Package leaflet: Information for the user

Labetalol Synchrony, 5mg/ml solution for injection
Labetalol Hydrochloride

Read all of this leaflet carefully before you start using 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, pharmacist or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Labetalol Synchrony is and what it is used for

Labetalol Synchrony contains the active substance Labetalol. This medicine belongs to a group of medicines called alpha and beta blockers. These medicines work by causing the heart to beat more slowly and with less force. It also widens the arteries in the body. The result is a rapid lowering of a person's blood pressure.

Labetalol is given in hospital and can be used in the treatment of severe hypertension (high blood pressure), including severe hypertension during pregnancy (gestational hypertension), when the blood pressure needs to be lowered rapidly. This medicine may also be used to control the blood pressure during anaesthesia and to lower high blood pressure after a heart attack.
It is very important that the doctor treats your high blood pressure, because left untreated it can cause damage to your blood vessels in the long-term. This could lead to heart attacks, kidney failure, stroke or blindness.

2. What you need to know before you are given Labetalol Synchrony

You should NOT be given this medicine if:
- you are allergic to labetalol or any of the other ingredients of this medicine (listed in section 6)
- your heart cannot maintain adequate circulation of blood (cardiogenic shock)
- you have heart failure that is out of control or not responding to treatment with digitalis
- you have a heart defect that leads to a decreased function of the heart (heart block)
- your heart has difficulty pumping the proper amount of blood to the body's tissues
- you have a problem that is common in the elderly, related to poor control of the working of your heart (sick sinus syndrome)
- you have low blood pressure (hypotension)
- you have a weak heart or a very slow heartbeat (less than 45 or 50 beats per minute)
- you suffer from angina (chest pains) when at rest
- you suffer from wheezing, obstructive airways disease or asthma – taking labetalol can make your breathing worse
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- you have a tumour near your kidneys (phaeochromocytoma)
- you have increased acid levels in the blood (metabolic acidosis)
- you have very bad circulation, especially in your hands and feet

If any of the above applies to you, talk to your doctor.

Warnings and precautions
Talk to your doctor or nurse before you are treated with Labetalol Synchrony if:
- you are about to receive an anaesthetic: as labetalol may mask the effects of a sudden loss of blood
- you suffer or have suffered from any serious allergic reactions in the past
- you have ever suffered from a skin condition called psoriasis
- you have kidney or liver problems
- you are receiving a procedure called MIBG scintigraphy (often used to detect certain tumours)
- you are elderly (65 years and over)
- you are scheduled for cataract surgery as labetalol may affect your pupils during this procedure. Please tell your eye surgeon before your surgery about your treatment with this medicine. You do not need to stop treatment with this medicine unless your surgeon advises otherwise
- your heart rate slows to less than 50 -55 beats per minute while at rest (bradycardia)
- you have a reduced blood supply to the heart muscle (ischaemic heart disease)
- you have poor circulation e.g. fingers and toes go numb and pale (Raynaud's syndrome) or you sometimes limp (intermittent claudication)
- you have an irregular heart beat (first degree atrioventricular block)

If treatment with this medicine leads to a slow heartbeat (bradycardia) your doctor may lower your dosage.

If you suffer from skin rash, dry eyes, or an allergic reaction during your treatment with this medicine, please contact your doctor for the dosage to be lowered or the treatment to be discontinued.

Other medicines and Labetalol Synchrony

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.
In particular tell your doctor if you are taking any of the following:
- **Medicines used to treat your heart or blood pressure** (such as digitalis, clonidine, hydralazine, disopyramide, quinidine, amiodarone, calcium antagonists such as verapamil, alpha blockers such as doxazosin, diltiazem, nifedipine, ACE inhibitors, angiotensin-II antagonists, xamoterol and diuretics (water tablets).
- **Medicines to treat depression** (such as monoamine oxidase inhibitors or tricyclic antidepressants).
- **Anxiolytic** and **hypnotic medicines** for anxiety and sedation
- **NSAIDs, corticosteroids** or other medicines to treat pain or inflammatory conditions
- **Cimetidine** used to treat stomach ulcers.
- **Medicines for stimulating the heart** e.g. adrenaline
- **Anaesthetic drugs** (such as cyclopropane, trichloroethylene, alcohol, barbiturates)
- **Insulin** or **oral anti-diabetic drugs**
- **Ergot derivatives** used to treat Parkinson's disease
- **Phenothiazines** such as chlorpromazine
- **Antimalarial medicines** such as halofantrine, mefloquine or quinine
- **Tropisetron** used to treat nausea.
- **Alprostadil** and **moxisylyte** to treat impotence
- **Aldesleukin** for the treatment of secondary cancer of the kidney
- **Hormones** such as oestrogen and progesterone used as contraceptives or for hormone replacement therapy
- Any other medicine, including medicines obtained without a prescription.

