1. Name of the medicinal product:

Randate – 200 Tablets (Labetalol Hydrochloride Tablets USP 200 mg)

2. Qualitative and quantitative composition

Each film-coated tablet contains:

Labetalol Hydrochloride USP 200mg

S.No.	Name of the Ingredient	Qty per tablet	Unit	Purpose of use
	Blending:			
1.	Labetalol Hydrochloride USP	200.000	mg	Active
2.	Lactose Monohydrate BP	93.000	mg	Diluent
3.	Sodium Starch Glycolate BP (Type-A)	8.000	mg	Disintegrant
4.	Pregelatinised Starch BP (Starch 1500)	40.000	mg	Glident
	Binder:			
5.	Povidone BP (K-30)	9.000	mg	Disintegrant
6.	Isopropyl Alcohol BP	80.000	mg	Solvent
7.	**Pre - Lubrication:**			
8.	Sodium Starch Glycolate BP (Type-A)	8.000	mg	Disintegrant
	Lubrication:			
9.	Magnesium Stearate BP	2.000	mg	Lubricant
	Coating			
10	Hypromellose BP (15cps)	9.600	mg	Film coating Polymer
11	Purified Talc BP	2.720	mg	Anti caking agent
12	Titanium Dioxide BP	2.000	mg	Opacifier
13	Ferric Oxide Red USP	0.400	mg	Colorant
14	Macrogol BP (6000)	1.200	mg	Plasticizer
15	Polysorbate BP (Tween 80)	0.080	mg	Emulsifier
16	Isopropyl Alcohol BP #	260.000	mg	Solvent
17.	Dichloromethane BP#	260.000	mg	Solvent
Total coated tablet weight		**376.000**	**mg**	

3. Pharmaceutical form

Film-coated tablet.

Brown color, Circular, biconvex, film coated tablets with breakline on one side and plain on the other side.

4. Clinical particular

4.1 Therapeutic indications:

Labetalol is a combined alpha and beta-adrenoceptor blocker indicated for:

- Hypertension, including hypertension in pregnancy.
- Angina pectoris with existing hypertension.

4.2 Posology and method of administration

For oral administration only.

Labetalol tablets should be taken with food.

Adults:

Hypertension: Initially, 100 mg twice daily. In patients already being treated with antihypertensive and in those of low body weight this may be sufficient to control blood pressure. In others, increases in dose of 100 mg twice daily should be made at intervals of 14 days. Many patients blood pressure is controlled by 200 mg twice daily. If necessary up to 800 mg daily may be given, as a twice daily regimen. In severe refractory hypertension, daily doses of up to 2400 mg have been given, divided into three or four times a day regimens.

Hypertension in Pregnancy: An initial dosage of 100 mg twice daily may be increased, if necessary at weekly intervals by 100 mg twice daily. During the second and third trimesters, the severity of hypertension may necessitate a further dose titration to a three times daily regimen ranging from 100 mg – 400 mg three times a day. The total daily dosage should not exceed 2400 mg.

Hospital in-patients with severe hypertension, particularly in pregnancy, may have daily increases in dosage.

Angina Co-Existing with Hypertension: The recommended dose is that which is necessary to control the hypertension.

Paediatric population:

Labetalol is not recommended for use in children due to a lack of data on safety and efficacy.

Elderly:

An initial dose of 50 mg twice daily is recommended and this has been sufficient in some cases to control hypertension.

General

Additive hypotensive effects may be expected if Labetalol tablets are administered together with other antihypertensives e.g. diuretics, methyldopa etc. When transferring patients from such agents, Labetalol tablets should be introduced with a dosage of 100 mg twice daily and the previous therapy gradually decreased. Abrupt withdrawal of clonidine or beta-blocking agents is undesirable.

4.3 Contraindications

- Hypersensitivity to labetalol hydrochloride
- Second or third degree heart block
- Cardiogenic shock
- Uncontrolled, incipient or digitalis-refractory heart failure
- Sick sinus syndrome (including sino-atrial block)
- Hypotension
- Untreated phaeochromocytoma
- Severe peripheral circulatory disturbances
- Bradycardia (<45-50 bpm)
- History of bronchspasm or chronic obstructive airways disease
- After prolonged fasting
- Prinzmetal's angina

- Metabolic acidosis (e.g. in some diabetics).

