1. NAME OF THE MEDICINAL PRODUCT:

EDEN PROPRANOLOL 40 MG TABLETS
(Propranolol 40 mg Tablets BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each Film Coated Tablet Contains:
Propranolol Hydrochloride BP (40 mg)
Approved Colour Used. (-)
Excipients (.QS)

Sr. No.	Ingredients	Specifi-cation	Label Claim / Tablet (In mg)	Over ages added (In %)	Qty. / Tablet (In mg)	Reason for Function
a)	**Dry Mixing**					
1.	Lactose Monohydrate	BP	NA	NA	77.00	Diluent
2.	Maize starch	BP	NA	NA	88.00	Diluent
3.	Povidone (K 30)	BP	NA	NA	4.00	Binder
b)	**Binder Preparation**					
4.	Maize starch	BP	NA	NA	8.00	Binder
5.	Purified water	BP	NA	NA	-----	Vehicle
c)	**Lubrication**					
6.	Propranolol Hydrochloride	BP	40 mg	NA	40	Medicament
7.	Magnesium stearate	BP	NA	NA	3.00	Lubricant
8.	Croscarmellose sodium	BP	NA	NA	4.00	Disintegrant
9.	Colloidal anhydrous silica	BP	NA	NA	1.00	Glidant
	Average Weight of Uncoated Tablet (In mg)				**225.00**	
d)	**For Pre-Coating**					
10.	Povidone (K 30)	BP	NA	NA	0.44	Binder
11.	Isopropyl alcohol	BP	NA	NA	--	Solvent
e)	**Film Coating**					
12.	Hypromellose (15 CPS)	BP	NA	NA	3.00	Film-Former
13.	Titanium dioxide	BP	NA	NA	0.50	Opacifier
14.	Erythrosine supra	IH	NA	NA	0.30	Colour
15.	Purified talc	BP	NA	NA	1.50	Antiadherant
16.	Macrogol 6000	BP	NA	NA	0.40	Plasticizer
17.	Purified water	BP	NA	NA	-----	Vehicle
18.	Isopropyl alcohol	BP	NA	NA	-----	Solvent
	Average Weight of Film Coated Tablet (In mg)				**230.00**	

3. PHARMACEUTICAL FORM: Film coated Tablet
Description: Pink coloured, round shaped, biconvex, film coated tablet, plain on both sides.

4. Clinical Particulars
4.1 Therapeutic indications
EDEN PROPRANOLOL 40 MG TABLETS (Propranolol 40 mg Tablets BP) are indicated for
- the control of hypertension;
- the management of angina pectoris;
- long-term management against re-infarction after recovery from acute myocardial infarction;
- the control of most forms of cardiac dysrhythmias;
- the prophylaxis of migraine;

- the management of essential tremor;
- relief of situational anxiety and generalised anxiety symptoms, particularly
- those of somatic type;
- prophylaxis of upper gastrointestinal 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 peri-operatively (with an alphablocker).

4.2 Posology and method of administration
Route: Oral
Method of Administration:
Adults:
Hypertension
A starting dose of 80 mg twice a day may be increased at weekly intervals according to response. The usual dose range is 160 to 320 mg per day. With concurrent diuretic or other antihypertensive drugs a further reduction of blood pressure is obtained.
Angina, migraine and essential tremor
A starting dose of 40 mg two or three times daily may be 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 to 160 mg/day and in angina in the range 120 to 240 mg/day.
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
A dosage range of 10 to 40 mg three or four times a day usually achieves the required response.
Post myocardial infarction
Treatment should start between days 5 and 21 after myocardial infarction, with an initial dose of 40mg four times a day for 2 or 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. Dosing 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 with an alpha-receptor blocking drug).
Pre-operative: 60 mg daily for 3 days is recommended. Non-operable malignant cases: 30 mg daily.
Elderly people
Evidence concerning the relationship between blood level and age is conflicting. Propranolol should be used to treat elderly with caution. It is suggested that treatment should start with the lowest dose. The optimum dose should be individually determined according to clinical response.
Paediatric population
Dysrhythmias, phaeochromocytoma, thyrotoxicosis
Dosage should be individually determined and the following is only a guide:
Oral: 0.25 to 0.5 mg/kg three or four times daily as required.
Migraine
Oral: Under the age of 12: 20 mg two or three times daily.
Over the age of 12: The adult dose.
Fallot's tetralogy
The value of propranolol in this condition is confined mainly to the relief of right-ventricular outflow tract shut-down. It is also useful for treatment of associated dysrhythmias and angina. Dosage should be individually determined and the following is only a guide:
Oral: Up to 1 mg/kg repeated three or four times daily as required.
Method of administration
For oral administration.

