Generic Name Sustained release Propranolol Hydrochloride & Flunarizine dihydrochloride

Trade Name: Migrabeta Plus

1. **NAME OF THE MEDICINAL PRODUCT: Sustained release Propranolol Hydrochloride & Flunarizine dihydrochloride**

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**
   Each uncoated bilayered tablet contains:
   Propranolol Hydrochloride IP..... 40 mg
   (As sustained release form)
   Flunarizine Hydrochloride BP
   Eq. to Flunarizine ……. 10 mg
   Colour: Sunset yellow FCF

3. **PHARMACEUTICAL FORM: Tablets**

4. **CLINICAL PARTICULARS**

4.1 Therapeutic Indications

The combination is indicated for the prophylaxis of migraine.

4.2 **Posology and Method of Administration**

Single tablet once daily.

4.3 Contraindications

- Hypersensitivity to propranolol or flunarizine or cinnarizine or to any of the excipients
- The presence of second or third degree heart block; cardiogenic shock
- A history of bronchospasm or bronchial asthma, chronic obstructive airways disease
- After prolonged fasting (ie hypoglycaemia)
- In metabolic acidosis (eg in diabetes)
- Bradycardia(heart rate <45-50 beats/min); hypotension
- Severe peripheral arterial disturbances; sick sinus syndrome; Prinzmetal's angina; untreated phaeochromocytoma.

- Suffering from depressive illness; Have Parkinson’s disease; and Suffering from extra-pyramidal disorders.

4.4 Special Warnings and Special Precautions for Use

Propranolol

One of the pharmacological actions of propranolol is to reduce the heart rate; in the instance when symptoms may be attributable to slow heart rate, the dose may be reduced.

Special care should be taken with patients whose cardiac reserve is poor. Beta-adrenoceptor blocking drugs should be avoided in overt heart failure; however, they may be used in patients whose signs of failure have been controlled.

Caution must be exercised if propranolol is given to patients with first degree heart block.

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

As with other beta-adrenoceptor blocking agents, in patients with ischaemic heart disease, treatment should not be discontinued abruptly. Either the equivalent dosage of another beta-adrenoceptor blocker may be substituted or the withdrawal of propranolol should be gradual.

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

Propranolol should be used with caution in patients with decompensated cirrhosis.

Liver function will deteriorate in patients with portal hypertension and hepatic encephalopathy may develop. There have been some reports suggesting that treatment with propranolol may increase the risk of developing hepatic encephalopathy.

Although contraindicated in severe peripheral circulatory disturbances, beta adrenoreceptor blocking drugs may also aggravate less severe forms. Therefore, propranolol should be used with great caution in conditions such as Raynaud's disease/syndrome or intermittent claudication.

Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported in patients administered propranolol.
Psoriasis may be aggravated by the use of beta adrenoreceptor blocking drugs.

Beta adrenoreceptor blocking drugs should not be used in untreated phaeochromocytoma, however, in patients with phaeochromocytoma an alpha-blocker may be given concomitantly.

Beta adrenoceptor blocking drugs 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. Particular caution is necessarily, when beta adrenoceptor blocking drugs are used in patients with a history of anaphylaxis.

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

Withdrawal
Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. In the rare event of intolerance, manifested as bradycardia and hypotension, the drug should be withdrawn and, if necessary, treatment for overdosage instituted. The sudden withdrawal of beta-receptor antagonists may result in severe exacerbation of angina pectoris, acute myocardial infarction, sudden death, malignant tachycardia, sweating, palpitation and tremor. Withdrawal should be accomplished over 10 to 14 days however caution must be exercised as this does not always prevent rebound effects.

When withdrawing a beta-blocker 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, although there may be an increased risk of hypertension. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs and the chosen anaesthetic should have as little negative inotropic activity as possible. The anaesthetist should always be informed about the use of a beta-blocking drug. The patient may be protected against vagal reactions by the intravenous administration of atropine

Flunarizine

General

Flunarizine may lead to drowsiness, which is aggravated by the simultaneous intake of alcohol or other central nervous system depressants.
Patients should be cautioned against driving motor vehicles or performing other potentially hazardous tasks where a loss of mental alertness may lead to accidents.
Flunarizine is not suited for aborting a migraine attack. The possible occurrence of an attack is, therefore, no reason to increase the dose of flunarizine.
This treatment may give rise to extra-pyramidal and depressive symptoms and reveal Parkinsonism, especially in predisposed patients such as the elderly. Flunarizine should, therefore, be used with caution in such patients.

