SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Normiten® 25
Normiten® 50
Normiten® 100

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Normiten 25: Atenolol 25 mg.

Normiten 50: Atenolol 50 mg.

Normiten 100: Atenolol 100 mg.

Excipients with known effect: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Normiten 25: white to off white octagonal flat tablet, debossed "Abic" on one side and "25" on the other side, with breakline between "2" and "5". The tablet can be divided into equal halves.

Normiten 50: white to off white octagonal flat tablet, debossed "Abic" on one side and "50" on the other side, with breakline between "5" and "0". The tablet can be divided into equal halves.

Normiten 100: white to off white octagonal flat tablet, debossed "ABIC" on one side and "100" on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Normiten is indicated in the treatment of:
• Hypertension.
• Angina pectoris.
• Myocardial infarction.

4.2 Posology and method of administration

Posology

The dose must always be adjusted to individual requirements of the patients, with the lowest possible starting dosage.

The following are guidelines:

Adults

Hypertension
Initially 25-50 mg once a day, the dosage being increased gradually to 100 mg a day after two weeks, as needed and tolerated.

Angina
Initially 50 mg once a day, the dosage being increased gradually to 100 mg after 1 week, as needed and tolerated.

Myocardial infarction
For patients who present some days after suffering an acute myocardial infarction, an oral dose of Normiten 100 mg daily is recommended for long-term prophylaxis of myocardial infarction

Older population
Dosage requirements may be reduced, especially in patients with impaired renal function.

Paediatric population
There is no paediatric experience with Atenolol and for this reason Normiten is not recommended for use in children.

Renal failure
Since Atenolol is excreted via the kidneys, the dosage should be adjusted in cases of severe impairment of renal function.

No significant accumulation of Atenolol occurs in patients who have a creatinine clearance greater than 35 ml/min/1.73 m^2 (normal range is 100–150 ml/min/1.73 m^2).

For patients with a creatinine clearance of 15–35 ml/min/1.73 m^2 (equivalent to serum creatinine of 300–600 micromol/litre), the oral dose should be 50 mg daily.

For patients with a creatinine clearance of less than 15 ml/min/1.73 m^2 (equivalent to serum creatinine of greater than 600 micromol/litre), the oral dose should be 25 mg daily or 50 mg on alternate days.

Patients on haemodialysis should be given 50 mg orally after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Method of administration
For administration by the oral route.

4.3 Contraindication

Normiten, as with other beta blockers, should not be used in patients with any of the following:
• hypersensitivity to the active substance, or to any of the excipients listed in section 6.1
• cardiogenic shock
• uncontrolled heart failure
• sick sinus syndrome
• second or third degree heart block
• untreated phaeochromocytoma
• metabolic acidosis
• bradycardia (<45 bpm)
• hypotension
• severe peripheral arterial circulatory disturbances.

4.4 Special warnings and precautions for use

PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETABLOCKERS.
Because of its relative beta selectivity, however, atenolol tablet, may be used with caution in patients with bronchospastic disease who do not respond to, cannot tolerate other treatment or medically necessary. Since beta selectivity is not absolute, the lowest possible dose of atenolol tablet and a beta - stimulating agent (bronchodilator) should be made available.
If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels .

Normiten as with other beta blockers:

