

APO-NADOLOL

1. APO-NADOLOL (40mg and 80mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nadolol 40mg

Nadolol 80mg

Excipient with known effect

Lactose: Apo-Nadolol 40mg and 80mg tablets contain Lactose. If you have been told by your doctor that you may have intolerance to some sugars, please contact your doctor before taking this medicinal product.

Gluten: Apo-Nadolol 40mg and 80mg tablets are gluten free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

APO-NADOLOL 40mg tablets are white, round, biconvex tablets, 8.0mm diameter, identified APO over breakline over N40 on one side. Each tablet contains 40mg nadolol and typically weighs 200mg.

APO-NADOLOL 80mg tablets are white, round, biconvex tablets, 11.2mm diameter, identified APO over breakline over N80 on one side. Each tablet contains 80mg nadolol and typically weighs 400mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Prophylaxis of angina pectoris
- Management of mild to moderate hypertension. Although nadolol may be used alone, it is more commonly prescribed in combination with other medicines, particularly thiazide diuretics. Nadolol is not recommended for the emergency treatment of hypertensive crises.
- Treatment of cardiac arrhythmias
- Prophylaxis of common and classic migraine headache
- Symptomatic treatment of hyperthyroidism and preoperative preparation of patients for thyroidectomy. It may be used with conventional antithyroid therapy.

4.2 Dose and method of administration

Dose

Angina Pectoris

The initial starting dose is 40mg once daily. This may be increased by 40mg at weekly intervals until an optimal response is obtained or excessive bradycardia exceeding 55 beats/minute results. Most patients will respond to 160mg or less per day.

Hypertension

The initial starting dose is 40mg once daily either alone or in combination with another anti-hypertensive agent, usually a thiazide diuretic. This may be increased by 40 to 80mg daily at 5 to 14 day intervals until optimal blood-pressure response is achieved. The usual maintenance dose is 80 to 120mg as a single dose but doses of up to 320mg may be required.

Arrhythmias

The initial starting dose is 40mg once daily. This may be increased by 40mg at weekly intervals to a maximum dose of 160mg. If bradycardia occurs the dose should be reduced to 40mg once daily.

Migraine

The initial starting dose is 40 to 80mg once daily. Dosage may be increased gradually in 40mg increments until optimal migraine prophylaxis is achieved. The usual maintenance dose is 80 to 160mg once daily. If after 4 to 6 weeks at the maximum dose a satisfactory response is not achieved then nadolol use should be discontinued gradually withdrawing the nadolol over a 2 week period.

Thyrotoxicosis

The initial starting dose is 80mg once daily. If after 1 to 2 weeks control of clinical symptoms has not been fully achieved the dose may be increased to 160mg. APO-NADOLOL may be used with anti-thyroid medicines. For the preparation of patients for partial thyroidectomy, nadolol should be administered in conjunction with potassium iodide for 10 days prior to the surgery. Nadolol should be administered on the morning of the surgery. After surgery, nadolol dosage should be slowly reduced and then withdrawn once the patient has been stabilised.

Elderly

Some dosage reduction in the elderly may be appropriate since decreased renal function is a physiological function of old age. (See dosage recommendations for impaired renal function)

Children

The safety and efficacy of Nadolol use in children has not been studied.

Patients with renal impairment

Nadolol is excreted mainly by the kidneys and increased blood levels of nadolol occur in the presence of renal failure. Dosage adjustments are recommended.

Creatinine clearance (mL/min/1.73m²)	Dosage interval in hours
>50	24
31-50	24-36
10-30	24-48
<10	40-60

Nadolol can be removed from the general circulation by haemodialysis.

Method of administration

Nadolol is administered orally once daily and may be taken with or without food. The dosage should be individualised to the patient's needs.