Potentially Life-Threatening Effects

Doses of flunarizine of 10–11.5 mg daily for periods of 1–16 months were associated with extra-pyramidal reactions in 10 patients. These included bradykinesia, rigidity, akathisia, orofacial dyskinesia, torticollis and tremor, of which elderly patients seem particularly at risk. The withdrawal of flunarizine resulted in recovery over a variable period of time (2 weeks to 6 months). However, akathisia may persist. Depression is also common feature. Epidemiological evidence suggests that patients older than 65 years, those with essential tremor, a family history of essential tremor, a history of iatrogenic extra-pyramidal effects or a history of Parkinson's disease are more prone to flunarizine-induced Parkinsonism. Long-term therapy should be avoided in these patients. A case of erythema multiforme, occurring 1 month after treatment with flunarizine, was reported.

Extra-pyramidal motor signs (including Parkinsonism, orofacial tardive dyskinesia and akathisia) have been reported in 12 patients given flunarizine 10–40 mg daily, for a period between 3 weeks and 15 months; 11 also had mental depression. Partial or complete improvement of symptoms occurred after withdrawal of flunarizine. There have been other reports of similar effects, but the association with flunarizine has always been certain. Some researchers have commented that flunarizine is often used in patients at increased risk of depression (migraine and geriatric patients) or extra-pyramidal symptoms (geriatric patients) or that flunarizine may unmask subclinical idiopathic Parkinson's disease.

Extra-pyramidal signs, including Parkinsonism, have also been associated with the related drug, cinnarizine. It has been suggested that such effects may be less likely to occur with cinnarizine than with flunarizine because of its shorter half-life and lower lipophilicity.

Porphyria

Flunarizine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in invitro system

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Propranolol

Adrenaline (epinephrine):
Care should be taken in the parenteral administration of preparations containing adrenaline (epinephrine) to patients taking beta-adrenoceptor blocking drugs as, in rare cases, vasoconstriction, hypertension and bradycardia may result.

Anaesthetics:
Care should be taken when using anaesthetic agents with propranolol. The anaesthetist should be informed and the choice of anaesthetic should be the agent with as little negative inotropic activity as possible.

Anti-arrhythmics:
Caution must be exercised in co-prescribing beta-adrenoceptor blockers with Class I anti-arrhythmic agents such as disopyramide, quinidine, flecainide and amiodarone may have potentiating effects on arterial conduction time and induce negative inotropic effect. 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.

Combined use of beta-adrenoceptor blocking drugs and calcium channel blockers with negative inotropic effects eg verapamil, diltiazem can lead to prolongation of SA and AV conduction particularly in patients with impaired ventricular function or 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 used in association with beta-adrenoceptor blockers may increase AV conduction time.

Anticoagulants:
Propranolol may cause a reduction in clearance and an increase in plasma concentrations of warfarin.

Antidiabetic drugs:
Propranolol modifies the tachycardia of hypoglycaemia; caution should therefore be exercised in the concomitant use of propranolol and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin.

Antihypertensives:
Beta-adrenoceptor blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the drugs are co-administered, the beta-adrenoceptor blocking drug should be withdrawn several days before discontinuing clonidine. If replacing clonidine with beta-adrenoceptor therapy the introduction of the beta-adrenoceptor blocking drug should be delayed for several days after

clonidine administration has stopped. Concomitant use of moxonidine and beta blockers may result in an enhanced hypotensive effect. The steps for moxonidine withdrawal/introduction should be the same as for clonidine. Hypotensive effect may be enhanced when propranolol is taken with diuretics, methyldopa or levodopa.

