SUMMARY OF PRODUCT CHARACTERISTICS

1.	**Name of the Medical Product**
	1.1 Product Name : Nebunta 5 (Nebivolol Tablets 5mg)
	1.2 Strength : Each tablet contains: Nebivolol Hydrochloride Equivalent to Nebivolol 5mg Contains Lactose
	1.3 Pharmaceutical Dosage Form : Tablet
2.	**Qualitative & Quantitative Composition:** Each tablet contains: Nebivolol Hydrochloride Equivalent to Nebivolol 5mg For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:**
	Tablet Beige coloured, mottled, triangular shaped biconvex uncoated tablets debossed with 'NE1' on one side and plain on other side.
4.	**Clinical Particulars**
	4.1 Therapeutic Indications: Hypertension Treatment of essential hypertension. Chronic heart failure (CHF) Treatment of stable mild and moderate chronic heart failure in addition to standard therapies in elderly patients 70 years old or above.
	4.2 Posology and Method of administration: Posology Hypertension Adults The usual dose is one tablet (5mg) daily, preferably taken at the same time of the day. Tablets may be taken with meals. The blood pressure lowering effect may take up to 1-2 weeks of treatment to become evident. Occasionally, the optimal effect is only reached only after 4 weeks. Beta-blockers can be used alone or concomitantly with other antihypertensive agents. Patients with renal insufficiency The recommended starting dose for patients with renal insufficiency is 2.5mg daily. If needed, the daily dose may be increased to 5mg.

	Patients with hepatic insufficiency Data in patients with hepatic insufficiency or impaired liver function are limited. Therefore, the use of nebivolol in these patients is contraindicated. Elderly In patients over 65 years, the recommended starting dose is 2.5mg daily. If needed, the daily dose may be increased to 5mg. However, in view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely. Paediatric population Nebivolol is not recommended for use in children and adolescents under the age of 18 years due to a lack of data on safety and efficacy. Chronic Heart Failure (CHF) The use of nebivolol for treatment of stable chronic heart failure should involve a gradual increase of dosage until the optimal individual maintenance dose is reached. Prior to starting treatment, patients should have stable chronic heart failure without acute failure during the past six weeks. It is recommended that the treating physician should be experienced in the management of chronic heart failure. For those patients receiving cardiovascular drug therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, these drugs should be maintained at a stable dose for the two weeks leading up to initiation of nebivolol treatment. The dose should be increased from the initial dose of 1.25mg daily to 2.5mg and then to 5mg daily and then 10mg daily at intervals of 1-2 weeks based on patient tolerability. The maximum recommended dose is 10mg nebivolol once daily. The initiation of therapy and all increases in dose should be carried out under the supervision of an experienced physician over a period of at least 2 hours to ensure that the clinical status (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening heart failure) remains stable. The occurrence of adverse events may prevent patients being treated with the maximum recommended dose. If necessary, the dose reached can also be decreased step by step and reintroduced as appropriate. During the initial dose increasing phase, in case of worsening of the heart failure or intolerance, it is recommended first to reduce the dose of nebivolol, or to stop it immediately if necessary (in case of sever hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or AV block). Treatment of stable chronic heart failure with nebivolol is generally a long-term treatment. The treatment with nebivolol is not recommended to be stopped abruptly since this might lead to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be decreased step-wise weekly. Patients with renal insufficiency

