PACKAGE LEAFLET: INFORMATION FOR THE USER

# Byol HL

**5mg/12.5mg** Film-coated Tablets

BISOPROLOL FUMARATE AND HYDROCHLOROTHIAZIDE

*• This leaflet is a copy of the Summary of Product Characteristics and Patient Information Leaflet for a medicine, which outlines the conditions under which the medicine should be used and information on its known safety • The product information may be updated several times within its shelf life, and there could be differences between the version of information shown here and other information in the public domain or in the package insert • This leaflet may not contain all the information about the medicine or the information may not be the most up to date version for this product • If you have any questions or are not sure about anything, ask your doctor or pharmacist • Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.*

*• Keep this leaflet • You may need to read it again • If you have any further questions, ask your doctor or pharmacist • This medicine has been prescribed for you only • Do not pass it on to others • It may harm them, even if their signs of illness are the same as yours • If you get any side effects, talk to your doctor or pharmacist • This includes any possible side effects not listed in this leaflet •*

**What is in this leaflet?**



## *1. WHAT BYOL HL IS AND WHAT IT IS USED FOR*

Selective beta-blocker and thiazide diuretic (medicines for excretion of fluid from the body).

Areas of application

High blood pressure (essential hypertension).

The fixed dose combination Byol HL is indicated in patients whose blood pressure is not adequately controlled with bisoprolol or hydrochlorothiazide alone.

## *2. WHAT YOU NEED TO KNOW BEFORE YOU USE BYOL HL*

***Do not use Byol HL,***

• If you are hypersensitive (allergic) to bisoprolol fumarate, hydrochlorothiazide or any of the excipients of Byol HL.

• If you suffer from acute heart failure or a deterioration (decompensation) of heart failure occurs which requires intravenous therapy with heart-strengthening substances

• If you are suffering from shock triggered by disturbances of cardiac function (cardiogenic shock)
• if higher-grade conduction disturbances from the atria to the ventricles occur (2nd or 3rd degree atrioventricular block) without a pacemaker
• If you suffer from the syndrome of sick sinus node (sick sinus syndrome)
• If an impaired impulse conduction between sinus node and atrium (sinoatrial block) occurs
• If you suffer from severely slow heart rate episode (heart rate less than 60 beats/min) before the start of treatment
• If you have tendency to severe bronchial asthma or severe chronic obstructive pulmonary disorder
• In case of late stages of peripheral arterial occlusive disease or vasospasm in toes and fingers (Raynaud's syndrome)
• If you have tumors of the adrenal medulla (pheochromocytoma)
• In case of acidification of blood (metabolic acidosis)
• In case of with severe renal impairment (kidney failure) with seriously impaired or lack of urine production (creatinine clearance less than or equal to 30 ml / min or serum creatinine above 1.8 mg / 100 ml).
• In case of acute inflammation of the kidneys (glomerulonephritis).
• In case of altered consciousness, caused by severe liver disease (coma / pre-coma hepaticum).
• In case of potassium deficiency (hypokalemia) which does not respond to treatment.
• In case of severe sodium deficiency (hyponatremia).
• In case of elevated calcium levels in the blood (hypercalcemia).
• In case of gout.

### *Take special care when taking Byol HL in case of:*

• heart failure (the treatment of stable chronic heart failure (myocardial insufficiency) should start with the single active ingredient bisoprolol followed by titration phase).
• bronchial spasm (bronchial asthma, obstructive lung disease).
• concomitant treatment with inhalation anesthetics.
• diabetes (diabetes mellitus) with widely fluctuating blood glucose levels; symptoms of very low blood sugar (symptoms of hypoglycemia) can be obscured.
• strict fasting.
• during desensitization therapy.
• low-grade disturbances of conduction from the atria to the ventricles (first-degree AV block).
• circulatory disorders of the heart caused by coronary vessel spasm (Prinzmetal angina).
• peripheral arterial occlusive disease (possible deterioration of discomfort especially in the beginning of treatment).
• reduction of blood volume (hypovolemia).
• hepatic impairment

### *Warnings and Precautions*

In case of bronchospasm (bronchial asthma) or other chronic obstructive pulmonary disorders, which are accompanied by symptoms, an accompanying bronchodilator therapy should be administered. Occasionally an increase in airway resistance in patients with asthma may occur and require an increase in dosage of beta-2-sympathomimetics.