4.4 Special warnings and precautions for use

There have been reports of skin rashes and/or dry eyes associated with the use of beta- adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Gradual discontinuance of the drug should be considered if any such reaction is not otherwise explicable.

There have been reports of severe hepatocellular injury with Labetalol therapy which has occurred after both short-term and long-term treatment and is usually reversible upon withdrawal of the drug. At the first sign or symptom of liver dysfunction appropriate laboratory testing should be carried out. If there is laboratory evidence of liver injury or the patient is jaundiced, Labetalol should be stopped and not re-started.

Particular care should be taken when labetalol is used in patients with hepatic impairment as these patients metabolise labetalol more slowly than patients without hepatic impairment. Lower doses may be required.

The occurrence of Intraoperative Floppy Iris Syndrome (IFIS, a variation of Small Pupil Syndrome) has been observed during cataract surgery in some patients on, or previously treated with, tamsulosin. Isolated reports have also been received with other alpha-1 blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during the cataract operation, current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

Beta-adrenoceptor blocking drugs reduce cardiac output through their negative inotropic and negative chronotropic effects. Beta-blockers may therefore cause worsening systolic heart failure or the development of heart failure in patients who depend on high sympathetic drive to maintain cardiac output.

Especially in patients with ischaemic heart disease, sudden withdrawal of beta-adrenoceptor blocking drugs may result in anginal attacks of increased frequency or severity. Therefore, withdrawal of Labetalol in patients with ischaemic heart disease should be gradual i.e. over 1-2 weeks, and if

necessary at the same time initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop.

Particular care is required with patients whose cardiac reserve is poor. Beta-adrenoceptor blocking drugs should be avoided in overt heart failure or poor left ventricular systolic function, although they may be used when cardiac failure has been controlled.

A reduction in heart rate (bradycardia) is a pharmacological effect of Labetalol. In rare cases where symptoms may be attributable to the heart rate decreasing to less than 50-55 beats per minute at rest, the dose should be reduced.

Airway obstructions may be aggravated in patients with chronic obstructive pulmonary disorders. Non-selective beta-blockers, such as Labetalol, should not be used for these patients unless no alternative treatment is available. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken. If bronchospasm should occur after the use of Labetalol it can be treated with a beta2-agonist by inhalation, e.g. salbutamol (the dose of which may need to be greater than the usual in asthma) and, if necessary, intravenous atropine 1 mg.

Labetalol should only be given with caution to patients with first-degree heart block due to its negative effect on conduction time. Patients with liver or kidney insufficiency may need a lower dosage, depending on the pharmacokinetic profile of the compound. Tolerance to Labetalol is usually good in the elderly, however, they should be treated with caution and with a lower starting dose.

Beta adrenoceptor blocking drugs may increase the number and duration of anginal attacks in patients with Prinzmetal's angina, due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Non-selective beta-blockers, such as Labetalol, should not be used for these patients.

Patients with a history of psoriasis should only be administered beta adrenoceptor blockers after careful consideration.

There have been reports of increased sensitivity towards allergens and the seriousness of anaphylactic reactions with the use of beta adrenoceptor blocking drugs. While taking beta- blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Labetalol modifies the tachycardia of hypoglycaemia and it may prolong the hypoglycaemic response to insulin. Care should be exercised during concomitant use of Labetalol and hypoglycaemic therapy in patients with diabetes mellitus.

As with other beta-adrenoceptor blocking drugs, labetalol may mask the symptoms of hypoglycaemia in diabetic patients and thyrotoxicosis.

Care is required when transferring patients from clonidine to a beta-adrenoceptor blocking drug. Labetalol should be introduced with a dosage of 100 mg twice daily and clonidine gradually decreased. Labetalol may prove useful in preventing rebound hypertension following clonidine withdrawal.

Because of negative inotropic effects, care is required when prescribing a beta-adrenoceptor blocking drug with class 1 antidysrhythmic agents such as disopyramide.