Taking labetalol at the same time as the drugs mentioned for treating your heart or blood pressure, can lead to a severe drop in blood pressure, reduced heart rate, heart failure or heart block. It is important to tell your doctor if you are taking these or any of the other drugs listed above.

Tests
This medicine may have a disruptive effect on certain medical or laboratory tests. This may lead to incorrect test results. Tell your doctor and the laboratory staff that you have been given this medicine if you need to have a blood or urine test.

Pregnancy, breast-feeding and fertility.
Labetalol should only be used during the first three months of pregnancy if it is absolutely necessary. If you are pregnant or think you may be pregnant or are planning to have ask your doctor for advice before being treated with this medicine.
Nipple pain and Raynaud's phenomenon of the nipple have been reported (see section 4).

Labetalol is not recommended whilst breast-feeding.

Driving and using machines
You may feel dizzy or tired when taking labetalol. If this happens to you, do not drive or operate machinery.

Important information about some of the other ingredients in Labetalol Synchrony
This medicinal product contains less than 1mmol (23mg) of sodium (salt) per vial, i.e. essentially sodium (salt) free.

3. How to use Labetalol Synchrony

This medicine always needs to be used as prescribed by your doctor. It is intended for intravenous treatment in hospitalized patients and needs to be given by a healthcare professional.
Remember: This drug should only be given if you are lying down.
You should avoid sitting upright for three hours after being given this medicine, as you may feel very dizzy and lightheaded (due to low blood pressure).
This medicine may be given as a bolus injection (which means that it will be given directly into a vein), or by intravenous infusion (which means that it will be given as a slow drip into a vein).
IMPORTANT: Your doctor will decide how this medicine will be given to you and the correct dose for you.

While you are having Labetalol Synchrony your doctor may check your heart rate, blood pressure and breathing, to check your medicine is working properly.

Adults:
Injection into a vein (to reduce blood pressure very quickly)
- A dose of 50mg of labetalol will be given into your vein over a period of one minute.
- If necessary this dose can be repeated every five minutes up to three times until your blood pressure has been lowered.
- The total dose should not exceed 200mg.
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Slow drip into a vein (to reduce blood pressure more slowly)
- A solution containing 1mg/ml Labetalol Synchrony will be made up by the doctor or nurse.
- The solution will then be given to you via a drip into your vein.
- The amount of the solution you will be given will depend on why your blood pressure needs to be lowered:

1. To lower high blood pressure in pregnancy
- 20mg of Labetalol Synchrony will be given over one hour.
- The dose may then be doubled every 30 minutes until your blood pressure has been reduced or the dose has reached 160mg per hour.
- Your doctor may occasionally need to use a higher dose.

2. To lower high blood pressure after a heart attack

- 15mg of Labetalol Synchrony will be given over one hour.
- The dose may then be gradually increased up to a maximum of 120mg per hour if needed.

3. To lower high blood pressure for other reasons
- 2mg of Labetalol Synchrony will be given per minute.
- When your blood pressure is low enough, the doctor will stop your drip.
- Your doctor may change the rate at which the drip goes in depending on how well you are responding to the medicine.
- The total dose given is usually between 50mg and 200mg, but occasionally higher doses may be needed.

To lower blood pressure during an operation
- Whilst you are under anaesthetic, 10-20mg Labetalol Synchrony (depending on your age and health) will be injected into your vein.
- If after five minutes your blood pressure has not been reduced, a dose of 5-10mg can be given every five minutes until your blood pressure is low enough.