Like other beta-blockers, bisoprolol may increase the sensitivity to allergy causing substances (allergens) and increase the severity of allergic (anaphylactic) reactions. This also applies to an ongoing desensitization therapy. Adrenaline does not always show the desired therapeutic effect in such cases.

In patients with confirmed psoriasis or history of psoriasis, beta-blockers (e.g. bisoprolol) should be administered only after a careful risk-benefit assessment.

In patients with an adrenal medulla tumor (pheochromocytoma) beta-blockers (e.g. bisoprolol) may be administered only after the administration of alpha-blockers.

Symptoms of serious hyperthyroidism (thyrotoxicosis) can be obscured by beta-blockers (e.g. bisoprolol).

In patients with elevated uric acid levels in the blood (hyperuricemia) there is increased risk of gout.

The treatment with beta-blockers (e.g. bisoprolol) should not be terminated abruptly without compelling indications.

Cases of acute inflammation of the gall bladder (cholecystitis) have been reported in patients with gallstone (cholelithiasis).

If you receive general anesthesia, the anesthesiologist should be informed of the beta-blocker therapy. The present recommendation is not to discontinue the existing beta-blocker therapy in case of surgeries, since it may positively affect rhythm and circulatory disorders in the heart that may occur in surgery. If the discontinuation of beta-blocker therapy before surgery is deemed necessary, it should be done gradually and completed by around 48 hours before the anesthesia.

Photosensitivity reactions can occur in association with thiazide diuretics. If photosensitivity reactions occur, it is recommended to protect exposed body areas from sun or UVA rays. In severe cases it may be necessary to discontinue the treatment with Concor plus.

Due to hydrochlorothiazide component, the long-term continuous administration of Byol HL may lead to disturbance of the electrolyte and fluid balance, especially hypokalemia and hyponatremia, but also hypomagnesemia, hypochloremia and hypercalcemia.

Severe potassium deficiency (hypokalemia) may lead to serious rhythm disturbances (arrhythmia), including torsades de pointes with a fatal outcome.

Disturbance of the acid-base balance (metabolic alkalosis) may be aggravated by the disturbed fluid and electrolyte balance.

Hydrochlorothiazide may cause a hypersensitivity reaction leading to temporary refractive error and angle-closure glaucoma. Symptoms include sudden onset of decreased visual acuity or ocular pain and typically occur within hours to weeks after the start of dosing. Non-treatment of narrow-angle glaucoma can lead to a permanent loss of vision. The fastest possible discontinuation of hydrochlorothiazide is the treatment of first choice.

### *The effect of incorrect use on doping tests*

The use of Concor plus may cause positive results in doping tests.

### *Advice*

During treatment with Byol HL, serum electrolytes (particularly potassium, sodium, calcium), creatinine and urea, blood lipids (cholesterol and triglycerides), uric acid and blood sugar should be regularly monitored, in order to recognize disturbances in the water / electrolyte balance, in particular hyponatraemia, hypochloraemic alkalosis, and hypokalemia.

### *Taking Byol HL with other drugs*

Tell your doctor or pharmacist if you are taking / using, have recently taken / used or intend to take / use other medicinal products, even if they are issued without prescription.

Concomitant therapy with the following medicinal products is not recommended:

When co-administered with calcium antagonists enhanced decreasing of blood pressure, delayed conduction from cardiac atria to the ventricles and a reduction in the strength of contraction of the myocardium were observed. In particular, the intravenous administration of calcium antagonists of the verapamil type may lead to marked hypotension and AV block.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonidine and reserpine) if taken concomitantly may reduce the heart rate and cardiac output, and cause vasodilation. In addition, after discontinuation of clonidine an exaggerated rise in blood pressure may occur.

The concomitant use of lithium may cause serious damage to the heart and nervous system due to reduced excretion of lithium.