Prazosin or other alpha-adrenoreceptor blockers may potentiate postural hypotension, tachycardia and palpitations.

Antimigraine drugs:
Caution is necessary if ergotamine, dihydroergotamine or related compounds are given in combination with propranolol since vasospastic reactions have been reported in a few patients. Propranolol inhibits the metabolism of rizatriptan which can significantly increases plasma concentration levels. A dose reduction to 5mg is recommended. Administration should be separated by 2 hours.

Barbiturates:
The metabolism of propranolol may be increased by potent liver enzyme inducer barbiturates.

Chlorpromazine:
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.

Cimetidine:
Concomitant use of cimetidine will increase, where as alcohol will decrease the plasma levels of propranolol.

Hydralazine:
Concomitant use of hydralazine will increase, where as alcohol will decrease the plasma levels of propranolol.

Imipramine:
Propranolol may cause plasma concentrations of imipramine to increase.

Monamine-oxidase Inhibitors:
The hypotensive effects of beta-blockers may be enhanced by MAOIs.

Non-steriodal anti-inflammatory drugs:
NSAIDs notably indometacin, may cause an increase in blood pressure. This may be particularly significant in patients with poorly controlled hypertension.

Rifampicin:

The metabolism of propranolol may be increased by potent liver enzyme inducer rifampicin.

Selective Serotonin Re-uptake Inhibitors:
Fluvoxamine inhibits oxidative metabolism and increases plasma concentrations of propranolol. This may result in severe bradycardia.

Theophylline:
Propranolol reduces the clearance and consequentially increases the plasma concentration of theophylline.

Tobacco:
Smoking tobacco may oppose the effects of beta blockers in the treatment of angina or hypotension. Patients should be encouraged to stop smoking, apart from its other toxic effects, it aggravates ocardial ischaemia, increases heart rate and can impair blood pressure control. If patient continues to smoke, dosage of the beta blocker may need to be increased or a cardio-selective beta blocker may be more appropriate.

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

Flunarizine

Amiodarone

As flunarizine is a calcium channel blocker, caution should be exercised with certain drugs, although clinical experience with flunarizine is limited. Concomitant treatment of a calcium channel blocker and amiodarone has been reported to result in sinus arrest and atrioventricular block.

Hypnotics and Tranquillizers

Excessive sedation can occur when alcohol, hypnotics or tranquillizers are taken simultaneously with flunarizine.

Adenosine

With adenosine, prolonged bradycardia may occur and calcium channel blocking agents may enhance the neuromuscular blockade induced by non-depolarizing agents such as tubocurarine, but flunarizine is not contraindicated in patients who use beta-blocking agents.

Hepatic Enzyme Inducers

Hepatic enzyme inducers such as carbamazepine, phenytoin and valproate may interact with flunarizine by increasing its metabolism; an increase in the dosage of flunarizine may be required.

Sumatriptan

Flunarizine 10 mg once daily for 8 days was found to have no influence on the single-dose pharmacokinetics of sumatriptan. In addition, no significant changes in heart rate or blood pressure occurred.

4.6 Fertility, Pregnancy and Lactation

Propranolol

Pregnancy

As with all other drugs, propranolol should not be given in pregnancy or lactation unless its use is essential. There is no evidence of teratogenicity with propranolol. However beta-adrenoceptor blocking drugs 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-adrenoceptor blocking drugs, particularly lipophilic compounds, will pass into breast milk although to a variable extent. Breast feeding is therefore not recommended following administration of these compounds**.**

Flunarizine

Pregnancy

The safety of flunarizine for use in human pregnancy has not been established. An evaluation of animal studies did not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or foetus, or the course of gestation or peri-natal and postnatal development.

Lactation

No data are available on the excretion of flunarizine in human breast milk. Breast-feeding should, therefore, be avoided in nursing mothers who are taking flunarizine

4.7 Effects on Ability to Drive and Use Machines

Flunarizine may lead to drowsiness, which is aggravated by the simultaneous intake of alcohol or other central nervous system depressants.
Patients should be cautioned against driving motor vehicles or performing other potentially hazardous tasks where a loss of mental alertness may lead to accidents.

