1.3.3.2 English leaflet.

English leaflet is enclosed overleaf.
Cardex® plus
Bisoprolol Fumarate / Hydrochlorothiazide Tablets

Composition:
Cardex Plus 10/25 mg: Each film coated tablet contains: Bisoprolol Fumarate 10 mg and Hydrochlorothiazide 25 mg. 
Cardex Plus 5/12.5 mg: Each film coated tablet contains: Bisoprolol Fumarate 5 mg and Hydrochlorothiazide 12.5 mg.
Excipients: Cellulose microcrystalline, starch pregelatinized, colloidal silicone dioxide, t alc, magnesium stearate, HPMC, PEG, titanium dioxide, ferric oxide red, lake of brilliant blue, and simethicone.

Properties:
In healthy volunteers, both Bisoprolol fumarate and hydrochlorothiazide are well absorbed following oral administration of Bisoprolol fumarate and hydrochlorothiazide tablets. No change is observed in the bioavailability of either agent when given together in a single tablet. Absorption is not affected whether Bisoprolol fumarate and hydrochlorothiazide tablets are taken with or without food. Mean peak Bisoprolol fumarate plasma concentrations of about 9.0 ng/mL, 19 ng/mL and 36 ng/mL occur approximately 3 hours after the administration of the 5 mg/6.25 mg and 10 mg/6.25 mg combination tablets, respectively. The elimination T 1/2 of Bisoprolol ranges from 7 to 15 hours and that of hydrochlorothiazide ranges from 4 to 10 hours. The percent of dose excreted unchanged in urine is about 55% for Bisoprolol and about 60% for hydrochlorothiazide.

Indications:
Cardex Plus is indicated for high blood pressure (essential hypertension). The fixed dose combination Cardex Plus is indicated in patients whose blood pressure is not adequately controlled on Bisoprolol or hydrochlorothiazide alone.

Contraindications:
Cardex Plus is contraindicated for patients with known hypersensitivity to Bisoprolol or hydrochlorothiazide or other thiazides, sulphonamides or any of its components. It is also contraindicated in the following cases:
- Acute myocardial insufficiency (heart failure) or during a deterioration (decompensation) of heart failure requiring intravenous therapy with substances increasing the contractility of the heart.
- Shock induced by disorders of cardiac function (cardiogenic shock).
- Severe disturbances of atrioventricular impulse conduction (second or third degree AV block) without a pacemaker.
- Sick sinus syndrome.
- Disturbed impulse conduction between sinus node and atrium (sinoatrial block).
- Markedly slowed heart beat (pulse rate less than 50 beats/min) before the start of treatment.
- Tendency to severe bronchospasm (bronchial asthma) or severe chronic obstructive airways diseases.
- Late stages of peripheral arterial occlusive disease or vascular spasms in toes and fingers (Raynaud’s syndrome).
- Tumours of the adrenal medulla (phaeochromocytoma).
- Excessive acidity of the blood (metabolic acidosis).
- Severe disturbances of kidney function (renal insufficiency) with severely impaired or absent urine production ( creatinine clearance less than or equal to 30 ml/minute or serum creatinine over 1.8 mg/100 ml).
- Acute inflammation of the kidney (glomerulonephritis).
- Disturbances of consciousness caused by severe liver disease (coma/ hepatic precoma).
- Potassium deficiency states (hypokalaemia) not responding to treatment.
- Severe sodium deficiency states (hyponatraemia).
- Increased calcium concentrations in the blood (hypercalcaemia).
- Gout.

Precautions:
Pregnancy and lactation: Cardex Plus must not be used during pregnancy as suspected to cause a deficiency of blood platelets (thrombocytopenia) in the newborn infant as well as a possible drop in heart rate (bradycardia), low blood pressure (hypotension) and excessively low blood glucose levels in the unborn or newborn infant.
Cardex Plus must also not be used during the nursing period (reduced milk production and/or excretion of hydrochlorothiazide in breast milk). If use during this period is essential, breast-feeding must be avoided.
In children:
Cardex Plus should not be used in children as no experience in this context is available.

Interactions with other drugs:
Simultaneous administration of the following drugs is not recommended:
- Delayed atrioventricular impulse conduction as well as reduced contractility of the heart muscle (heart failure) have been observed in simultaneous use of calcium antagonists.
- Invasive administration of calcium antagonists of the verapamil type may lead to pronounced hypotension and AV blockade.
- Simultaneous use of clonidine increases the risk of an excessive drop in heart rate and delayed cardiac impulse conduction. Discontinuation of clonidine may also cause an excessive increase in blood pressure.
- Clonidine must not be withdrawn until treatment with Cardex Plus has been discontinued for several days. Subsequently clonidine is discontinued on a gradual basis.
- Simultaneous use of monoaminoxidase inhibitors (except MAO-B inhibitors) may intensify the blood pressure lowering effect of beta-blockers, but also increase the risk of a hypertensive crisis.
- The simultaneous use of lithium may cause severe damage to the heart and nervous system due to reduced lithium excretion.
- Nonantiarrhythmic drugs that may induce torsade de pointes: astemizole, i.v. erythromycin, halofantrine, pentamidine, sparfloxazin, terfendadine and vincamine. In case of hypokalaemia use drugs that do not produce torsade de pointes.
- Concomitant administration with the following drugs only with caution:
- Calcium antagonists of the dihydropyridine type (e.g. nifedipine) increased risk of hypotension, especially at the beginning. In patients with latent heart failure, concomitant treatment with beta-blockers may lead to manifestation of the heart failure.
- Reserpine, a-methyldopa, guanfacine or clonidine may lead to an excessive decrease in blood pressure and heart rate or to delayed cardiac conduction.
- Other beta-blockers, including those contained in eye drops, exert additive effects.
- Nonsteroidal anti-inflammatory drugs: in patients with reduced blood milk production and/or excretion of hydrochlorothiazide in breast milk).