Maximum tolerated Daily Dose

See above section on Dose

4.3 Contraindications

- Bronchial asthma or other obstructive lung disorders
- Uncontrolled heart failure
- Cardiogenic shock
- Sick-sinus syndrome
- Grade 2 and 3 A-V block and infranodal A-V block
- Severe bradycardia
- Hypersensitivity to nadolol or any of the tablet components of APO-NADOLOL

4.4 Special warnings and precautions for use

Special caution should be exercised when administering nadolol to patients with a history of heart failure since cardiac failure may be precipitated in some patients dependent on sympathetic stimulation for circulatory function. In addition, the concurrent use of beta-blockers and digitalis over a period of time can, in some cases, lead to cardiac failure. Patients should be carefully monitored. At the first sign of impending failure patients should be fully digitalised and/or given a diuretic. Beta-blockers do not block the inotropic action of digitalis. If cardiac failure continues nadolol should be withdrawn.

Discontinuation of nadolol in patients with angina pectoris or other evidence of coronary insufficiency should be gradual with dosage reduction over two weeks if possible; the same frequency of administration should be maintained. Abrupt discontinuation can lead to severe exacerbation of angina and/or myocardial infarction or ventricular arrhythmias.

Nadolol should be administered with caution to patients prone to non-allergic bronchospasm (e.g. chronic bronchitis, emphysema) since it may block the bronchodilation produced by stimulation of beta-2 receptors.

Also caution in patients with allergic rhinitis.

Concomitant therapy of beta-adrenergic blockers and calcium antagonists should be used together with a lot of caution. Beta-adrenergic blockers and calcium antagonists potentiate the depressant action of each other on the myocardium and reinforce the tendency of each other to impair AV conduction.

Peripheral circulation impairment may occur with beta blockade as systematic vascular resistance can rise at rest and during exercise.

The management of patients being treated with beta-blockers and undergoing elective or emergency surgery is controversial. Patients with angina undergoing elective surgery should ideally have their nadolol slowly withdrawn at least 72 hours before

anaesthesia. In emergency surgery, or if beta blockade is considered desirable, the anaesthetic used should have little negative inotropic action and the patient may be administered atropine. Any untoward effects of beta-blockade may be reversed, if necessary, by sufficient doses of agonists such as isoprenaline or ephedrine.

Nadolol should be used with caution in diabetic patients receiving insulin or oral hypoglycaemic agents or patients subject to spontaneous hypoglycaemia. Although hypoglycaemia has not been reported with nadolol, the possibility exists since several non-selective beta-blockers can block catecholamine-induced glycogenolysis. Nadolol may also modify some of the warning symptoms of impending hypoglycaemia e.g. tachycardia and tremor. Alternatively, beta-blockade can reduce the release of insulin in response to hyperglycaemia so that dosage adjustment of anti-diabetic drugs may be necessary.

Abrupt withdrawal of nadolol in patients with thyrotoxicosis may be followed by an exacerbation of the symptoms of hyperthyroidism including thyroid storm.

Nadolol should be used with caution in patients with impaired renal function (see Dose and Method of Administration).

If a patient on beta-blockers experiences an anaphylactic type allergic reaction to an allergen, adrenaline may have to be used in larger doses than normal to overcome the bronchospasm. Caution is necessary as the higher doses needed may produce excessive alpha-receptor stimulation with consequent hypertension, reflex bradycardia and heart block. Alternative management includes vigorous supportive care such as fluids, beta-2 agonists such as parenteral salbutamol or isoprenaline to overcome bronchospasm, and noradrenaline to overcome hypotension.

4.5 Interaction with other medicines and other forms of interaction

Nadolol should be used with caution in combination with calcium channel blocking agents such as verapamil and diltiazem in patients with impaired ventricular function.

Beta-blockers may exaggerate the hypotension induced by general anaesthetics.

Catecholamine-depleting medicines e.g. reserpine have an additive effect and patients should be monitored closely for hypotension and/or excessive bradycardia.

Extreme caution is necessary when nadolol and digoxin are prescribed concurrently in patients with AV-nodal conduction abnormalities

Facilities for cardiac monitoring should be available initially when prescribing beta-blockers with other antiarrhythmic drugs such as lignocaine, phenytoin, procainamide, diisopyramide, or quinidine. Dosages of these medicines may need to be modified. If lignocaine is administered IV concurrently with nadolol there can be a significant reduction of lignocaine clearance.

Adrenaline and noradrenaline should not be given to patients receiving nadolol as severe vasoconstriction may occur.

Adjust the dosage of antidiabetic drugs accordingly for hypoglycaemia and hyperglycaemia.