4.3 Contraindications

EDEN PROPRANOLOL 40 MG TABLETS must not be used:

if there is a history of bronchial asthma or bronchospasm. The product label states the following warning: "Do not take Propranolol if you have a history of asthma or wheezing". 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.

EDEN PROPRANOLOL 40 MG TABLETS as with other beta-blockers must not be used in patients with any of the following conditions: known hypersensitivity to the substance; bradycardia; cardiogenic shock; hypotension; metabolic acidosis; after prolonged fasting; severe peripheral arterial circulatory disturbances; second or third degree heart block; sick sinus syndrome; untreated phaeochromocytoma; uncontrolled heart failure or Prinzmetal's angina.

EDEN PROPRANOLOL 40 MG TABLETS must not be used in patients prone to hypoglycaemia, i.e., patients after prolonged fasting or patients with restricted counter-regulatory reserves. 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 catecholamines.

4.4 Special warnings and precautions for use

EDEN PROPRANOLOL 40 MG TABLETS as with other beta-blockers: - although contraindicated in uncontrolled heart failure may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

- 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. - although contraindicated in severe peripheral arterial circulatory disturbances may also aggravate less severe peripheral arterial circulatory disturbances. - due to its negative effect on conduction time, caution must be exercised if it is given to patients with first degree heart block.

- may block/modify the signs and symptoms of the hypoglycaemia (especially tachycardia). **EDEN PROPRANOLOL 40 MG TABLETS** 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. **EDEN PROPRANOLOL 40 MG TABLETS** may prolong the hypoglycaemic response to insulin.

- may mask the signs of thyrotoxicosis.

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

- will reduce heart rate as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate, the dose may be reduced.

- may cause a more severe reaction to a variety of allergens when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions. Abrupt withdrawal of beta-blockers is to be avoided. The dosage should be withdrawn gradually over a period of 7 to 14 days. Patients should be followed during withdrawal especially those with ischaemic heart disease. When a patient is scheduled for surgery and a decision is made to discontinue beta-blocker therapy, this should be done at least 48 hours prior to the procedure. The risk/benefit of stopping beta blockade should be made for each patient. 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. **EDEN PROPRANOLOL 40 MG TABLETS** must be used with caution in patients with decompensated cirrhosis.
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.

4.5 Interaction with other medicinal products and other forms of interaction
EDEN PROPRANOLOL 40 MG TABLETS modifies the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of Inderal and hypoglycaemic therapy in diabetic patients. **EDEN PROPRANOLOL 40 MG TABLETS** may prolong the hypoglycaemic response to insulin.

Simultaneous administration of rizatriptan and propranolol can cause an increased rizatriptan AUC and C_{max} 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 (eg, 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, eg, nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Concomitant use of sympathomimetic agents eg, 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 **EDEN PROPRANOLOL 40 MG TABLETS** during infusion of lidocaine may increase the plasma concentration of lidocaine by approximately 30%. Patients already receiving Inderal 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 beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers 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 **EDEN PROPRANOLOL 40 MG TABLETS** 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 **EDEN PROPRANOLOL 40 MG TABLETS**.

Concomitant administration of **EDEN PROPRANOLOL 40 MG TABLETS** 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 Inderal.

Caution must be exercised when using anaesthetic agents with **EDEN PROPRANOLOL 40 MG TABLETS**. The anaesthetist should be informed and the choice of anaesthetic should be an 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.

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 Pregnancy and Lactation

Pregnancy

As with all drugs **EDEN PROPRANOLOL 40 MG TABLETS** should not be given during pregnancy unless its use is essential. There is no evidence of teratogenicity with **EDEN PROPRANOLOL 40 MG TABLETS**. However beta-blockers reduce placental perfusion, which may result in intra-uterine foetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia 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.

Lactation

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

4.7 Effects on ability to drive and use machines

EDEN PROPRANOLOL 40 MG TABLETS has no or negligible influence on the ability to drive and use machines. However it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

EDEN PROPRANOLOL 40 MG TABLETS 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 de{nitions 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); Frequency not known (cannot be estimated from the available data).

