called beta-blockers. Beta-blockers slow the heart and circulation and can affect other parts of the body, e.g. liver.

Propranolol can be used for many conditions including:
- Hypertension (high blood pressure), angina (chest pain), some arrhythmias (disorders of heart rhythm), protection of the heart after a myocardial infarction (heart attack).
- Hypertrophic cardiomyopathy (thickening heart muscle).
- Prevention of migraine, essential tremor and anxiety.
- Thyrotoxicosis (thyroid condition caused by an overactive thyroid gland).
- Phaeochromocytoma (high blood pressure due to a tumour usually near the kidney).
- Bleeding in the oesophagus caused by high blood pressure in the liver.

2. Before you take Propranolol Tablets

Do not take Propranolol Tablets:
- If you have a history of wheezing or asthma.
- If you are allergic (hypersensitive) to propranolol or any of the other ingredients in propranolol tablets.
- If you suffer with heart failure which is not under control.
- If you suffer from conditions such as heart block, very slow or irregular heartbeats, very low blood pressure or very poor circulation.
- If you have phaeochromocytoma (high blood pressure due to a tumour usually near the kidney) which is not being treated.
- If you have been fasting for a long time.
- If you have metabolic acidosis (diabetes).
- If you have Pheochromocytoma (certain type of chest pain).

Take special care with Propranolol Tablets:
Tell your doctor before you start taking these tablets:
- If you have an allergy as these tablets may increase your sensitivity.
- If you have diabetes as propranolol may change your normal response to low sugar which usually involves an increase in heart rate.
- If you have thyrotoxicosis as propranolol may hide the symptoms of this condition.
- If you have liver or kidney problems (including cirrhosis of the liver) because you may need to have some check ups during your course of treatment.
- If you have circulatory disorders such as Raynaud's syndrome.
- If you have heart problems.
- If you have had jaundice previously.

Taking other medicines:
Please tell your doctor before using Propranolol if you are taking any of the following medicines:
- Verapamil, diltiazem, hydralazine used to treat hypertension or angina.
- Digoxin for heart failure.
- Cardiac for high blood pressure or migraine.
- Anticonvulsant antiepileptics for depression.
- Dipyridamole, warfarin and indomethacin used to treat irregular heart beats.
- Insulin and other oral diabetic drugs.
- Anesthetics if you are going into hospital for an operation, tell the anesthetist or medical staff that you are taking propranolol.
- Adrenaline a heart stimulant.
- Chlorpromazine for certain psychiatric disorders.
- Cimetidine for stomach problems.
- Hydralazine for high blood pressure.

If you are taking clonidine and propranolol together, you must not stop taking clonidine unless your doctor tells you to do so. If it becomes necessary for you to stop taking clonidine, your doctor will give you careful instructions on how to do it.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines without prescription.

Taking Propranolol Tablets with food and drink:
Propranolol tablets should be swallowed with a drink of water. If you frequently drink a lot of alcohol, this may reduce the effect of your medicine.

Pregnancy and Breastfeeding:
Before taking these tablets tell your doctor if you are, you think you might be, or are planning to become pregnant. You should not use propranolol tablets if you are breastfeeding or are planning to breastfeed your baby.

Driving and using machines:
Propranolol tablets may make you feel dizzy or tired. If affected do not drive or operate machinery.

Important information about some of the ingredients of Propranolol tablets:
This product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Propranolol Tablets
Always take Propranolol Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Propranolol tablets should be swallowed with a drink of water.
The following table shows the usual total daily oral dosage for an adult:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (high blood pressure)</td>
<td>160 to 320mg</td>
</tr>
<tr>
<td>Angina (chest pain)</td>
<td>120 to 240mg</td>
</tr>
<tr>
<td>Atrial fibrillation (disorders of the heart rhythm)</td>
<td>30 to 160mg</td>
</tr>
<tr>
<td>Prevention of a heart attack after a heart attack</td>
<td>160mg</td>
</tr>
<tr>
<td>Prevention of migraine and essential tremor</td>
<td>80 to 160mg</td>
</tr>
<tr>
<td>Anxiety</td>
<td>40 to 120mg</td>
</tr>
<tr>
<td>Certain thyroid conditions (such as thyrotoxicosis)</td>
<td>30 to 160mg</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy (thickening heart muscle)</td>
<td>30 to 160mg</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>30 to 60mg</td>
</tr>
<tr>
<td>Bleeding of the oesophagus caused by high blood pressure in the liver</td>
<td>80 to 160mg</td>
</tr>
</tbody>
</table>

*Under some circumstances, propranolol can be used to treat children with these conditions. The dosage will be adjusted by the doctor according to the child’s age or weight.

