SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nadolol 80 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Nadolol 80.0 mg.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

White or slightly mottled, capsule-shaped, biconvex tablet engraved “80” on one side and with a break line on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nadolol is indicated in the management of:

Angina Pectoris:
For the long-term management of patients with angina pectoris by continuous medication.

Hypertension:
For the long-term management of essential hypertension, either alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Arrhythmias:
For the treatment of cardiac tachyarrhythmias.

Migraine:
For the prophylactic management of migraine headache. The efficacy of Nadolol in the treatment of a migraine attack that has already started has not been established, and Nadolol is not indicated for such use.

Thyrotoxicosis:
For the relief of the symptoms of hyperthyroidism and the pre- operative preparation of patients for surgery. Nadolol may be used in conjunction with conventional antithyroid therapy.

4.2 Posology and method of administration

Adults:
Dosage should be titrated gradually with at least a week between increments to assess response; individuals show considerable variation in their response to beta-adrenergic blockade.

Nadolol may be given in a once daily dosage without regard to meals. The dosage interval should be increased when creatinine clearance is below 50 ml/min/1.73 m^2.

If Nadolol is to be discontinued, reduce dosage over a period of at least two weeks (see warnings).

Angina pectoris:
Initially 40 mg once daily. This may be increased at weekly intervals until an adequate response is obtained or excessive bradycardia occurs. Most patients respond to 160 mg or less daily. The value and safety of daily doses exceeding 240 mg have not been established.

Hypertension:
Initially 80 mg once daily. This may be increased by a weekly increment of 80 mg or less until an optimum response is obtained. Many patients respond to 80 mg daily, and most patients respond to 240 mg or less, daily, but higher doses have been required for a few patients. In some patients it is necessary to administer a diuretic, peripheral vasodilator and/or other antihypertensive agents in conjunction with nadolol in order to achieve satisfactory response.

Treatment of hypertension associated with phaeochromocytoma may require the addition of an alpha-blocking agent.

Cardiac tachyarrhythmias:
Initially 40 mg once daily. This may be increased if necessary to 160 mg once daily. If bradycardia occurs dosage should be reduced to 40 mg once daily.

Migraine:
The initial dose of nadolol is 40 mg once daily. Dosage may be gradually increased in 40 mg increments until optimum migraine prophylaxis is achieved. The usual maintenance dose is 80 to 160 mg administered once daily. After 4 to 6 weeks at the maximum dose if a satisfactory response is not obtained, therapy with nadolol should be withdrawn gradually.

Thyrotoxicosis:
The dosage range is 80-160 mg once daily. It has been found that most patients require a dose of 160 mg once daily. Nadolol may be used together with conventional

anti-thyroid treatment. For the preparation of patients for partial thyroidectomy, nadolol should be administered in conjunction with potassium iodide for a period of 10 days prior to operation. Nadolol should be administered on the morning of operation. Post-operatively, nadolol dosage should be slowly reduced and then withdrawn following clinical stability.

Renal or hepatic impairment:
As with all drugs patients with impaired renal or hepatic function should be monitored.

Paediatric population:
The safety and efficacy of nadolol in children has not been established.

Elderly:
In elderly patients a low initial dose should be used so that sensitivity to side effects may be assessed.

4.3 Contraindications

- Hypersensitivity to the active substance, nadolol or to any of the excipients listed in section 6.1
- Bronchial asthma or a history of asthma
- Sinus bradycardia
- Greater than first degree atrioventricular conduction block
- Cardiogenic shock
- Right ventricular failure secondary to pulmonary hypertension
- Overt cardiac failure (see section 4.4 Special warnings and precautions for use)
- Previously demonstrated hypersensitivity to nadolol

4.4 Special warnings and precautions for use

Warnings

Exacerbation of Ischaemic Heart Disease Following Abrupt Withdrawal
Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina, hypertension, and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered nadolol, particularly in patients with ischaemic heart disease, the dosage should be gradually reduced over a period of one to two weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, nadolol administration should be re-instituted promptly (at least

temporarily), and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognised, it may be prudent not to discontinue nadolol therapy abruptly, even in patients under treatment for hypertension alone.

Patients with a History of Cardiac Failure
Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and beta-blockade may worsen failure.

Although beta-blockers including nadolol should be avoided in overt congestive heart failure, they can be cautiously used, if necessary, in patients with a history of heart failure who are well compensated (usually with digitalis and diuretics). Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

Patients Without a History of Heart Failure
Continued depression of the myocardium with beta-blockade over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending heart failure, the patient should be fully digitalised and/or treated with diuretics, and the response observed closely.

If cardiac failure continues despite adequate digitalisation and diuresis, Nadolol should be withdrawn (gradually, if possible).