Concomitant administration of Byol HL with the following medicines is allowed only under certain conditions and with high caution:

When co-administered with calcium channel blockers of the dihydropyridine type (e.g. nifedipine, amlodipine), increased blood pressure reduction and in patients with heart failure a further reduction of the contractility of the heart muscle may occur.

The antihypertensive effect may be strengthened by combination with tricyclic antidepressants, barbiturates, phenothiazines and other substances that reduce high blood pressure.

In case of concomitant use of ACE inhibitors such as captopril and enalapril and angiotensin II antagonists excessive blood pressure lowering in patients with existing sodium deficiency (sodium depletion) and particularly in patients with renal artery stenosis (narrowing of the renal artery) and / or acute renal failure (kidney failure) is possible at the onset of treatment with ACE inhibitors. In case of sodium deficiency caused by treatment with diuretics, the diuretics should be discontinued 3 days before the start of ACE inhibitor therapy or the treatment with ACE inhibitors should start slowly at low dosage.

Antiarrhythmics may induce torsades de pointes: class I antiarrhythmic products (e.g. quinidine, disopyramide) and class III (e.g. amiodarone and sotalol). The occurrence of hypokalemia can further torsades de pointes. Hypokalemia should be avoided and, if necessary, corrected. The QT interval should be checked. In case of torsades de pointes, no antiarrhythmics should be administered (pacing therapy).

The effect of Byol HL may be enhanced by concomitant administration of antiarrhythmic drugs.

Substances that do not belong to the class of antiarrhythmics that can trigger torsades de pointes: astemizole, erythromycin i.v., halofantrine, pentamidine, sparfloxacin, terfenadine and vincamine. In the event of hypokalemia products that cannot trigger torsades de pointes should be used.

Parasympathomimetics may be cause disturbance of the heart rhythm and increase the risk of bradycardia (slow heart rate).

The topical application of beta-adrenergic receptor blockers (e.g. in eye drops for glaucoma treatment) may increase the effects of Byol HL.

In concomitant use of Byol HL and insulin or other anti-diabetic products (sulfonylurea derivatives) their effects may be intensified. Warning signs of low blood sugar (hypoglycemia) – in particularly rapid pulse (tachycardia) - may be obscured or mitigated.

Concomitant use of Byol HL and anesthetics may enhance the blood pressure lowering effect.
Counter regulatory mechanisms, for example, increasing heart rate (reflex tachycardia), can be affected. Continuation of beta blockade reduces the risk of arrhythmia during induction of anesthesia and intubation. The anesthesiologist should be informed of the treatment with Byol HL.

Concomitant treatment with Byol HL and digitalis, potassium deficiency precipitates the onset of digitalis-induced side effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. acetylsalicylic acid) may reduce the antihypertensive effect of Byol HL.

NSAIDs: In patients with reduced blood volume, concomitant use may precipitate acute renal failure.

A combination of bisoprolol fumarate with beta-sympathomimetics can reduce the effects of both substances. In the treatment of allergic reactions an increased dose of epinephrine may be required.

Sympathomimetic agents that activate α- and β-receptors (e.g. epinephrine, norepinephrine): Possible increase in blood pressure and strengthening of claudicatio intermittens. Such interactions are more likely with non-selective beta-blockers.

The effect of uric acid-lowering drugs may be weakened by concurrent use of Byol HL.

Elevated potassium losses may occur in concomitant use of Byol HL with glucocorticoids, ACTH, carbenoxolone, amphotericin B, furosemide or laxatives.

Cholestyramine, colestipol: Reduces the absorption of hydrochlorothiazide.

Methyldopa: In isolated cases, hemolysis due to antibody formation against hydrochlorothiazide was reported.

Concomitant administration with the following medicinal products must be considered:

Cortisone preparations may reduce the antihypertensive effect of Concor plus.

Application with mefloquine: Increased risk of drop in heart rate.

The concomitant use of monoamine oxidase inhibitors (except MAO-B inhibitors) may increase the blood pressure lowering effect of beta blockers, but also increase the risk of hypertension crisis.

In case of administration of high doses of salicylates, their toxic effect on the central nervous system may be strengthened.