Anti-muscarinic agents may counteract the bradycardia caused by F¹-blockers.

Isolated cases of bradycardia have occurred during concurrent use of F¹-blockers and MAO inhibitors.

The antihypertensive effects of F¹-blockers may be reduced during concurrent administration of indomethacin and possibly other NSAIDs.

Additive antihypertensive effects have occurred when other F¹-blockers have been given concurrently with phenothiazines or haloperidol.

If vasoconstrictor agents e.g. ergot alkaloids are given concurrently with nadolol the effects can be additive.

4.6 Fertility, pregnancy and lactation

Pregnancy
Category C.

Nadolol crosses the placental barrier and should not be used during pregnancy unless the benefits strongly outweigh the possible risks. Neonates whose mothers were receiving nadolol at parturition have exhibited bradycardia, hypoglycaemia, and associated symptoms.

Animal studies have shown evidence of embryo and foetal toxicity in rabbits but not in rats or hamsters at doses of 100 to 300mg/kg. No teratogenic potential was observed in any of these species.

Breast-feeding

Nadolol is excreted into breast milk at concentrations higher than those in the maternal serum. Because of the potential for adverse effects in breast feeds infants a decision should be made on whether to discontinue breastfeeding or discontinue Nadolol therapy.

Fertility

In fertility and general reproductive studies in rats nadolol caused no adverse effects.

4.7 Effects on ability to drive and use machines

Likely to produce minor or moderate adverse effects on the ability to drive or use machinery.

Especially when therapy is being initiated, the patient's ability to drive or operate machinery may be impaired. Care should be taken until the effects of the therapy are known.

4.8 Undesirable effects

Nervous system disorders

Central nervous system

Infrequent, mild or transitory adverse reactions: Lethargy, fatigue, irritability, tinnitus, headache and slurred speech.

Rarely: depression, anxiety, insomnia and hallucinations due to the hydrophilic nature of nadolol.

Eye disorders

Ophthalmologic

Infrequent, mild or transitory adverse reactions: conjunctivitis, diplopia, blurred vision, dry eyes.

Cardiac disorders

The most serious adverse reactions encountered are congestive heart failure (CHF), and A-V block.

The most common adverse reactions reported are severe bradycardia (3%), CHF (1%). Other infrequent, mild or transitory adverse reactions: Pulmonary oedema, cardiac enlargement, rhythm or conduction disturbances including A-V block, bigeminy, Adams-Stokes syndrome, chest pain

Vascular disorders

The most common adverse reactions reported: dizziness (3%), fatigue (2%), hypotension (1%), cold sensations (1%),

Infrequent, mild or transitory adverse reactions: hypotension, syncope, peripheral vascular insufficiency including intermittent claudication, cold extremities and oedema.

Respiratory, thoracic and mediastinal disorder

Infrequent, mild or transitory adverse reactions: bronchospasm, dyspnoea, cough

Gastrointestinal disorders

Infrequent, mild or transitory adverse reactions: abdominal discomfort, nausea, vomiting, diarrhoea, constipation, flatulence, gastritis and anorexia

Skin and subcutaneous tissue disorders

Infrequent, mild and transitory adverse reactions: skin rash, pruritus, dry skin, sweating

Musculoskeletal and connective tissue disorders

Infrequent, mild or transitory adverse reactions: exacerbation of myasthenia gravis

Reproductive system

Infrequent, mild or transitory adverse reactions: impotence, decreased libido

Miscellaneous:

Infrequent, mild or transitory adverse reactions: fluid retention and weight gain, nasal stuffiness, alopecia, hypertriglyceridaemia and acute pancreatitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

professional are asked to report any suspected adverse reactions
<https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Symptoms

The most common symptoms to be expected are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycaemia.

Treatment

Nadolol should be discontinued and the patient monitored closely. In addition to gastric lavage the patient can be treated using the following therapeutic measures:

Bradycardia: Atropine 0.25 to 1.0mg intravenously. If additional measures are necessary, isoprenaline or ephedrine may be used cautiously.

Heart block (second or third degree): Isoprenaline or transvenous cardiac pacemaker.