System organ class	**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 available data)**
Blood and lymphatic system disorders			Thrombocytopenia		Agranulocytosis
Immune system disorders			Angioedema		
Metabolism and nutrition disorders				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. Changes in lipid metabolism(changes	

				in blood concentrations of triglycerides and cholesterol). Severe hypoglycemia may rarely lead to seizures or coma	
Psychiatric disorders*	Sleep disturbances, nightmares		Hallucinations, psychoses, mood changes		Depression
Nervous system disorders*			Confusion, memory loss, paraesthesia, dizziness	Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported	Headache, seizure linked to hypoglycaemia
Eye disorders*			Dry eyes, visual disturbances		Conjunctivitis
Cardiac disorders	Bradycardia, cold extremities		Heart failure deterioration, precipitation of heart block, postural hypotension, which may be associated with syncope		Worsening of attacks of angina pectoris
Vascular disorders	Raynaud's phenomenon		Exacerbation of intermittent claudication		
Respiratory, thoracic and mediastinal disorders	Breathlessness		Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome		Dyspnoea
Gastro-intestinal disorders		Gastrointestinal disturbance, such as nausea, vomiting, diarrhoea			Constipation, dry mouth
Skin and subcutaneous tissue disorders [b]			Purpura, alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes	Isolated cases of hyperhidrosis has been reported	
Musculoskeletal and connective tissue disorders					Arthralgia
Renal and					Reduced renal

Urinary disorders					blood flow and GFR
Reproductive system and breast disorders					Impotence
General disorders and administration site conditions*	Fatigue and/or lassitude (often transient)		Dizziness		
Investigations			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 wellbeing 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. 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 Yellow Card Scheme.

4.9 Overdose

Symptoms:

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 (beta blocker) ATC code: C07AA05.

EDEN PROPRANOLOL 40 MG TABLETS 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 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.
It 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.
EDEN PROPRANOLOL 40 MG TABLETS is effective and well tolerated in most ethnic populations, although the response may be less in black patients.

5.2 Pharmacokinetic properties
Absorption
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
Distribution
Propranolol is completely absorbed after oral administration and peak plasma concentrations occur 1 to 2 hours after dosing in fasting patients.
Metabolism and Elimination
It is metabolised in the liver, the metabolites being excreted in the urine together with only small amounts of unchanged Propranolol; at least one of its metabolites is considered to be biologically active. The biological half-life of Propranolol is longer than would be anticipated from its plasma half-life of about 3-6 hours.

5.3 Preclinical safety data
Propranolol is a drug on which extensive clinical experience has been obtained.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose Monohydrate, Maize Starch, Povidone (K 30), Purified Water, Magnesium Stearate, Croscarmellose sodium, Colloidal Anhydrous Silica, Isopropyl Alcohol, Hypromellose (15 CPS), Erythrosine supra, Titanium Dioxide, Macrogol-6000, Purified Talc.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store in a cool, dry place.
Store below 30°C

6.5 Nature and contents of container
For ALU-PVC pack style:
Primary packing: 10 Tablets in an ALU-PVC Blister.
Secondary packing: 10 Blisters are packed in a carton along with leaflet.
Tertiary packing: Shrink such 10 cartons with shrinkable PVC sleeves. Such 10 Shrinks are packed in a 5 Ply corrugated box sealed with BOPP tape & strap with strapping roll.

For Jar pack style:
Primary packing: 1000 Tablets are packed in a polybag and sealed.
Secondary packing: Sealed polybag containing 1000 tablets are packed in a HDPE Jar along with silica gel sachet and leaflet then close with HDPE Cap. Stick printed sticker Label to the HDPE Jar.
Tertiary packing: Shrink individual HDPE Jar. Such 50 HDPE Jars are packed in a 7 ply corrugated box sealed with BOPP tape & strap with strapping roll.

6.6 Special precautions for disposal and other handling
None

7 APPLICANT / MANUFACTURER

Applicant

Applicant name and address	**M/s. EDEN U-K PHARM LTD** J116, Daminja Avenue, Housing Estate, Fegge, Anambra State.
Contact person's phone number	
Contact person's email	

Manufacturer

Manufacturer name and address	**M/s. IMPULSE PHARMA PVT. LTD.** J-201, J-202/1 , MIDC Tarapur, Boisar, Dist. Palghar - 401506, Maharashtra State, India.
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