Maintaining your blood pressure
- After you have had Labetalol Synchrony, your doctor may suggest you take labetalol tablets to keep your blood pressure low.
- If this applies to you, your doctor or pharmacist will tell you exactly how many tablets to take and when to take them.

People with liver or kidney problems:
If you have problems with your liver or kidneys, your doctor may give you a lower dose of Labetalol Synchrony.

The elderly (65 years and over):
Your doctor may start you on a lower dose than the usual adult dose to make sure that the medicine is working properly.

Children:
Labetalol Synchrony is not recommended for use in children.

If you are given more of this medicine than you should
Symptoms of an overdose of Labetalol Synchrony are, among others, extreme dizziness when you sit up and sometimes a slowing heartbeat, which can be measured by a low pulse (bradycardia).
If you think you have been given too much of this medicine, tell your doctor immediately.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Remember:
You should avoid sitting upright for three hours after being given Labetalol Synchrony as you may feel very dizzy and lightheaded.
Tell your doctor or nurse immediately if you have an allergic reaction. This includes any of the following symptoms:
- **difficulty in breathing**
- **swelling of your eyelids, face or lips**
- **rash or itching**

Other side effects

Common (may affect up to 1 in 10 people)

- Congestive heart failure
- Dizziness due to low blood pressure when sitting upright or standing up too quickly (postural hypotension). This can happen within the first three hours after this medicine has been given, and is short-lasting in nature. This will occur in the first weeks of treatment.
- Nasal congestion, this is usually short-lived and will occur in the first weeks of treatment
- Increased liver function. This will usually be short-lived after treatment has stopped.
- Erectile dysfunction (impotency).

Rare (may affect up to 1 in 1,000 people)
- Slow heart beat which can be measured by a low pulse (bradycardia).
- Constriction of the muscles in the walls of the bronchioles causing breathlessness (bronchospasm).

Very rare (may affect up to 1 in 10,000 people)
- Blocking of the electrical signals controlling the heart rhythm (heart block)
- Worsening of blood circulation leading to nipple pain, cold or blue extremities with numbness or tingling in your fingers and toes
- Inflammation of the liver (hepatitis), usually short-lived when the treatment is discontinued.
- Hepatocellular jaundice (skin and whites of the eyes become yellow), cholestatic jaundice (symptoms include tiredness and nausea followed by itchiness, dark urine, and jaundice, and also skin rash and fever) and liver necrosis (damaged liver tissue). These symptoms will disappear after the treatment with this medicine has stopped.

Not known (cannot be estimated from the available data)

- Nipple pain
- Intermittent decrease in blood flow to your nipples, which may cause your nipples to go numb, pale, and painful (Raynaud's phenomenon)

Most of the side effects related to Labetalol Synchrony will wear off after the first few weeks. These include:
- headaches, tiredness or dizziness
- depression or exhaustion (lethargy)
- tingling of the scalp
- swollen ankles or sweating
- difficulty passing urine or not being able to pass urine
- stomach pain, feeling sick or being sick
- the shakes after taking labetalol when pregnant
- low blood pressure (hypotension)
- increase of existing leg pain on walking
- mental disturbances such as delusions and altered thought patterns, hallucinations or confusion
- sleep disturbances including nightmares
- diarrhoea
- wheezing or shortness of breath (in patients with asthma)
- the symptoms of an overactive thyroid (increased heart rate) or low blood sugar (as seen in blood test results) may be hidden
- high blood potassium levels (hyperkalaemia) especially if you have reduced kidney function
- hair loss; this may grow back after stopping treatment
- worsening of psoriasis

If any of these side effects occur, speak to your doctor immediately:
- problems with the immune system (e.g. systemic lupus erythematosus) causing shortness of breath, joint pain, or a rash on the cheeks and arms that worsen with sun exposure
- thrombocytopenia causing nosebleeds or bleeding in the mouth or bruising because your blood does not clot as it should
- drug fever making you feel hot and flu-like

- muscle disease (toxic myopathy) causing weakness and wasting of the muscles in the arms and legs
- flat topped bumps on your skin that join up into scaly patches (lichenoid rash)
- blurred vision or dry eyes
- cramps
- cough or breathing problems that may indicate inflammation of the lungs (interstitial lung disease)

Rare side effects on your baby
If you are being treated for high blood pressure during pregnancy, your baby may suffer the following effects for a few days after birth:
- low blood pressure
- slow heartbeat
- shallow or slow breathing
- low blood sugar
- feeling cold

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the Yellow Card Scheme, at www.mhra.gov.uk/yellowcard. By reporting side effects you can help provide more information the safety of this medicine.