Cardiac failure: Digitalisation and diuretics. Glugagon may also be useful.

Hypotension: If fluid administration is ineffective, administer vasopressors such as dopamine, noradrenaline or isoprenaline.

Bronchospasm: Aminophylline or isoprenaline.

Hypoglycaemia: Intravenous glucose.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Beta Blocking Agent

ATC code: C07AA12

Mechanism of Action

Nadolol is a hydrophilic, non-selective beta-blocker. It inhibits response to adrenergic stimulation by competitively blocking beta-1 receptors within the myocardium and beta-2 receptors within bronchial and vascular smooth muscle. Beta-1 receptor blockade by nadolol decreases resting heart rate, inhibits exercise-induced increases in heart rate, and decreases conduction velocity through the atrioventricular (AV) node and myocardial automaticity. Nadolol does not possess membrane stabilising or intrinsic sympathomimetic (partial agonist) activities.

Nadolol reduces blood pressure in both supine and standing positions, and the effects are evident for at least 24 hours after a single daily dose. Patient compliance is thus encouraged.

The mechanisms for the antihypertensive effect are not fully understood but appear to include:

- a) Reduction in cardiac output as a result of its competitive ability to antagonise catecholamine- induced tachycardia at the beta-receptors in the heart
- b) Inhibition of central vasomotor centres with decreased sympathetic outflow from the CNS
- c) Inhibition of renin release by the kidneys.

The exact mechanism by which nadolol exercises its anti-anginal effect is not certain. An important factor may be the reduction of myocardial oxygen requirements by blocking catecholamine-induced increases in heart rate, systolic blood pressure and the velocity and extent of myocardial contraction. However, oxygen requirements may be increased by such actions as increases in left ventricular fibre length, end diastolic pressure and the systolic ejection period. When the net physiological effect is advantageous in anginal patients, it manifests itself during exercise or stress by delaying the onset of pain and reducing the incidence and severity of anginal attacks. Nadolol can therefore increase the capacity for work and exercise in such patients.

The mechanism of the anti-migraine effect has not been established.

The Class II anti-arrhythmic activity of β - blockers is primarily due to its selective blocking β -adrenergic modulation of the atrioventricular node which increases the effective refractory period of the AV node.

β -adrenergic blockade controls symptoms associated with hyperthyroidism including tremor, anxiety and muscle weakness.

5.2 Pharmacokinetic properties

Following orally administered nadolol, 30-40% of the dose is slowly absorbed from the gastro-intestinal tract. The rate and extent of absorption is not affected by the presence of food. Peak plasma concentrations are reached 3 to 4 hours after ingestion while steady state serum concentrations are reached after 6 to 9 days. Nadolol has a serum half-life of 20-24 hours, which enables once daily dosing. Nadolol elimination is proportional to creatinine clearance in patients with renal impairment. In patients with severe renal impairment (creatinine clearance <5ml/min), the average serum half-life is 45 hours and non-renal clearance of the drug is increased. Nadolol is widely distributed into body tissues but because of its low lipid solubility, only minimal quantities are detected in the brain.

Nadolol crosses the placenta and is distributed into milk and bile. About 30% of nadolol in serum is reversibly bound to plasma proteins.

Nadolol does not appear to be metabolized in man and is excreted mainly in the urine with approximately 70% of the absorbed dose being eliminated via the kidneys and the remainder being excreted via the bile.

Nadolol can be removed by haemodialysis.

5.3 Preclinical safety data

In chronic toxicological studies (1-2 years) in mice, rats and dogs, nadolol did not produce any neoplastic, preneoplastic or nonneoplastic pathological lesions. In fertility and general reproductive studies in rats nadolol caused no adverse effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Apo –Nadolol 40mg and 80mg tablet contains the following excipients:

- Colloidal silicon dioxide
- Croscarmellose sodium
- Lactose
- Magnesium Stearate
- Microcrystalline cellulose

Apo-Nadolol 40mg and 80mg are gluten free.