4.8 Undesirable Effects

Propranolol

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).

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

Blood and lymphatic system disorders
Rare: thrombocytopenia,
Frequency not known: agranulocytosis

Endocrine disorders
Frequency not known: masking signs of thyrotoxicosis.

Metabolic and nutritional disorders
Frequency 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. Changes in lipid metabolism (changes in blood concentrations of triglycerides and cholesterol)

Psychiatric disorders
Common: Sleep disturbances, nightmares.
Frequency not known: depression, confusion

Nervous system disorders
Rare: Hallucinations, psychoses, mood changes, confusion, memory loss, dizziness, paraesthesia.
Very rare: Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported.
Frequency not known: headache, seizure linked to hypoglycaemia.

Eye disorders
Rare: visual disturbances, dry eyes
Frequency not known: conjunctivitis

Cardiac disorders
Common: bradycardia
Rare: Heart failure deterioration, precipitation of heart block, postural hypotension which may be associated with syncope,
Frequency not known: worsening of attacks of angina pectoris

Vascular disorders
Common: cold extremities, Raynaud's syndrome
Rare: exacerbaction 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.
Frequency not known: dyspnoea.

Gastrointestinal disorders
Uncommon: diarrhoea, nausea, vomiting
Frequency not known: constipation, dry mouth

Skin and subcutaneous tissue disorders
Rare: alopecia, purpura, psoriasiform skin reactions, exacerbation of psoriasis, rash
Musculoskeletal system and connective tissue disorders
Frequency not known: arthralgia

Renal and urinary disorders
Frequency not known: reduced renal blood flow and GFR

Reproductive system and breast disorders
Frequency not known: sexual dysfunction

General disorders and administration site conditions
Common: fatigue and/or lassitude (often transient)

Investigations:
Very rare: An increase in ANA (antinuclear antibodies) has been observed with many beta blockers, 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 manifested as bradycardia and hypotension, the drug should be withdrawn and, if necessary, treatment for overdosage instituted.

Flunarizine

The most common set of undesirable effects seen with flunarizine are weight gain, particularly in migrainous patients, depression, extra-pyramidal symptoms (sometimes associated with depression) and, rarely, galactorrhoea in female patients on oral contraceptives within 2 months of flunarizine treatment.

Some of the undesirable effects often seen with flunarizine include drowsiness, headache, insomnia, asthenia, depression, heartburn, nausea, dry mouth, gastralgia, constipation and diarrhoea.

4.9 Overdose

Propranolol

Clinical features:

Cardiac - Bradycardia, hypotension, pulmonary oedema, syncope and cardiogenic shock may develop. Conduction abnormalities such as first or second degree AV block may occur. Rarely arrhythmias may 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. The elderly 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, vomiting and occasionally CNS-mediated respiratory depression may occur. The concept of cardioselectivity is much less applicable in the overdose situation and systemic effects of beta-blockade include bronchospasm and cyanosis, particularly in those with pre-existing airways disease. Hypoglycaemia and hypocalcaemia are rare and occasionally generalised spasm may also be present.

Management

In cases of overdose or extreme falls in the heart rate or blood pressure, treatment with propranolol must be stopped. In addition to primary poison elimination measures, vital parameters must be monitored and corrected accordingly in intensive care.

This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal (50 g for adults, 1 g/kg for children) if an adult presents within 1 hour of ingestion of more than a therapeutic dose or a child for any amount. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose.

Bradycardia may respond to large doses of atropine (3 mg intravenously for an adult and 0.04 mg/kg for a child).

For severe hypotension, heart failure or cardiogenic shock in adults a 5-10mg IV bolus of glucagon (50-150 micrograms/kg in a child) should be administered over 10 minutes to reduce the likelihood of vomiting, followed by an infusion of 1-5 mg/hour (50 micrograms/kg/hour), titrated to clinical response. If glucagon is not available or if there is severe bradycardia and hypotension, which is not improved by glucagon, isoprenaline at an infusion rate of 5-10 micrograms/minute (0.02 micrograms/kg/min in children increasing to a maximum of 0.5 micrograms/kg/min) and increased as necessary depending on clinical response.