5. How to store Labetalol Synchrony

Keep the ampoules in the original packaging (to protect from light).
Keep this medicine out of the sight and reach of children.

Do not use Labetalol Synchrony after the expiry date which is stated on the carton and the ampoule label. The expiry date refers to the last day of that month.

Any unused dilution should be disposed of after 24 hours.

Discard any unused material.
Medicines should not be disposed of via wastewater or household waste.
Ask your pharmacist what to do with any leftover medicine. These measurements will protect the environment.

6. Contents of the pack and other information

What Labetalol contains
- The active ingredient is labetalol hydrochloride.
- The other ingredients are dilute hydrochloric acid (E507), sodium hydroxide (E524) for pH adjustment, and water for injections.

What Labetalol looks like and contents of the pack
Labetalol is a clear colourless solution.
Labetalol comes in 10ml amber glass ampoules with a white break ring, with ten ampoules in each pack.

Marketing Authorisation Holder
Synchrony Pharma Ltd,
3 Bunhill Row, London EC1Y 8YZ, United Kingdom

Manufacturer
Kleva SA, 189 Parnithos Ave, 136 75 Acharnes, Greece

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The following information is intended for healthcare professionals only:

Administration

Labetalol Synchrony is meant for intravenous use in hospitalized patients and should always be given by healthcare professionals. Patients should always receive the drug whilst in the supine or left lateral position. Raising the patient into the upright position within 3 hours of intravenous labetalol administration should be avoided since severe postural hypotension may occur.
It is desirable to check the blood pressure and heart rate after the injection and during the infusion. The heart rate will decrease slightly. Severe bradycardia is not usual, but can be controlled by an intravenous injection of 1 to 2mg of atropine. The breathing should be carefully checked in patients with known airway disease. Labetalol Synchrony can be given as a bolus injection or intravenously. Labetalol Synchrony injection is administered to patients who suffer from uncontrolled hypotension and who have been given other hypotensive substances, including beta- blockers, without suffering from side effects.

Oral maintenance

When the blood pressure has been lowered sufficiently through either the bolus injection or intravenously, the treatment should be maintained by labetalol tablets with a starting dose of 100mg, twice a day.

Indication	**Dosage**
Severe hypertension	*Bolus injection:* If it is essential to reduce blood pressure quickly, as for example in hypertensive encephalopathy, a dose of 50mg of labetalol hydrochloride should be given by intravenous injection (over a period of at least one minute). If necessary, doses of 50mg may be repeated at five minute intervals until a satisfactory response occurs. The total dosage should not exceed 200mg. After bolus injection, the maximum effect usually occurs within five minutes and the effective duration of action is usually about 6 hours but may be as long as 18 hours.

Intravenous infusion

An alternative method of administering labetalol is intravenous infusion of a solution made by diluting the contents of four 10ml ampoules (200mg) to 200ml with Sodium Chloride and Dextrose Injection or 5% Dextrose Intravenous Infusion or Potassium Chloride and Glucose solution or Ringer Lactate. The resultant infusion solution contains 1 mg/ml of labetalol hydrochloride. It should be administered using a paediatric giving set fitted with a 50 ml graduated burette to facilitate dosage.