Major Surgery
Beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anaesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output. It has generally been suggested that beta-blocker therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, beta-blockers including nadolol should be withdrawn well before surgery takes place.

In no circumstances should beta-blockers be discontinued prior to surgery in patients with phaeochromocytoma or thyrotoxicosis.

In the event of emergency surgery, the anaesthesiologist should be informed that the patient is on beta-blocker therapy. The effects of nadolol can be reversed by administration of beta-receptor agonists such as isoprenaline or dobutamine. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta- adrenergic receptor blocking agents.

(An exception to the above paragraph is thyroid surgery – see under ‘Thyrotoxicosis’ in section 4.1 Indications and section 4.2 Posology and method of administration).

Nonallergic Bronchospasm (e.g. chronic bronchitis, emphysema)
Patients with bronchospastic diseases should not, in general, receive beta-blockers since they may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta receptors.
(NOTE: Nadolol is contra-indicated in asthmatic patients.)

Diabetes and Hypoglycaemia
Beta-adrenergic blockade may prevent the appearance of warning signs and symptoms (e.g. tachycardia and blood pressure changes) of acute hypoglycaemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycaemia; therefore, it may be necessary to adjust the dose of anti-diabetic drugs.

Occasionally causes hypoglycaemia, even in non-diabetic patients, e.g., neonates, infants, children, elderly patients, patients on haemodialysis or patients suffering from chronic liver disease and patients suffering from overdose. Severe hypoglycaemia associated with nadolol has rarely presented with seizures and/or coma in isolated patients.

Skin Rashes
There have been reports of skin rashes (including a psoriasiform type) and/or ocular changes (conjunctivitis and `dry eye') associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of the therapy with a beta-adrenergic blocker should be gradual.

Treatment for Anaphylactic Reaction
While taking beta-blockers, patients with a history of severe anaphylactic reaction may be more reactive to repeated challenge, accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction. (NOTE: Epinephrine combined with non-cardioselective beta-blockers such as nadolol can cause a hypertensive episode followed by bradycardia.)

Thyrotoxicosis
Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism (e.g. tachycardia). Abrupt withdrawal of nadolol in thyroid patients can precipitate thyroid storm.

Hypoglycaemic seizures
In children, the hypoglycaemic effect can occur more rapidly, leading to an increased risk of hypoglycaemic seizures in this age group.

<u>Precautions</u>

Occasionally, beta-blockade with drugs such as nadolol may produce hypotension and/or marked bradycardia, resulting in vertigo, syncope or orthostatic hypotension.

Impaired Renal or Hepatic Function
Nadolol should be used with caution in patients with impaired renal or hepatic function (see section 4.2 Posology and method of administration).

Carcinogenesis, Mutagenesis, Impairment of Fertility
In chronic oral toxicologic studies lasting one to two years, nadolol did not produce any significant toxic effects in mice, rats, or dogs. In two-year oral carcinogenic studies in rats and mice, nadolol did not produce any neoplastic, pre-neoplastic, or non-neoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, nadolol caused no adverse effects.

Stress tests
Beta-blockers including nadolol significantly affect the accuracy of all types of stress tests.

4.5 Interaction with other medicinal products and other forms of interaction

General anaesthetics
Those which cause myocardial depression such as chloroform, cyclopropane, trichloroethylene and ether should be avoided as the patient may be subject to protracted severe hypotension. (See Major Surgery in section 4.4 Special warnings and special precautions for use).

Myocardial depressants
Myocardial depressants such as lidocaine and procainamide may subject the patient to protracted severe hypotension.

Adrenoceptor stimulants
Beta-adrenoceptor stimulants such as isoprenaline and verapamil, or alpha-adrenoceptor stimulants such as noradrenaline and adrenaline will reverse the hypotensive effects and increase vasoconstrictor activity.

Catecholamine-depleting drugs
Additive effects may occur with nadolol; monitor closely for evidence of hypotension and/or excessive bradycardia (e.g. vertigo, syncope, postural hypotension).

Antihypertensives (*e.g. neurone-blocking drugs, vasodilators, diuretics*)
Additive hypotensive effect.

Clonidine
If Nadolol and clonidine are given concurrently, clonidine should not be discontinued until several days after Nadolol withdrawal.

Antidiabetic drugs *(oral agents and insulin)*

Hypoglycaemia or hyperglycaemia; adjust dosage of anti-diabetic drug accordingly (see Diabetes and Hypoglycaemia in section 4.4 Special warnings and special precautions for use).

Monoamine oxidase inhibitors (MAOIs)
Isolated cases of bradycardia have occurred during concurrent use of beta-blockers and MAOIs.