	No dose adjustment is required in mild to moderate renal insufficiency since up-titration to the maximum tolerated dose is individually adjusted. There is no experience in patients with severe renal insufficiency (serum creatinine ≥ 250µmol/L). Therefore, the use of nebivolol in these patients is not recommended. Patients with hepatic insufficiency Data in patients with hepatic insufficiency are limited. Therefore, the use of nebivolol in these patients is contraindicated. Elderly No dose adjustment is required since up-titration to the maximum tolerated dose is individually adjusted. Children and adolescents Nebivolol is not recommended for use in children and adolescents under the age of 18 years due to a lack of data on safety and efficacy. Method of administration Oral use. Tablets may be taken with meals. **Administration:** For oral use. Tablets may be taken with meals.
	4.3 Contraindications: • Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. • Liver insufficiency or liver function impairment. • Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring I.V. inotropic therapy. In addition, as with other beta-blocking agents, nebivolol is contra-indicated in: • Sick sinus syndrome, including sino-atrial block. • Second and third degree heart block (without a pacemaker). • History of bronchospasm and bronchial asthma. • Untreated phaeochromocytoma • Metabolic acidosis. • Bradycardia (heart rate < 60bpm prior to start of therapy) • Hypotension (systolic blood pressure <90mmHg) • Severe peripheral circulatory disturbances.
	4.4 Special warning and precautions for use: <u>Anaesthesia</u> Continuation of beta blockade reduces the risk of arrhythmias during induction and intubation. If beta blockade is interrupted in preparation for surgery, the beta-adrenergic antagonist should be discontinued at least 24 hours beforehand. Caution should be observed with certain anaesthetics that cause myocardial depression. The patient can be protected against vagal reactions by intravenous administration of atropine.

	Cardiovascular In general, beta-adrenergic antagonists should not be used in patients with untreated congestive heart failure (CHF), unless their condition has been stabilised. In patients with ischaemic heart disease, treatment with a beta-adrenergic antagonist should be discontinued gradually, i.e. over 1-2 weeks. If necessary, replacement therapy should be initiated at the same time to prevent exacerbation of angina pectoris. Beta-adrenergic antagonists may induce bradycardia. If the pulse rate drops below 50-55 bpm at rest and/or the patient experiences symptoms suggestive of bradycardia, the dosage should be reduced. Beta-adrenergic antagonists should be used with caution in the following conditions: Peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), as aggravation of these disorders may occur upon use of beta blockers. First degree heart block, because of the negative effect of beta-blockers on conduction time Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Beta-adrenergic antagonists may increase the number and duration of anginal attacks. Concomitant treatment with calcium channel antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic drugs, and with centrally acting antihypertensive drugs. Metabolic/Endocrinological Nebivolol does not affect glucose levels in diabetic patients. Care should be taken in diabetic patients however, as nebivolol may mask certain symptoms of hypoglycaemia (tachycardia, palpitations). Beta-adrenergic blocking agents may mask tachycardic symptoms in hyperthyroidism. Abrupt withdrawal may aggravate symptoms. Respiratory In patients with chronic obstructive pulmonary disorders, beta-adrenergic antagonists should be used with caution as airway constriction may be aggravated. Other This medicine contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. Caution should be exercised when treating patients with a history of psoriasis with beta-adrenergic antagonists as they may increase the sensitivity to allergens and the severity of anaphylactic reactions. The initiation of Chronic Heart Failure treatment with nebivolol necessitates regular monitoring. Treatment discontinuation should not be done abruptly unless clearly indicated.
	4.5 Interactions with other medicinal products and other forms of Interactions : Pharmacodynamic interactions:

Combinations not recommended:

• Class I anti-arrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone) as the effect on atrio-ventricular conduction time may be potentiated and the negative inotropic effect increased.

• Calcium channel antagonists of verapamil/diltiazem the type due to a negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients with ß-blocker treatment may lead to profound hypotension and atrio-ventricular block.

• Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine). Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of hypertension.

Combinations to be used with caution:

• Class III anti-arrhythmic drugs (Amiodarone) as the effect on atrio-ventricular conduction time may be potentiated.

• Volatile halogenated anaesthetics as concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension. Sudden withdrawal of beta-blocker treatment should be avoided if possible. The anaesthesiologist should be informed when the patient is receiving Nebivolol Tablets.

• Insulin and oral anti-diabetic drugs as, although nebivolol does not affect glucose levels, concomitant use may mask symptoms of hypoglycaemia (palpitations, tachycardia).