- Should not be withdrawn abruptly. The dosage should be withdrawn gradually over a period of 7–14 days, to facilitate a reduction in beta blocker dosage. Patients should be followed during withdrawal, especially those with ischaemic heart disease.
- When a patient is scheduled for surgery, and a decision is made to discontinue beta blocker therapy, this should be done at least 24 hours prior to the procedure. The risk benefit assessment of stopping beta blockade should be made for each patient. If treatment is continued, an anaesthetic with little negative inotropic activity should be selected to minimise the risk of myocardial depression. The patient may be protected against vagal reactions by intravenous administration of atropine.
- Although contraindicated in uncontrolled heart failure (see section 4.3), may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.
- May increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha receptor mediated coronary artery vasoconstriction. Normiten is a beta1 selective beta blocker; consequently, its use may be considered although utmost caution must be exercised.
- Although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3), may also aggravate less severe peripheral arterial circulatory disturbances.
- Due to its negative effect on conduction time, caution must be exercised if it is given to patients with first degree heart block.
- May mask the symptoms of hypoglycaemia, in particular, tachycardia.
- May mask the signs of thyrotoxicosis.
- Will reduce heart rate as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate and the pulse rate drops to less than 50–55 bpm at rest, the dose should be reduced.
- May cause a more severe reaction to a variety of allergens when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat the allergic reactions.
- May cause a hypersensitivity reaction including angioedema and urticaria.
- Should be used with caution in the elderly, starting with a lesser dose (see Section 4.2).

Since Atenolol is excreted via the kidneys, dosage should be reduced in patients with a creatinine clearance of below 35 ml/min/1.73 m^2.

Although cardio selective (beta1) beta blockers may have less effect on lung function than non-selective beta blockers, as with all beta blockers, these should be avoided in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use. Where such reasons exist, Normiten may be used with caution.
Occasionally, some increase in airways resistance may occur in asthmatic patients however, and this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline. The label and patient information leaflet for this product state the following warning: “If you have ever had asthma or wheezing, you should not take this medicine unless you have discussed these symptoms with the prescribing doctor”.

As with other beta blockers, in patients with a phaeochromocytoma, an alpha blocker should be given concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

Combined use of beta blockers and calcium channel blockers with negative inotropic effects, e.g. verapamil and diltiazem, can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sinoatrial or atrioventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridines, e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Digitalis glycosides, in association with beta blockers, may increase atrioventricular conduction time.

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co administered, the beta blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped. (See also prescribing information for clonidine.)

Class I antiarrhythmic drugs (e.g. disopyramide) and amiodarone may have a potentiating effect on atrial-conduction time and induce negative inotropic effect.

Concomitant use of sympathomimetic agents, e.g. adrenaline (epinephrine), may counteract the effect of beta blockers.

Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs. Symptoms of hypoglycaemia, particularly tachycardia, may be masked (see section 4.4).

Concomitant use of prostaglandin synthetase inhibiting drugs, e.g. ibuprofen and indometacin, may decrease the hypotensive effects of beta blockers.

Caution must be exercised when using anaesthetic agents with Normiten. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta blockers with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

4.6 Fertility, pregnancy and lactation

Caution should be exercised when Normiten is administered during pregnancy or to a woman who is breast feeding.

Pregnancy
Atenolol crosses the placental barrier and appears in the cord blood. No studies have been performed on the use of Atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of Atenolol to pregnant women in the management of mild to moderate hypertension has been associated with intrauterine growth retardation.

The use of Normiten in women who are, or may become, pregnant requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters, since beta blockers, in general, have been associated with a decrease in placental perfusion which may result in growth retardation, intrauterine deaths, abortion, immature and premature deliveries.

Breastfeeding
There is significant accumulation of Atenolol in breast milk.

Neonates born to mothers who are receiving Atenolol at parturition or breastfeeding may be at risk of hypoglycaemia and bradycardia.

4.7 Effects on ability to drive and use machines

Atenolol has no or negligible influence on the ability to drive and use machines. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Atenolol is well tolerated. In clinical studies, the undesired events reported are usually attributable to its pharmacological actions of atenolol.
The following undesired events, listed by body system, have been reported with the following frequencies: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100),

rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) including isolated reports, not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Rare	Purpura, thrombocytopenia
Psychiatric disorders	Uncommon	Sleep disturbances of the type noted with other beta blockers
	Rare	Mood changes, nightmares, confusion, psychoses and hallucinations
	Not known	Depression
Nervous system disorders	Rare	Dizziness, headache, paraesthesia
Eye disorders	Rare	Dry eyes, visual disturbances
Cardiac disorders	Common	Bradycardia
	Rare	Heart failure deterioration, precipitation of heart block
Vascular disorders	Common	Cold extremities
	Rare	Postural hypotension which may be associated with syncope, intermittent claudication may be increased if already present, in susceptible patients Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints
Gastrointestinal disorders	Common	Gastrointestinal disturbances
	Rare	Dry mouth
Hepatobiliary disorders	Uncommon	Elevations of transaminase levels
	Rare	Hepatic toxicity including intrahepatic cholestasis
Skin and subcutaneous tissue disorders	Rare	Alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes
	Not known	Hypersensitivity reactions, including angioedema and urticaria
Musculoskeletal and connective tissue disorders	Not known	Lupus like syndrome
Reproductive system and breast disorders	Rare	Impotence
General disorders and administration site conditions	Common	Fatigue
Investigations	Very rare	An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear

Discontinuance of the drug should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

The symptoms of over dosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision; treatment in an intensive care ward; the use of gastric lavage; activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract; the use of plasma or plasma substitutes to treat hypotension and shock. The use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be countered with atropine 1–2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1–10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta blocker blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, plain, selective, ATC code: CO7A B03.

Mechanism of action

Atenolol is a beta blocker which is beta1-selective, (i.e. acts preferentially on beta1-adrenergic receptors in the heart). Selectivity decreases with increasing dose.
Atenolol is without intrinsic sympathomimetic and membrane stabilising activities and as with other beta-blockers, has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure).

As with other beta-blockers, the mode of action of atenolol in the treatment of hypertension is unclear.

It is probably the action of atenolol in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina.

It is unlikely that any additional ancillary properties possessed by S (-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

Clinical efficacy and safety

Atenolol is effective and well tolerated in most ethnic populations although the response may be less in black patients.

Atenolol is effective for at least 24 hours after a single oral dose. The drug facilitates compliance by its acceptability to patients and simplicity of dosing. The narrow dose range and early patient response ensure that the effect of the drug in individual patients is quickly demonstrated. Normiten is compatible with diuretics, other hypotensive agents and antianginals (see section 4.5). Since it acts preferentially on beta receptors in the heart, Normiten may, with care, be used successfully in the treatment of patients with respiratory disease, who cannot tolerate non-selective beta blockers.

Early intervention with Atenolol in acute myocardial infarction reduces infarct size and decreases morbidity and mortality. Fewer patients with a threatened infarction progress to frank infarction; the

incidence of ventricular arrhythmias is decreased and marked pain relief may result in reduced need of opiate analgesics. Early mortality is decreased. Atenolol is an additional treatment to standard coronary care.

5.2 Pharmacokinetic properties

Absorption

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40–50%) with peak plasma concentrations occurring 2–4 hours after dosing. The atenolol blood levels are consistent and subject to little variability. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered.

Distribution

Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (approximately 3%).

Elimination

The plasma half life is about 6 hours but this may rise in severe renal impairment since the kidney is the major route of elimination.

5.3 Preclinical safety data

Atenolol is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Prescribing Information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium carbonate heavy
Starch
Magnesium stearate
Sodium lauryl sulphate
Gelatin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store in a dry, dark place below 25°C

6.5 Nature and contents of container

Normiten 25: 30 tablets in PVC/Aluminium blister packs.

Normiten 50: 12, 28, 30, 480 or 500 tablets in PVC/Aluminium blister.

Normiten 100: 12, 24, 28, 30, 480 or 500 tablets in PVC/Aluminium blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for storage.

7. LICENCE HOLDER AND MANUFACTURER

Licence Holder:
Abic Ltd
P.O.Box 8077, Kiryat Nordau, Netanya.

Manufacturer:

Teva Pharmaceutical Industries Ltd.

P.O.Box 3190, Petach Tikva.

8. REGISTRATION NUMBERS

Normiten 25: 104.02.28834

Normiten 50: 051.72.24149

Normiten 100: 045.35.24916

this leaflet was revised in September 2021 according to MOHs guidelines