Please note that this information may also apply to recently administered medicines!

### *Taking Byol HL with food and beverages*

During the treatment with Byol HL patients should ensure sufficient fluid intake and consume potassium-rich foods (for example, bananas, vegetables, nuts), due to increased potassium loss. The potassium loss may be prevented or reduced by simultaneous treatment with potassium-sparing diuretics.

Fertility, pregnancy and lactation

Ask your doctor or pharmacist for advice before taking any medicine.

### *Pregnancy*

You must tell your doctor about confirmed or suspected pregnancy. Usually, your doctor will then advise you to take another drug as Byol HL is not recommended during pregnancy. This is because Byol HL passes through the placenta and if used after the third month of pregnancy it may have adverse effects on the health of the fetus and the newborn.

### *Breastfeeding*

Consult with your doctor if you are breastfeeding or about to start breastfeeding. Byol HL is not recommended for use in nursing mothers. Your doctor may prescribe a different treatment for you if you wish to breastfeed.

### *Fertility*

There are no data on the use of the combination preparations and their impact on fertility in humans. In studies in animals bisoprolol and hydrochlorothiazide showed no effects on fertility.

### *Driving and operating machines*

Byol HL has no or negligible influence on the ability to drive and use machines. Nevertheless individually occurring different reactions to the medicine may affect the ability to participate actively in road traffic or to operate machinery. This should particularly be considered at the start of treatment, as well as change of medication, and in combination with alcohol.

## *3. HOW TO USE BYOL HL*

Always use Byol HL exactly as your doctor or pharmacist has told you. Check with your doctor, or pharmacist if you are not completely sure.

Byol HL can be used in patients whose blood pressure is not adequately controlled with bisoprolol or hydrochlorothiazide alone.

Individual dose titration with the individual components (i.e. bisoprolol and hydrochlorothiazide) is recommended.

When clinically appropriate, direct switch from monotherapy to fixed combination may be considered.

### *Dosage in renal impairment*

In renal impairment the excretion of hydrochlorothiazide component of Byol HL is reduced.

What to consider in children?

Children should not take Byol HL, because the safety and efficacy has not been investigated.

Manner of administration

You should take film tablets whole with some liquid in the morning, before, during or after breakfast.

During treatment with Byol HL you should take care of sufficient fluid intake and consume potassium-rich foods (e.g. bananas, vegetables, nuts), due to increased potassium loss.

### *Duration of administration*

The duration of administration is not limited. It depends on the type and severity of the disease. The attending doctor decides on the duration of treatment.

The dosage of Byol HL may not be changed without the doctor's advice.

Please talk to your doctor or pharmacist if you feel that the effect of Byol HL is too strong or too weak.

### *If you take more Byol HL than you should*

If you suspect an overdose with Byol HL please notify your doctor immediately. Depending on the severity of overdose, the doctor may decide on the necessary measures.

The most frequent signs of overdose with Byol HL are slow heart rate (bradycardia), bronchial spasm (bronchospasm), strong fall in blood pressure, acute cardiac insufficiency (heart failure) and low blood sugar (hypoglycemia). In addition, dizziness, nausea, drowsiness, reduction of blood volume (hypovolemia) may occur as clinical signs of acute or chronic hydrochlorothiazide overdose.

In case of overdose, treatment with Byol HL should be discontinued after consultation with the attending doctor.

### *If you forget to take Byol HL*

Do not use a double dose to make up for a forgotten dose. Instead, continue taking the medicine as described in the dosage instructions or prescribed by your doctor.

### *If you stop taking Byol HL*

Please do not pause or stop treatment with Byol HL without discussing it with your doctor first.

Treatment with Byol HL should not be discontinued abruptly, as this may lead to deterioration in heart failure. The medicine should be phased out gradually (i.e. halve the dose in 7-10 day intervals) because abrupt discontinuation may result in acute deterioration of the patient's condition.

If you have further questions on the use of this product, contact your doctor or pharmacist.

## *4. POSSIBLE SIDE EFFECTS*

Like all medicines, Byol HL can cause side effects, although not everybody gets them.