Beta-adrenoceptor blocking drugs should be used with caution in combination with verapamil where ventricular function is impaired. The combination should not be given to patients with conduction abnormalities, nor should either drug be administered intravenously within 48 hours of discontinuing the other.

Care is required during parenteral administration of preparations containing adrenaline to patients receiving beta-adrenoceptor blocking drugs, as in rare instances vasoconstriction, hypertension and bradycardia may occur. A reduced dosage of adrenaline should be used.

Beta-blockade therapy should be discontinued for at least 24 hours if it is decided ***to*** interrupt it prior to surgery. Continuation of beta-blockade during surgery reduces the risk of arrhythmias during induction and intubation but may increase the risk of hypertension.

Great care should be taken with patients with peripheral circulatory disorders such as Raynaud's disease or syndrome or intermittent claudication. Beta adrenoceptor blockers may lead to the aggravation of such disorders.

Care is required when administering anaesthetic agents to patients receiving Labetalol. The anaesthetist should always be informed of the use of a beta-adrenoceptor blocking drug. The risks and benefits of continued beta-adrenoceptor blocking therapy in the peri-operative period should be carefully evaluated. Halothane in high concentrations (≥3%) and other halogenated hydrocarbon anaesthetics should be avoided with Labetalol due to risk of excessive hypotension, large decrease in

cardiac output and increase in central venous pressure. Patients should receive intravenous atropine prior to induction. During anaesthesia Labetalol may mask the compensatory physiological responses to sudden haemorrhage (tachycardia and vasoconstriction). Close attention must therefore be paid to blood loss and the blood volume maintained.

The presence of Labetalol metabolites in the urine may result in falsely elevated levels of urinary catecholamines, metaneprine, normataneprine and vanillylmandelic acid when measured by flourometric or photometric methods.

In patients with phaeochromocytoma, labetalol may be administered only after adequate alpha-blockade is achieved.

All labelling for Labetalol will carry the following warning:

Do not take this medicine if you have wheezing or asthma.

This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Tricyclic antidepressants, barbiturates and phenothiazines as well as other antihypertensive agents will potentate the hypotensive action of Labetalol. Concomitant use of tricyclic antidepressants may increase the incidence of tremor.

Parenteral administration of preparations containing sympathomimetics, such as adrenaline, to patients taking beta-adrenoceptor blocking drugs, may in rare cases, result in vasoconstriction, hypertension and bradycardia. Labetalol is less likely to cause acute hypertensive reactions than other beta-blockers due to its alpha-blocking activity.

Beta-adrenoceptor blocking drugs may enhance the negative inotropic and chronotropic actions of verapamil, and to a lesser extent diltiazem. Therefore, concurrent use is not recommended.

Care should be taken if beta adrenoceptor blocking drugs are used in conjunction with Class 1 anti-arrhythmic agents such as disopyramide, quinidine and amiodarone, as they may have a potentiating effect on atrial-conduction time and induce a negative inotropic effect.

Beta adrenoceptor blockers should not be used in conjunction with digitalis glycosides as they may increase auriculo-ventricular conduction time.

Non selective beta-blockers increase the risk of “rebound hypertension” when used in conjunction with clonidine. Treatment with clonidine should be continued for some time after treatment with the beta-blocker has been discontinued.

Beta adrenoceptor blocking drugs should not be used concomitantly with monamine oxidase inhibitors (MAOIs) with the exception of MAO-B inhibitors.

Administration of anaesthetic drugs with beta adrenoceptor drugs may lead to attenuation of the reflex tachycardia and increase the risk of hypotension. Continuation of beta-blockers reduces the risk of arrhythmia during induction and intubation. The anaesthetist should be informed when the patient is receiving a beta-blocking agent. Anaesthetic agents which can cause myocardial depression, such as cyclopropane and trichlorethylene, should be avoided.

Beta-blockers may enhance hypoglycaemic effects of antidiabetic agents and mask the warning signs of hypoglycaemia such as tremor and tachycardia.

Cimetidine, hydralazine and alcohol increase the bioavailability of beta-blockers which are mainly metabolised by the liver; The effect of Labetalol may therefore be potentiated by concomitant treatment with these drugs.