Antimuscarinic agents
May counteract the bradycardia caused by beta-blockers.

Calcium-channel blockers
Calcium channel blockers generally potentiate the pharmacologic effects of beta-blockers. Patients taking both agents should be carefully monitored for adverse cardiovascular events.

Diltiazem
An increased risk of depression has been reported when beta-blockers are co-administered with diltiazem.

Other antiarrhythmic agents
Additive or antagonistic effects may occur with nadolol.

Fingolimod
Concomitant use of fingolimod with beta-blockers may potentiate bradycardic effects and is not recommended. Where such co-administration is considered necessary, appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.

Lidocaine, IV
Significant reduction of lidocaine clearance can occur when a beta-blocker is administered concurrently.

Non-steroidal anti-inflammatory agents (NSAIDs)
The antihypertensive effects of beta-blockers may be reduced during concurrent administration of indometacin and possibly other NSAIDs.

Phenothiazines and other antipsychotic agents
Additive antihypertensive effects have occurred with other beta-blockers when they were given concurrently with phenothiazines or haloperidol.

Vasoconstrictor agents
Effects with nadolol can be additive (e.g. with ergot alkaloids).

4.6 Fertility, pregnancy and lactation

Fertility
In fertility and general reproductive performance studies in rats, nadolol caused no adverse effects. No other data is available on nadolol and its effects on fertility.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. In animal reproduction studies with nadolol, evidence of embryo- and foetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose. No teratogenic potential was observed in any of these species.

Nadolol should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Fetal growth retardation has been reported.

Neonates whose mothers are receiving nadolol at parturition have exhibited bradycardia, hypoglycaemia, respiratory distress, and associated symptoms.

Breastfeeding

Nadolol is excreted in human milk. Because of the potential for adverse effects in nursing infants, a decision should be made whether to discontinue nursing or to discontinue therapy, taking into account the importance of nadolol to the mother.

4.7 Effects on ability to drive and use machines

There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: Very common ≥ 10 %; Common ≥ 1 % and < 10 %; Uncommon ≥ 0.1 % and < 1 %; Rare ≥ 0.01 % and < 0.1 %; Very rare < 0.01%; Unknown (cannot be estimated from available data)

Most adverse effects have been mild and transient and have rarely required withdrawal of therapy. The percentages given below were based on a population of 1440 patients taking nadolol in clinical trials.

ADVERSE REACTION REPORTED		
System Organ Class	**Frequency**	**Adverse Reaction (MedDRA Terms)**
Metabolism and nutrition disorders	Uncommon	Anorexia (0.1 – 0.5%)
	Unknown	Hypoglycaemia in neonates, infants, children, elderly patients, patients on haemodialysis, patients on concomitant anti-diabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported (see section 4.4)
Psychiatric disorders	Uncommon	Change in behaviour (about 2%)

	Unknown	Insomnia
Nervous system disorders	Common	Dizziness (about 2%)
	Uncommon	Paraesthesias and sedation (about 0.6%), Headache and slurred speech (0.1 – 0.5%)
	Unknown	Light headedness
Eye disorders	Uncommon	Dry eyes and blurred vision (0.1 – 0.5%)
Ear and labyrinth disorders	Uncommon	Tinnitus (0.1 – 0.5%)
Cardiac disorders	Common	Bradycardia (heart rate < 60 BPM), Heart rate < 40 BPM and/or symptomatic bradycardia (about 2%), Cardiac failure, Rate and rhythm disorders/conduction disorders (about 1%)
	Unknown	First-degree and third-degree heart block
Vascular disorders	Common	Symptoms of peripheral vascular insufficiency usually of the Raynaud type (about 2%), Hypotension (about 1%)
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough and nasal stiffness (0.1 – 0.5%), Bronchospasm (about 0.1%) (see section 4.3 and section 4.4)
Gastrointestinal disorders	Uncommon	Nausea, diarrhoea, abdominal discomfort, constipation, vomiting, indigestion, bloating and flatulence (0.1 – 0.5%), Dry mouth (0.1 – 0.5%)
Skin and subcutaneous tissue disorders	Uncommon	Rash, pruritus; dry skin; facial swelling and sweating (0.1 – 0.5%)
	Unknown	Reversible alopecia (has been reported infrequently)
Reproductive system and breast disorders	Uncommon	Impotence or decreased libido (0.1 – 0.5%)
General disorders and administration site conditions	Common	Fatigue (about 2%)
	Unknown	Cold extremities
Investigations	Uncommon	Weight gain (0.1 – 0.5%)

The events listed below have also occurred with nadolol and/or other beta-adrenergic blocking agents; however, no causal relationship to nadolol was established:

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Hypertensive reaction in patients with pheochromocytoma

Blood and lymphatic system disorders
Agranulocytosis and thrombocytopenic purpura.