• Baclofen (antispastic agent), amifostine (antineoplastic adjunct): concomitant use with antihypertensives is likely to increase the fall in blood pressure, therefore the dosage of the antihypertensive medication should be adjusted accordingly.

Combinations to be used only after careful consideration:

• Digitalis glycosides as concomitant use may increase atrio-ventricular conduction time although clinical trials with nebivolol have not shown any clinical evidence of an interaction. Nebivolol does not influence the kinetics of digoxin.

• Calcium antagonists of the dihydropyridine type (amlodipine, felodipine, lacidipine, nifedipine, nicardipine, nimodipine, nitrendipine) because concomitant use may increase the risk of hypotension, and cause an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure.

• Antipsychotics and antidepressants (tricyclics, barbiturates and phenotiazines). Concomitant use may enhance the hypotensive effect of the beta-blockers (additive effect).

• Non-steroidal anti-inflammatory drugs (NSAID) are thought to have no effect on the blood pressure lowering effect of nebivolol.

• Sympathomimetic agents. Concomitant use may counteract the effect of beta-adrenergic antagonists. Beta-adrenergic agents may lead to unopposed alpha-adrenergic activity of sympathomimetic agents with both alpha- and beta-adrenergic effects causing increased risk of hypertension, severe bradycardia and heart block.

	Pharmacokinetic interactions: As nebivolol metabolism involves the CYP2D6 isoenzyme, co-administration with substances inhibiting this enzyme, especially paroxetine, fluoxetine, thioridazine, quinidine and bupropion, chloroquine, levomepromazine, dextrometorphan and terbinafine may lead to increased plasma levels of nebivolol associated with an increased risk of excessive bradycardia and adverse events. Co-administration of cimetidine increased the plasma levels of nebivolol, without changing the clinical effect. Co-administration of ranitidine did not affect the pharmacokinetics of nebivolol. Provided nebivolol is taken with the meal, and an antacid between meals, the two treatments can be co-prescribed. Combining nebivolol with nicardipine slightly increased the plasma levels of both drugs, without changing the clinical effect. Co-administration of alcohol, furosemide or hydrochlorothiazide did not affect the pharmacokinetics of nebivolol. Nebivolol does not affect the pharmacokinetics and pharmacodynamics of warfarin.
	4.6 Pregnancy and Lactation: Pregnancy Nebivolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/new-born. In general, beta-blockers reduce placental profusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and new-born infant. If treatment with beta-adrenoreceptor blockers is necessary, $beta_1$-selective adrenoreceptor blockers are preferable. Nebivolol should not be used during pregnancy unless clearly necessary. If treatment with nebivolol is considered necessary, the uteroplacental blood flow and foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus, alternative treatment should be considered. The new-born infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected in the first 3 days. Breast-feeding Animal studies have shown that nebivolol is excreted in breast milk. It is not known whether this drug is excreted into human milk. Most beta-blockers, particularly lipophilic compounds like nebivolol and its active metabolites, pass into breast milk although to a variable extent. Therefore, breast feeding in not recommended during administration of nebivolol.
	4.7 Effects on ability to drive and use machine: No studies on the effects on the ability to drive and use machines have been performed. Pharmacodynamic studies have shown that nebivolol does not affect psychomotor function. When driving vehicles or operating machines it should be taken into account that dizziness and fatigue may occasionally occur.
	4.8 Undesirable Effects: Adverse events are listed separately for hypertension and CHF because of differences in the background diseases. Hypertension

The adverse reactions reported, which are in most of the cases of mild to moderate intensity are tabulated below, classified by system organ class and ordered by frequency:

Organ class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Very rare (<1/10,000)	Not K
Immune system disorders				angio oeder hyper
Psychiatric disorders		nightmares, depression		
Nervous system disorders	headache, dizziness, paraesthesia		syncope	
Eye disorders		impaired vision		
Cardiac disorders		bradycardia, heart failure, slowed AV conduction/AV-block		
Vascular disorders		hypotension, (increase of) intermittent claudication		
Respiratory, thoracic and mediastinal disorders	dyspnoea	bronchospasm		
Gastrointestinal disorders	constipation, nausea, diarrhoea	dyspepsia, flatulence, vomiting		
Skin and subcutaneous tissue disorders		pruritus, rash erythematous	psoriasis aggravated	urtica
Reproductive system and breast disorders		impotence		
General disorders and administration site conditions	tiredness, oedema			

The following adverse reactions have also been reported with some beta adrenergic antagonists: hallucinations, psychoses, confusion, cold/cyanotic extremities, Raynaud phenomenon, dry eyes, and oculo-mucocutaneous toxicity of the practolol-type.

Chronic heart failure

Data on adverse reactions in CHF patients are available from one placebo-controlled clinical trial involving 1067 patients taking nebivolol and 1061 patients taking placebo. In this study, a total of 449 nebivolol patients (42.1%) reported at least possibly causally related adverse reactions compared to 334 placebo patients (31.5%). The most commonly reported adverse reactions in nebivolol patients were bradycardia and dizziness, both occurring in

	approximately 11% of patients. The corresponding frequencies among placebo patients were 2% and 7%, respectively. The following incidences were reported for adverse reactions (at least possibly drug-related) which are considered specifically relevant in the treatment of chronic heart failure: Aggravation of cardiac failure occurred in 5.8% of nebivolol patients compares to 5.2% of the placebo patients. Orthostatic hypotension was reported in 2.1% of nebivolol patients compared to 1.0% of placebo patients. Drug intolerance occurred in 1.6% of the nebivolol patients compared to 0.8% of the placebo patients. First degree atrio-ventricular block occurred in 1.4% of nebivolol patients compared to 0.9% of placebo patients. Oedema of the lower limb were reported in 1.0% of nebivolol patients compared to 0.2% of placebo patients.
	4.9 Overdosage: No data are available on overdosage with Nebivolol 5mg Tablets. *Symptoms of overdose with beta-adrenergic antagonists:* • Bradycardia • Hypotension • Bronchospasm • Acute cardiac insufficiency. *Treatment* In case of overdose or hypersensitivity, the patient should be kept under close supervision and b treated in an intensive care ward. Blood glucose levels should be checked. Absorption of any dr residues still present in the gastro-intestinal tract can be prevented by gastric lavage and the 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, i necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 µg/ minute dobutamine, starting with a dose of 2.5 µg/minute, until the required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desir effect either, intravenous administration of glucagon 50-100 µg/kg i.v. 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 70 µg/kg/h. In extreme cases of treatment-resistant bradycardia, a pacemak may be inserted.
5.	**Pharmacological properties**
	ATC code: C07AB12 **Therapeutic class: Antihypertensive** **5.1 Pharmacodynamic Properties:**

	Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSS-nebivolol (or l-nebivolol). It is a competitive and selective beta-receptor antagonist, due to the SRRR-enatiomer (d-enantiomer), and also it has mild vasodilating properties due to an interaction with the L-arginine/nitric oxide pathway. Single and repeated doses of nebivolol reduce heart rate and blood pressure at rest and during exercise, both in normotensive subjects and in hypertensive patients. The antihypertensive effect is maintained during chronic treatment. At therapeutic doses, nebivolol is devoid of alpha-adrenergic antagonism. During acute and chronic treatment with nebivolol in hypertensive patients, systemic vascular resistance is decreased. Despite heart rate reduction, a reduction in cardiac output during rest and exercise may be limited due to an increase in stroke volume. The clinical relevance of these haemodynamic differences as compared to other beta-1 receptor antagonists has not been fully established. In hypertensive patients, nebivolol increases the Nitric Oxide-mediated vascular response to acetylcholine (ACh) which is reduced in patients with endothelial dysfunction. In vitro and in vivo experiments in animals showed that nebivolol has no intrinsic sympathomimetic activity. In vitro and in vivo experiments in animals showed that at pharmacological doses nebivolol has no membrane stabilising action. In healthy volunteers, nebivolol has no significant effect on maximal exercise capacity or endurance. Available preclinical and clinical evidence in hypertensive patients has not shown that nebivolol has a detrimental effect on erectile function.
	5.2 Pharmacokinetics Properties: Both nebivolol enantiomers are rapidly absorbed after oral administration. The absorption of nebivolol is not affected by food. It can be given with or without meals. Nebivolol is extensively metabolised, partly to active hydroxy-metabolites. Nebivolol is metabolised via alicyclic and aromatic hydroxylation, N-dealkylation and glucuronidation. In addition, glucuronides of the hydroxy-metabolites are formed. The metabolism of nebivolol by aromatic hydroxylation is subject to the CYP2D6 dependent genetic oxidative polymorphism. The oral bioavailability of nebivolol averages 12% in fast metabolizing patients and is virtually complete in slow metabolisers. At steady state and at the same dose level, the peak plasma concentration of unchanged nebivolol is about 23 times higher in poor metabolisers than in extensive metabolisers. When unchanged drug plus active metabolites are considered, the difference in peak plasma concentrations is 1.3 to 1.4 fold. Because of the variation in rates of metabolism, the dose of nebivolol should always be adjusted to the individual requirements of the patient. Poor metabolisers therefore may require lower doses. In fast metabolisers, elimination half-lives of the nebivolol enantiomers average 10 hours. In slow metabolisers, they are 3-5 times longer. In fast metabolisers, plasma levels of the RSSS-enantiomer are slightly higher than for the SRRR-enantiomer. In slow metabolisers, this difference is larger. In fast metabolisers, elimination half-lives of the hydroxymetabolites of both enantiomers average 24 hours, and are about twice as long in slow metabolisers.

	Steady-state plasma levels in most subjects (fast metabolisers) are reached within 24 hours for nebivolol and within a few days for the hydroxy-metabolites. Plasma concentrations are dose-proportional between 1 and 30 mg. The pharmacokinetics of nebivolol are not affected by age. In plasma, both nebivolol enantiomers are predominantly bound to albumin. Plasma protein binding is 98.1% for SRRR-nebivolol and 97.9% for RSSS-nebivolol. One week after administration, 38% of the dose is excreted in the urine and 48% in the faeces. Urinary excretion of unchanged nebivolol is less than 0.5% of the dose.
	5.3 Preclinical Safety data: No information available
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: Nebunta 5(Nebivolol Tablets 5mg), Pregelatinized Starch(1500 LM), Lactose monohydrate(Pharmatose 200M), croscarmellose sodium (Ac di sol type SD 711), Hypromellose (Methocel E15 Premium LV), Polysarbate 80 (Tween 80-LQ), Sodium Lauryl Sulfate (Koliphore SLS Fine), Purified water, Microcrystalline cellulose (Avicel PH-102),Lake Pigment HT 6027 D&C Red #27 (Phloxine Aluminum Lake), Lake Pigment HT 5284 FD&C yellow #6 (Sunset yellow FCF Aluminum Lake), Lake Pigment HT 5624 FD&C Blue #2(Indigo Carmine Aluminum Lake),Magnesium Stearate.
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 24 months
	6.4 Special Precautions for storage: Store below 30°C.
	6.5 Nature and contents of container: 10 tablets in Alu-Alu blister pack, 3 such blister in a printed carton along with Pack Insert.
	6.6 Special precautions for disposal: Not applicable
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400 067, India **Manufacturing Site Address:** Ajanta Pharma Limited Z/103/A, Dahej Sez II, City: Bharuch – 392 130., Dist. Bharuch, Gujarat State, India. Telephone : (0091) 022- 66061000 Fax : (0091) 022-66061200/300 e-mail : info@ajantapharma.com
8.	**Marketing Authorization Numbers:** Not applicable

9.	**Date of first registration /renewal of the registration:** Not Applicable
10.	**Date of revision of text:** Apr 30, 2021