Beta-blockers, when used with dihydropyridine derivatives such as nifedipine, increase the risk of hypotension. In patients with latent cardiac insufficiency, treatment with beta- blocking agents may lead to cardiac failure.

Prostaglandin synthetase inhibiting drugs may decrease the hypotensive effects of beta- blockers. Dosage adjustments may therefore be necessary.

The central depressant effect of alcohol, analgesics and tricyclic antidepressants is potentiated.

Several different drugs or drug classes may enhance the hypotensive effects of labetalol: ACE inhibitors; angiotensin-II antagonists; aldesleukin, alprostadil; anxiolytics; hypnotics; moxisylyte; diuretics; alpha-blockers.

Several different drugs or drug classes may antagonise the hypotensive effects of labetalol: NSAIDs, corticosteroids; oestrogens; progesterones.

Labetalol has been shown to reduce the uptake of radioisotopes of metaiodobenzylguanidine (MIBG), and may increase the likelihood of a false negative study. Care should therefore be taken in interpreting results from MIBG scintigraphy. Consideration should be given to withdrawing labetalol

for several days at least before MIBG scintigraphy, and substituting other beta or alpha-blocking drugs.

Antimalarials such as mefloquine or quinine may increase the risk of bradycardia. Ergot derivatives may increase the risk of peripheral vasoconstriction.

4.6 Fertility, pregnancy and lactation

Pregnancy

While no teratogenic effects have been demonstrated in animals, Labetalol should only be used during the first trimester of pregnancy if the potential benefits are likely to outweigh the possible risk to the foetus.

Labetalol crosses the placental barrier and the possible consequences of alpha- and beta- adrenoceptor blockade in the foetus and neonate should be borne in mind. Perinatal and neonatal distress (bradycardia, hypotension, respiratory depression, hypoglycaemia, hypothermia) has been rarely reported. Sometimes these symptoms have developed a day or two after birth. Response to supportive measures (e.g. intravenous fluids and glucose) is usually prompt but with severe pre-eclampsia, particularly after prolonged intravenous labetalol, recovery may be slower. This may be related to diminished liver metabolism in premature babies.

Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries.

There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Intra-uterine and neonatal deaths have been reported with Trandate but other drugs (e.g. vasodilators, respiratory depressants) and the effects of pre- eclampsia, intra-uterine growth retardation and prematurity were implicated. Such clinical experience warns against unduly prolonging high dose labetalol and delaying delivery and against co- administration of hydralazine.

Breast-feeding

Labetalol is excreted in breast milk in small amounts (approximately 0.004% of the maternal dose). Adverse events of unknown causality (sudden death syndrome, diarrhoea, hypoglycaemia) have been reported very rarely in breast-fed neonates. Caution should be exercised when labetalol is administered to breast-feeding women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The use of labetalol is unlikely to result in any impairment. However, when driving or operating machines, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Most side effects are transient and occur during the first few weeks of treatment with Labetalol. They include:

Immune system disorders

Very common: Positive antinuclear antibodies unassociated with disease.

Common: Hypersensitivity (rash, pruritus, angioedema and dyspnoea).

Blood and the lymphatic system disorders

Not known: Hyperkalaemia, particularly in patients who may have impaired renal excretion of potassium, thrombocytopenia.

Psychiatric disorders

Not known: Depressed mood and lethargy, hallucinations, psychoses, confusion, sleep disturbances, nightmares.

Nervous system disorders

Common: Dizziness, tingling sensation in scalp usually transient may occur in a few patients early in treatment.

Very rare: Tremor has been reported in the treatment of hypertension of pregnancy.

Not known: Headache, tiredness.

Eye disorders

Not known: Impaired vision, dry eyes.

Cardiac disorders

Common: Heart failure.

Rare: Bradycardia.

Very rare: Heart block

Not known: Hypotension.

Vascular disorders

Very rare: Exacerbation of the symptoms of Raynaud's Syndrome.

Not known: Ankle oedema, increase of an existing intermittent claudication, postural hypotension is uncommon except at very high doses, or if the initial dose is too high or doses are increased too rapidly.

Respiratory, thoracic and mediastinal disorders

Uncommon: Bronchospasm (in patients with asthma or a history of asthma).