In severe hypotension additional inotropic support may be necessary with a beta agonist such as dobutamine 2.5-40 micrograms/kg/min (adults and children).

Nebulised salbutamol 2.5-5 mg should be given for bronchospasm. Intravenous aminophylline may be of benefit in severe cases (5 mg/kg over 30 mins followed by an infusion of 0.5-1 mg/kg/hour). Do not give the initial loading dose of 5 mg/kg if the patient is taking oral theophylline or aminophylline.

Cardiac pacing may also be effective at increasing heart rate but does not always correct hypotension secondary to myocardial depression.
In cases of generalised spasm, a slow intravenous dose of diazepam may be used (0.1-0.3 mg/kg body weight).

Flunarizine

On the basis of the pharmacological properties of the drug, sedation and asthenia may be expected to occur. A few cases of acute over dosage (up to 600 mg in one intake) have been reported and the observed symptoms were sedation, agitation and tachycardia. No specific antidote is known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Propranolol

ATC code: C07A A05
Propranolol hydrochloride is a beta-adrenoceptor blocking agent.

Mode of Action

Propranolol is a competitive antagonist at both beta, and beta2-adrenoceptor, but has membrane stabilising activity at concentrations exceeding 1-3mg/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.

Flunarizine

Flunarizine (0.01–10 µmol.l -1) inhibits the entry of Ca 2+ into cells via voltage-gated calcium channels. It has a higher affinity for the T-type compared with the L- and N-type voltage-operated channel. In consequence, it exhibits greater potency against neuronal than non-neuronal calcium channels, inhibiting (to a greater extent than verapamil or diltiazem) the uptake of calcium by cortical synaptosomes, but with less effect on the calcium channels of smooth muscle than the dihydropyridines. Flunarizine inhibits the Ca 2+ -Mg 2+ ATPase activity of synaptic plasma membranes, decreasing the V max by 37% with no significant effects on the K m for Ca 2+ (162.7 + 14.9 nM free); this is an effect mediated by the inhibition of the calmodulin interaction with the enzyme.

5.2 Pharmacokinetic Properties

Propranolol

Propranolol is almost completely absorbed from the gastrointestinal tract, but it is subject to considerable first-pass metabolism. Peak plasma concentrations occur about 2 hours after a dose. 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.

Flunarizine

Flunarizine is a highly lipophilic and poorly water soluble compound. It distributes preferentially in adipose tissues, tightly to plasma and tissue proteins and readily crosses the blood brain barrier. The blood level of the drug is low whereas tissues level is much higher. It is readily absorbed in gastrointestinal tract and having high first pass metabolism. Peak plasma concentration achieved 2-4 hours after oral administration in healthy volunteers. With repeated administration of 10 mg daily, plasma concentration increases very gradually reaching a steady state concentration after about 5-6 weeks of drug administration. It has large volume of distribution i.e. 43.2 L/kg. Its half-life is 7-10 days and metabolic degradation occurs by aromatic hydroxylation and oxidative dealkylation

5.3 Preclinical Safety Data

In dietary administration studies in which mice and rats were treated with propranolol hydrochloride for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. On a body surface area basis, this dose in the mouse and rat is, respectively, about equal to and about twice the maximum recommended human oral daily dose (MRHD) of 640 mg propranolol hydrochloride. In a study in which both male and female rats were exposed to propranolol hydrochloride in their diets at concentrations of up to 0.05% (about 50 mg/kg body weight and less than the MRHD), from 60 days prior to mating and throughout pregnancy and lactation for two generations, there were no effects on fertility. Based on differing results from Ames Tests performed by different laboratories, there is equivocal evidence for a genotoxic effect of propranolol hydrochloride in bacteria (S. typhimurium strain TA 1538).

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

24 Months

6.2 Special Precautions for Storage

Store in a cool dry & dark place

6.3 Nature and Contents of Container

06x10

Marketed By

Alkem Laboratories Limited,
Alkem House, S.B. Road,
Lower Parel (West)
Mumbai 400013