Dosage and Administration:
Cardex Plus may be administered in patients whose blood pressure is not adequately controlled on Bisoprolol or hydrochlorothiazide alone.
Oral: Adults: Dose is individualized, given once daily.

Notes to be taken into account in concomitant administration with the following drugs:
When used together with mefloquine: increased risk of drop in heart rate.
Please take into account that this applies also to drugs that you have taken recently.

Warnings:
You may take Cardex Plus only under certain conditions and only with special caution in the following:
- Heart failure (treatment of stable chronic heart failure with Cardex Plus must be started by gradually increasing the dose with fractions of the available tablet strength).
- Bronchospasm (bronchial asthma, obstructive airways diseases).
- Concomitant treatment with inhalation anesthetics.
- Diabetes mellitus with extremely fluctuating blood glucose levels; symptoms of markedly reduced blood glucose (hypoglycemia) may be masked.
- Strict fasting.
- Ongoing desensitisation therapy.
- Mild disturbances of atrioventricular impulse conduction (first degree AV block).
- Disturbed cardiac blood flow due to spasmodic constrictions of the coronary vessels (Prinzmetal’s angina).
- Peripheral arterial occlusive disease (intensification of complaints may occur especially when starting therapy).
- Reduced blood volume (hypovolaemia).
- Disturbed liver function.
- In bronchial asthma or other chronic obstructive pulmonary diseases that may be associated with symptoms, concomitant bronchodilator therapy is indicated. An increase in airways resistance may occasionally occur in asthma patients, requiring a higher dose of bronchodilators (β2-sympathomimetics).

As with other beta-blockers, Bisoprolol may increase both the sensitivity towards allergy-triggering substances (allergens) and the severity of allergic (anaphylactic) reactions. Adrenaline does not always produce the desired therapeutic effect in these cases.
Individual dose adjustment (dose titration) with the single agents (i.e. Bisoprolol and hydrochlorothiazide) can be recommended. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

**Dosage in liver or kidney function disorders**

In impaired kidney or liver function, the excretion of the hydrochlorothiazide component of Cardex Plus is reduced. You should swallow the film coated tablets whole with some liquid, if possible in the morning with the breakfast. During treatment with Cardex Plus you should ensure an adequate supply of fluid and food rich in potassium to compensate for the increased loss of potassium.

The potassium losses may be reduced or prevented by concomitant therapy with potassium-sparing diuretics.

**Overdosage:**

In the case of suspected overdosage with Cardex Plus, please inform your doctor immediately. Depending on the extent of overdosage your doctor can then decide which measure to take. The most frequent signs of overdosage with Cardex Plus include slowed heart beat (bradycardia), bronchospasm, marked drop in blood pressure, acute heart failure and reduced blood glucose (hypoglycemia). In the event of overdosage the treatment with Cardex Plus must be stopped immediately.

**Side Effects:**

The side effects are listed according to the following definition:

- **Very common:** > 1/10
- **Common:** <1/10 and > 1/100
- **Uncommon:** < 1/100 and >1/1000
- **Rare:** <1/1000 and > 1/10000
- **Very rare:** < 1/10000

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>Decrease of white blood cells (leucopenia), deficiency of platelets (thrombocytopenia)</td>
<td>Rare</td>
</tr>
<tr>
<td>Extreme reduction of granulated white blood cells (agranulocytosis)</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Increase in blood lipids (triglycerides, cholesterol), increased blood glucose levels (hyperglycemia) and excretion of glucose in the urine (glucosuria), hyperuricemia, hypokalemia, hyponatremia, hypomagnesemia, hypochloridemia, hypercalcemia, metabolic acidosis</td>
<td>Common</td>
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<tr>
<td>Tiredness*, exhaustion*, dizziness*, headache*</td>
<td>Common</td>
</tr>
<tr>
<td>Sleep disorders, depression, Nightmares, hallucinations</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Visual disturbances, reduced tear flow (to be taken into consideration in patients wearing contact lenses)</td>
<td>Rare</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Muscle weakness and cramps</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Reversible increase of serum creatinine and urea</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hypersensitivity reactions: itching, flush, inflammatory skin change ( rash), photodermatitis, purpura, urticaria</td>
<td>Rare</td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, constipation</td>
<td>Common</td>
</tr>
<tr>
<td>Loss of appetite, abdominal complaints, pancreatitis</td>
<td>Common</td>
</tr>
<tr>
<td>Increased liver enzymes (ALAT, ASAT), hepatitis, jaundice</td>
<td>Rare</td>
</tr>
<tr>
<td>Hypersensitivity reactions: itching, flush, inflammatory skin change (rash), photodermatitis, purpura, urticaria</td>
<td>Rare</td>
</tr>
</tbody>
</table>

* These symptoms occur especially at the start of treatment. They are mild and mostly disappear within 1-2 weeks. Consult your Pharmacist or Physician if any side effect is observed.

**Pharmaceutical Precautions:**

Keep at room temperature (15-30°C). Do not use beyond the expiry date or if the product shows any sign of deterioration.

**Presentations:**

- **Cardex Plus 10/25 mg:** Packs of 30 Film Coated Tablets.
- **Cardex Plus 5/12.5 mg:** Packs of 30 Film Coated Tablets. Hospital packs are available.

® is a trademark.

**THIS IS A MEDICAMENT**

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Strictly follow the doctor’s prescription, the method of use and the instruction of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks. Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children.

Council of Arab Health Ministers & Union of Arab Pharmacists.