Not known: Nasal congestion, interstitial lung disease.

Gastrointestinal disorders

Not known: Epigastric pain, nausea, vomiting, diarrhoea.

Hepatobiliary disorders

Common: Raised liver function tests.

Very rare: Jaundice (both hepatocellular and cholestatic), hepatitis and hepatic necrosis. When mild, hepatotoxicity is usually reversible on withdrawal of the drug.

Skin and subcutaneous tissue disorders

Not known: Sweating, reversible lichenoid rash, cold or cyanotic extremities, paraesthesia of the extremities, photosensitivity reactions, exacerbation of psoriasis, reversible alopecia.

Musculoskeletal and connective tissue disorders:

Very rare: toxic myopathy, systemic lupus erythematous.

Not known: Cramps. toxic myopathy, systemic lupus erythematous.

Renal and urinary disorders

Common: Difficulty in micturition.

Not known: Acute retention of urine.

Reproductive system and breast disorders

Common: Ejaculatory failure, erectile dysfunction.

General disorders and administration site conditions

Common: Drug fever.

Not known: Masking of the symptoms of thyrotoxicosis or hypoglycaemia.

4.9 Overdose

Clinical features of overdosage may include bradycardia, hypotension, bronchospasm, acute cardiac insufficiency, hypoglycaemia, delirium and unconsciousness. In the case of large overdosages, beta-blockers can cause a membrane-stabilising action.

After ingestion of an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive-care ward. Following recent overdose, the stomach should be emptied by gastric aspiration and lavage, administration of activated charcoal and a laxative. 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 5μg/min, or dobutamine, starting with a dose of 2.5 μg/min, until the required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of 8-10 mg glucagon may be considered. If required the injection should be repeated within one hour, to be followed, if required, by an i.v. infusion of glucagon at an administration rate of 1-3 mg/hour. Administration of calcium ions, or the use of a cardiac pacemaker may also be considered.

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.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmatherapeutic group: Alpha and beta blocking agents, **ATC code:** C07AG01

Labetalol combines selective alpha$_1$-blocking activity with non-selective beta-blockade. Through alpha-blockade, it reduces peripheral resistance, decreasing myocardial after-load and oxygen demand. Concurrent beta-blockade protects against reflex sympathetic cardiac effects. Cardiac output

is not significantly reduced at rest or with moderate exercise. Systolic blood pressure elevation during exercise is reduced, but corresponding changes in diastolic pressure are essentially normal.
In patients with angina pectoris co-existing with hypertension, the reduced peripheral resistance decreases myocardial afterload and oxygen demand. All these effects would be expected to benefit hypertensive patients and those with co-existing angina.

5.2 Pharmacokinetic properties

Labetalol is completely absorbed after oral administration. Bioavailabilty is significantly reduced to first-pass metabolism in the liver, but can be enhanced by concurrent administration of food. Peak effects are seen 2-4 hours after dosing and the plasma half-life is 6-8 hours. Labetalol exhibits moderately high (~50%) plasma protein binding. It undergoes hepatic biotransformation with inactive metabolites being excreted in the urine (55-60%) and faeces. Less than 5% of an oral dose is excreted unchanged in the urine.

5.3 Preclinical Safety Data:

There is no preclinical safety data

6. Pharmaceutical particulars

6.1 List of excipients

Core tablet:
Lactose Monohydrate, Sodium starch Glycolate , Pregelatinised Starch (Starch 1500)
Povidone (K-30), Magnesium Stearate .

Coating material:
Hypromellose (15cps), Purified Talc
Titanium Dioxide , Ferric Oxide Red , Macrogol (6000) & Polysorbate (Tween 80)

6.2 Incompatibilities Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage

Store below 30°C in the original package in order to protect from moisture.

6.5 Nature and contents of container

Printed Aluminum foil / Clear PVC film 4 x 14's.

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder

8. Marketing authorisation number(s): NA

ANNYGOD PHARMA. CO. LTD

28 Ukwulu Street,

Awada Obosi,

Anambra State.

Nigeria.

9. Date of first authorisation/renewal of the authorisation: NA