Side effects are classified using the following convention:
**Common**: 1 to 10 users in 100
**Uncommon**: 1 to 10 users in 1,000
**Rare**: 1 to 10 users in 10,000
**Very rare**: less than 1 user in 10,000
**Not known**: frequency cannot be estimated based on the available data

### *Possible side effects*

Blood and lymphatic system disorders

**Rare**: reduced number of white blood cells (leukopenia), lack of blood platelets (thrombocytopenia)
**Very rare**: reduced number of granular leukocytes (agranulocytosis)

### *Psychiatric disorders*
**Uncommon**: depression, sleep disturbance
**Rare**: nightmares, hallucinations

### *Metabolism and nutrition disorders:*
**Common**: increased blood sugar levels (hyperglycemia) and elevated levels of uric acid in the blood (hyperuricemia), disturbances in fluid and electrolyte balance, especially reduced potassium and sodium levels in the blood (hypokalemia and hyponatremia),decreased magnesium and chloride levels and calcium in the blood(hypomagnesemia, hypochloremia, hypercalcemia).
**Uncommon**: loss of appetite.
**Very rare:** metabolic increase of bases in the blood (metabolic alkalosis).

### *Nervous system disorders:*
**Common**: dizziness *, headache *

### *Eye disorders*
**Rare**: decreased lacrimation (to consider if wearing eye lenses), blurred vision
**Very rare:** conjunctivitis

### *Ear and labyrinth disorders:*
**Rare**: hearing disorders

### *Heart and circulatory disorders:*
**Uncommon**: strong reduction of heart rate (bradycardia), disturbances in conduction from the atria to the ventricles (AV block), deterioration of heart failure (congestive heart failure)

### *Vascular disorders:*
**Common**: cold feeling or numbness in the extremities
**Uncommon**: drop in blood pressure in transition from lying to standing (orthostatic dysregulation)
**Rare**: circulatory collapse (syncope).

### *Respiratory, thoracic and mediastinal disorders*
**Uncommon**: bronchospasm in patients with bronchial asthma or a history of obstructive pulmonary disease
**Rare**: allergic rhinitis (rhinitis)
**Unknown**: interstitial lung disease

### *Gastrointestinal tract disorders:*
**Common**: Nausea, vomiting, diarrhea, constipation
**Uncommon**: Abdominal discomfort, inflammation of the pancreas (pancreatitis)

### *Hepatobiliary disorders:*
**Rare**: Liver inflammation (hepatitis), jaundice (icterus).

### *Skin and subcutaneous tissue disorders*
**Rare**: Hypersensitivity reactions: itching, redness (flushing), inflammatory skin changes (exanthema), rash when exposed to light (photodermatitis), skin bleeding (purpura), intensely itchy hives (urticaria)

**Very rare**: β blockers can trigger psoriasis or worsen psoriasis or similar cause exanthema, hair loss, skin lichen (cutaneous lupus erythematosus)

***Musculoskeletal and connective tissue disorders:***

**Uncommon**: muscle weakness, muscle cramps

***Reproductive organs and breast disorders:***

**Rare**: erectile dysfunction

***General disorders and administration site conditions***

**Common**: fatigue*
**Uncommon**: exhaustion* (asthenia)
**Very rare**: chest pain

***Investigations***:

**Common**: increased blood lipids (triglycerides, cholesterol), increased elimination of sugar in the urine (glycosuria)
**Uncommon**: increased amylase, reversible increases in serum creatinine and urea
**Rare**: elevated liver enzymes (ALAT, ASAT)

*These symptoms occur particularly in the beginning of treatment. They are of mild intensity and disappear usually within 1 to 2 weeks after the start of treatment.

***Reporting side effects***

If you notice any side effects, contact your doctor or pharmacist. This also applies to side effects not listed in this leaflet. By reporting side effects, you help ensure that more information on the safety of this product is made available.

## *5. HOW TO STORE BYOL HL*

Keep this medicine out of the reach of children!

Do not store above 30 ° C!

Do not use this medicine after the expiry date which is stated on the box and blister after “best before”. The expiry date refers to the last day of that month.

***This leaflet was last revised in May 2014.***