If you take more Propranolol Tablets than you should:
If you swallow too many tablets or someone else accidentally takes your medicine, contact your doctor, pharmacist or nearest hospital straight away.

If you forget to take Propranolol Tablets:
If you forget to take your medicine, take your dose when you remember and then take your next dose at the usual time. Do not take two doses at the same time.

If you stop taking Propranolol Tablets:
Do not stop taking Propranolol Tablets without first discussing it with your doctor. In some cases it may be necessary to stop taking the medicine gradually.

If you have any further questions on the use of Propranolol Tablets ask your doctor or pharmacist.

4. Possible side effects
Like all medicines Propranolol Tablets can cause side effects, although not everyone gets them.
If you experience sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing, then go to the hospital immediately.

Rare: (between 1 in 1000 to 1 in 10,000)
Contact your doctor or pharmacist if any of the following side effects noticed:
- Numbness and spasm in the fingers (Raynaud’s phenomenon)
- Heart block which may cause dizziness or fainting
- Worsening of heart failure (breathlessness and/or swollen ankles)
- Worsening of breathing difficulties in people with asthma or breathing problems
- Worsening of circulation in people with poor circulation

- Increased bruising, nosebleeds, sore throat or infections due to changes in the number and types of blood cells which can be measured by a blood test at your doctor’s.

Commons: (between 1 in 10 to 1 in 100 patients)
- Nausea, vomiting and diarrhoea
- Disturbed sleep, tiredness and muscle weakness

These may occur at the beginning of the treatment but should go if these signs do not get better after a few days then contact the doctor.

Occasionally people suffer with:
- Headache, disturbances of vision, hallucinations, psychoses, confusion, mood changes, dizziness, impotence, nightmares.
- Cold hands and feet, tingling of the hands.
- Skin rash or dry eyes.
If these continue contact your doctor or pharmacist for advice.

If you think you have any other side effect from taking this medicine, please tell your doctor or pharmacist.

5. How to store Propranolol Tablets
Keep out of the reach and sight of children.
Do not use Propranolol Tablets after the expiry date which is stated on the carton. The expiry date refers to the last day of the month.
Do not store the tablets above 25°C. Store in the original container.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information
What Propranolol Tablets contain
The active substance is Propranolol hydrochloride. The other ingredients are lactose, microcrystalline cellulose, talc, stearic acid, magnesium stearate, hypromellose, polyethylene glycol, titanium dioxide (E171) and carmine (E120).

What Propranolol Tablets look like and contents of the pack
The 40mg tablets are pink, film-coated biconvex tablets embossed '40' on one face.
Propranolol 40mg tablets are available in packs of 20, 50 and 1000 tablets and blister packs of 28 tablets.

Marketing Authorisation Holder and Manufacturer
Renopharm Limited, 27, Old Gloucester Street, London, WC1 N 3XG.

Date leaflet last revised May 2011

POM
UKPAR Propranolol 40 mg Tablets

LABELLING

Carton – pack size 28

Propranolol 40 mg Tablets
Each tablet contains 40mg of Propranolol Hydrochloride.
Also contains Lactose.
For oral administration.
Do as directed by your doctor.
Do not stop taking this medicine except on your doctor’s advice.
Do not take this medicine if you have a history of wheezing or asthma.
Please read the enclosed Patient Information Leaflet before taking
this medicine.
KEEP MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.
Do not store above 25°C. Store in the original package.

PL 20395/0082
Pl. Holder: Relonchem Ltd., 27 Old Gloucester Street, London WC1 3OX

Braille

Propranolol 40 mg Tablets
no. 40 mg Tablets

Blister foil