Apo-Nadolol 40mg and 80mg contain lactose.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Apo-Nadolol 40mg:

PVC/PVdC blister packs (30 tablets): 24 months from date of manufacture

PVC/PE/PVdC blister packs (30 tablets): 24 months from date of manufacture

HDPE bottles (50, 100 or 500 tablets): 36 months from date of manufacture

Apo-Nadolol 80mg:

PVC/PVdC blister packs (30 tablets): 24 months from date of manufacture

PVC/PE/PVdC blister packs (30 tablets): 24 months from date of manufacture

HDPE bottles (50 tablets): 24 months from date of manufacture

HDPE bottles (100 or 500 tablets): 36 months from date of manufacture

6.4 Special Precautions for Storage

Store at or below 30°C

Protect from heat, light and moisture.

Keep the container tightly closed.

6.5 Nature and contents of container

APO-NADOLOL 40mg:

PVC/PVdC or PVC/PE/PVdC blisters containing 30 tablets

HDPE bottles of (50, 100 and 500 tablets)

APO-NADOLOL 80mg:

PVC/PVdC or PVC/PE/PVdC blisters containing 30 tablets

HDPE bottles of (50, 100 and 500 tablets)

Not all pack sizes maybe marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Apotex NZ Ltd.
32 Hillside Road
Glenfield
AUCKLAND 0627
Telephone: (09) 444 2073
Fax: (09) 444 2951
E-mail: NZcustomerservice@apotex.com

9. DATE OF FIRST APPROVAL

05 November 1992

10. DATE OF REVISION OF THE TEXT

16 June 2017

Summary Table of Changes

Section changed	Summary of new information
Whole data sheet	Reformatted as per Medsafe new data sheet
2	Apo-Nadolol 40mg and 80mg tablets are gluten free. Apo-Nadolol 40mg and 80mg tablets contain lactose.
4.2	Maximum tolerated Daily Dose See above section on Dose
4.7	Likely to produce minor or moderate adverse effects on the ability to drive or use machinery. Especially when therapy is being initiated, the patient's ability to drive or operate machinery may be impaired. Care should be taken until the effects of the therapy are known.

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4.8	<p>Reporting of suspected adverse reactions</p> <p>Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professional are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/</p>
5.1	<p>Pharmacotherapeutic group: Beta Blocking Agent</p> <p>ATC code: C07AA12</p>
6.1	<p>Apo –Nadolol 40mg and 80mg tablet contains the following excipients:</p> <ul style="list-style-type: none"> • Colloidal silicon dioxide • Croscarmellose sodium • Lactose • Magnesium Stearate • Microcrystalline cellulose <p>Apo-Nadolol 40mg and 80mg are gluten free. Apo-Nadolol 40mg and 80mg contain lactose.</p>
6.2	<p>Incompatibilities</p> <p>Not applicable</p>
6.3	<p><i>Apo-Nadolol 40mg:</i> PVC/PVdC blister packs (30 tablets): 24 months from date of manufacture PVC/PE/PVdC blister packs (30 tablets): 24 months from date of manufacture HDPE bottles (50, 100 or 500 tablets): 36 months from date of manufacture</p> <p><i>Apo-Nadolol 80mg:</i> PVC/PVdC blister packs (30 tablets): 24 months from date of manufacture PVC/PE/PVdC blister packs (30 tablets): 24 months from date of manufacture HDPE bottles (50 tablets): 24 months from date of manufacture HDPE bottles (100 or 500 tablets): 36 months from date of manufacture</p>
6.4	<p>Keep the container tightly closed.</p>
6.5	<p>APO-NADOLOL 40mg: PVC/PVdC or PVC/PE/PVdC blisters containing 30 tablets HDPE bottles of (50, 100 and 500 tablets)</p> <p>APO-NADOLOL 80mg: PVC/PVdC or PVC/PE/PVdC blisters containing 30 tablets HDPE bottles of (50, 100 and 500 tablets)</p> <p>Not all pack sizes maybe marketed.</p>
8	<p>Apotex NZ Ltd. 32 Hillside Road Glenfield AUCKLAND 0627 Telephone: (09) 444 2073 Fax: (09) 444 2951 E-mail: NZcustomerservice@apotex.com</p>
9	<p>DATE OF FIRST APPROVAL 05 November 1992</p>



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10	DATE OF REVISION OF THE TEXT 16 June 2017
Summary Table of Changes	Table added