Psychiatric disorders
Reversible depression progressing to catatonia; hallucinations; an acute reversible syndrome characterised by disorientation for time and place, emotional lability, and decreased performance on neuropsychologic tests; sleep disturbances.

Nervous system disorders
An acute reversible syndrome characterised by short term memory loss and slightly clouded sensorium.

Eye disorders
Visual disturbances.

Vascular disorders
Mesenteric arterial thrombosis.

Gastrointestinal disorders
Ischaemic colitis.

Reproductive system and breast disorders
Peyronie's disease.

Skin and subcutaneous tissue disorders
Non-thrombocytopenic purpura; pemphigoid rash.

General disorders and administration site conditions
Fever combined with aching.

Investigations
Elevated liver enzymes.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of overdosage, nadolol may cause excessive bradycardia, cardiac failure, hypotension, bronchospasm or hypoglycaemic seizures.

Transitory increase in BUN has been reported, and serum electrolyte changes may occur, especially in patients with impaired renal function.

Treatment
Nadolol can be removed from the general circulation by haemodialysis. In determining the duration of corrective therapy, note must be taken of the long duration of the effect of nadolol.

In addition to gastric lavage, the following measures should be employed, as appropriate:

Excessive Bradycardia
Administer atropine (0.25 – 1.0 mg). If there is no response to vagal blockade, administer isoprenaline cautiously.

Cardiac Failure
Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension
If fluid administration is ineffective, administer vasopressors such as dopamine, dobutamine or adrenaline.

Bronchospasm
Administer a beta-2-agonist agent and/or a theophylline derivative.

Stupor or coma
Supportive therapy as warranted.

Gastrointestinal Effects
Symptomatic treatment as needed.

BUN and/or Serum Electrolyte Abnormalities
Institute supportive measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents; Beta blocking agents, non-selective.

ATC code: C07AA12
Nadolol is a beta-adrenergic receptor blocking agent with a prolonged activity, permitting once-daily dosage in angina, hypertension, cardiac arrhythmias, the prophylaxis of migraine, and the relief of hyperthyroid symptoms.

Nadolol is not metabolised. It has no membrane stabilising or intrinsic sympathomimetic activity, and its only effect on the autonomic nervous system is one of beta-adrenergic blockade. Nadolol is nonselective.

Receptor blockade by nadolol results in protection from excessive inappropriate sympathetic activity. Nadolol reduces the number and severity of attacks of angina pectoris by blocking response to catecholamine stimulation and thus lowers the oxygen requirement of the heart at any given level of effort.

Nadolol reduces both supine and erect blood pressure. Like other beta-blockers nadolol exerts an antiarrhythmic action. Nadolol has been shown to reduce the rapid ventricular response which accompanies atrial fibrillation/flutter by slowing conduction through the A-V node. Beta-blockade is of particular value in arrhythmias caused by increased levels of, or sensitivity of the heart to,

circulating catecholamines, e.g. arrhythmias associated with phaeochromocytoma, thyrotoxicosis, or exercise. Nadolol is effective in reducing ventricular premature beats in selected patients.

Nadolol exerts an effect in the prophylaxis of migraine by a mechanism which may involve prevention of vasoconstriction in the area served by the internal carotid artery and prevention of excessive adrenergic vasodilation in the external carotid artery.

Nadolol alleviates the symptoms of thyrotoxicosis and provides symptomatic control before and during thyroid surgery.

Beta-blocking agents have been shown in large scale studies to reduce mortality by preventing reinfarction and sudden death in patients surviving their first myocardial infarction.

5.2 Pharmacokinetic properties

Absorption:
About 30 percent of an oral dose of Nadolol is absorbed. The presence of food in the gastrointestinal tract does not affect the rate or extent of Nadolol absorption.

Distribution:
Peak serum concentrations usually occur in 3 to 4 hours after drug administration. Approximately 30 percent of the Nadolol present in serum is reversibly bound to plasma protein.

Biotransformation:
Nadolol is not metabolised.

Elimination:
Unlike most available beta-blocking agents, Nadolol is not metabolised, and is excreted unchanged principally by the kidneys. The serum half- life of therapeutic doses of Nadolol is relatively long, ranging from 20 to 24 hours (permitting once daily dosage).

Characteristics in specific groups of subjects or patients:
A significant correlation between minimum steady-state serum concentrations of Nadolol and total oral daily dose has been demonstrated in hypertensive patients; however, the observed dose-response range is wide and proper dosage requires individual titration.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

PVC/aluminium foil blister packs in the cartons containing 28 tablets.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 45043/0062

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