In hypertension due to other causes: The rate of infusion of labetalol hydrochloride should be about 2mg (2ml of infusion solution) per minute, until a satisfactory response is obtained; the infusion should then be stopped. The effective dose is usually in the range of 50-200mg depending on the severity of the hypertension. For most patients it is unnecessary to administer more than 200mg but larger doses may be required, especially in patients with phaeochromocytoma. The rate of infusion may be adjusted according to the response, at the discretion of the physician. The blood pressure and pulse rate should be monitored throughout the infusion.
It is desirable to monitor the heart rate after injection and during infusion. In most patients, there is a small decrease in the heart rate; severe bradycardia is unusual but may be controlled by injecting atropine 1-2 mg intravenously.
Respiratory function should be observed particularly in patients with any known impairment.
Once the blood pressure has been adequately reduced, maintenance therapy with labetalol tablets should be instituted with a starting dose of one 100 mg tablet twice daily (see labetalol tab-let SmPC for further details).
Labetalol Synchrony has been administered to patients with uncontrolled hypertension already receiving other hypotensive agents, including beta-blocking drugs, without adverse effects.

In the hypertension of pregnancy: In severe cases of hypertension of pregnancy a lower, increasing infusion rate needs to be administered. The infusion needs to be started at the rate of 20mg/ hour, and this dose may be doubled every 30 minutes until a satisfactory result has been obtained, or a dosage of 160mg/hour is reached. Occasionally, higher doses may be necessary.

In hypertensive episodes following acute myocardial infarction: The infusion should be commenced at 15mg per hour and gradually increased to a maximum of 120mg per hour depending on the control of blood pressure.

Hypotensive Anaesthesia	Induction should be with standard agents (e.g. sodium thiopentone) and anaesthesia maintained with nitrous oxide and oxygen with or without halothane. The recommended starting dose of Labetalol injection is 10-20mg intravenously, depending on the age and condition of the patient. Patients for whom halothane is contraindicated usually require a higher initial dose of labetalol hydrochloride (25-30 mg). If satisfactory hypotension is not achieved after five minutes, increments of 5-10mg should be given until the desired level of blood pressure is attained. Halothane and labetalol act synergistically therefore the halothane concentration should not exceed 1-1.5% as profound falls in blood pressure may be precipitated. Following labetalol injection the blood pressure can be quickly and easily adjusted by altering the halothane concentration and/or adjusting table tilt. The mean duration of hypotension following 20 to 25mg of labetalol is 50 minutes. Hypotension induced by labetalol injection is readily reversed by atropine 0.6 mg and discontinuation of halothane. Tubocurarine and pancuronium may be used when assisted or controlled ventilation is required. Intermittent Positive Pressure Ventilation (IPPV) may further increase the hypotension resulting from labetalol injection and/or halothane.

Paediatric patients

The safety and efficacy of labetalol administered to children between 0 to 18 years of age have not been established. No data is available.

Compatibility

Labetalol injection is compatible with the following solutions for infusion
- Dextrose 5% (w/v)
- Sodium Chloride 0.18% (w/v) and dextrose 4% (w/v)
- Potassium Chloride 0.2% (w/v) and glucose 5% (w/v)
- Ringer Lactate

Incompatibilities

Labetalol injection has been shown to be incompatible with sodium bicarbonate injection 4.2% w/v

Overdose

Signs and symptoms:

Symptoms of overdosage are bradycardia, hypotension, bronchospasm and acute cardiac insufficiency. Oliguric renal failure has been reported after massive overdosage of labetalol orally. In one case, the use of dopamine to increase the blood pressure may have aggravated the renal failure.
Labetalol does have membrane stabilising activity which may have clinical significance in overdosage.

Treatment:
After an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive-care ward. Artificial respiration may be required. Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5mcg/min, or dobutamine, starting with a dose of approximately 2.5mcg/min, until the required effect has been obtained. If this does not produce the desired effect, intravenous administration of 8-10 mg glucagon may be considered. If required the injection should be repeated within one hour, to be followed, if necessary, by an IV infusion of glucagon at 1-3 mg/hour. Administration of calcium ions, or the use of a cardiac pacemaker, may also be considered.

Haemodialysis removes less than 1% labetalol hydrochloride from the circulation.

Shelf Life

Chemical and physical in-use stability diluted in dextrose 5% (w/v); sodium chloride 0.18% (w/v) and dextrose 4% (w/v); potassium chloride 0.3% (w/v) and dextrose 5% (w/v) and Ringer Lactate has been demonstrated for 24 hours at 25 ºC.

From a microbiological point of view, the product should be used immediately after dilution. If not used immediately in-use storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Any unused dilution should be disposed after 24 hours.