1. NAME OF THE MEDICINAL PRODUCT

NIF-TEN 50 mg/20 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg atenolol and 20 mg nifedipine.

Excipient(s) with known effect:
Each capsule contains 10 mg of lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard.
Reddish-brown capsules containing atenolol and a slow-release formulation of nifedipine.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NIF-TEN is indicated for:
i) Management of Hypertension
ii) Management of Angina pectoris

4.2 Posology and method of administration

Posology
Adults
Hypertension:
One capsule daily. NIF-TEN is recommended for use in hypertensive patients where monotherapy may prove inadequate. If necessary, the dosage may be increased to one capsule twice daily.

Angina
One capsule twice daily. NIF-TEN is recommended for use in angina patients where monotherapy may prove inadequate. Where additional efficacy is necessary, prophylactic nitrate therapy or additional nifedipine may be of benefit.

Elderly

Dosage should not exceed one capsule daily in hypertension, or one capsule twice daily in angina.

Paediatric population
The safety and efficacy of NIF-TEN has not yet been established. No data are available. Therefore it is not recommended for use in children.

Renal Impairment
NIF-TEN should not be used in patients with marked renal impairment (see section 4.3).

Method of administration
For administration by the oral route.

4.3 Contraindications

NIF-TEN should not be used in patients with any of the following:

- Hypersensitivity to either active substance or to any of the excipients listed in section 6.1.
- Bradycardia.
- Cardiogenic shock.
- Hypotension;
- Metabolic acidosis.
- Severe peripheral arterial circulatory disturbances.
- Second- or third-degree heart block.
- Sick sinus syndrome.
- Untreated phaeochromocytoma.
- Uncontrolled heart failure.
- During pregnancy or lactation.
- Women of child bearing potential (not taking effective contraception).
- Patients with severe aortic stenosis (see section 4.4).
- Patients with marked renal impairment (i.e. creatinine clearance below 15 ml/min/1.73 m^2; serum creatinine greater than 600 micromol/litre; GFR less than 30 ml/min).
- Patients receiving calcium channel blockers with negative inotropic effects e.g. verapamil and diltiazem (see section 4.5).
- Within one month of acute coronary syndromes (ST- or non-ST-elevation myocardial infarction and unstable angina pectoris).
- Severe hepatic insufficiency.

Due to the nifedipine content, NIF-TEN must not be used in combination with rifampicin because plasma levels of nifedipine, predictive of efficacy, may not be attained due to enzyme induction (see section 4.5).

4.4 Special warnings and precautions for use

Due to its beta-blocker component, NIF-TEN:

- Although contraindicated in uncontrolled heart failure (see section 4.3), may be substituted with care in patients already treated with a beta-blocker, and/or where signs of heart failure have been controlled. Caution must be exercised in patients with conduction defects or whose cardiac reserve is poor, especially as nifedipine also has negative inotropic effects.
- May increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Atenolol is a $beta_1$-selective beta-blocker; consequently the use of NIF-TEN may be considered although utmost caution must be exercised.
- Although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3), NIF-TEN may also aggravate less severe peripheral arterial circulatory disturbances. Due to its negative effect on conduction time by atenolol, caution must be exercised if NIF-TEN is given to patients with first-degree heart block. However, the properties of the nifedipine component of NIF-TEN will to some degree counteract the negative dromotropic effect from atenolol.
- Atenolol should be used with caution in diabetics subject to frequent episodes of hypoglycaemia. Symptoms of hypoglycaemia may be masked (may modify the tachycardia of hypoglycaemia).
- 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, the dose may be reduced. This effect is however opposed by the properties of the nifedipine component of NIF-TEN.
- Should not be discontinued abruptly in patients suffering from ischaemic heart disease.
- In patients with treated phaeochromocytoma NIF-TEN must be administered only after alfa-receptor blockade. Blood pressure should be monitored closely.
- 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.
- Caution must be exercised when using anaesthetic agents with NIF-TEN. The anaesthetist should be informed and the choice of anaesthetic should be the 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.
- Administration of NIF-TEN may lead to positive result in doping tests.

Obstructive airways disease

Patients with bronchospastic disease should, in general, not receive beta-blockers due to increasing in airways resistance.

May cause an increase in airways resistance in asthmatic patients. Atenolol is a $beta_1$-selective beta-blocker, however this selectivity is not absolute. Consequently the use of NIF-TEN may be considered if there is no alternative to the use of a beta-blocker. Although the lowest possible dose of NIF-TEN should be used and utmost caution must be exercised. If increased airways resistance does occur, NIF-TEN should be discontinued and bronchodilator therapy (e.g. salbutamol) administered if necessary.

Due to its nifedipine component it should be noted that:

- The nifedipine component has no diabetogenic effect. In rare cases, a transient increase in blood glucose has been observed with nifedipine in acute studies. This should be considered in patients suffering from diabetes mellitus.
- Ischaemic pain occurs in a small proportion of patients following introduction of nifedipine monotherapy. Although a "steal" effect has not been demonstrated, patients experiencing this effect should discontinue nifedipine therapy.

Hypertensive or anginal patients with clinically significant liver disease have not been studied and no dosage adjustment is suggested from the systemic availability of the monocomponents in patients with cirrhosis. However, such patients should be carefully monitored and, as a precaution, it is recommended that the dose should not exceed one capsule daily.

Lactose intolerance
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 eg, verapamil, diltiazam can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sino atrial or atrio ventricular 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.

Digitalis glycosides, in association with NIF-TEN, may increase atrioventricular conduction time.

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

Atenolol monotherapy

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.

Class I anti-arrhythmic drugs (eg, 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 of prostaglandin synthetase-inhibiting drugs e.g. ibuprofen, indometacin, may decrease the hypotensive effects of beta-blockers.

Baclofen
Concurrent use of baclofen may increase the antihypertensive effect of NIF-TEN.

MAO inhibitors
Combination with a beta-blocker can cause an increase of the pharmacodynamic effects and an increase in blood pressure up to hypertension crises.

Nifedipine monotherapy:
Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine. The extent as well as the duration of interactions should be taken into account when administering NIF-TEN together with the following drugs.

Rifampicin
Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of NIF-TEN in combination with rifampicin is therefore contraindicated. Upon co-administration of the following weak to moderate inhibitors of the cytochrome P450 3A4 system the blood pressure should be monitored and, if necessary, a reduction in the dose considered.

Due to enzyme induction, rifampicin has been shown to decrease the nifedipine AUC and C_{max} by 95% (288 ng l/ml to 8 ng l/ml and 154 ng/ml to 7.5 ng/ml respectively. This may result in reduced efficacy, therefore co-administration of nifedipine is contraindicated (see section 4.3).

Macrolide antibiotics (e.g. erythromycin)
No interaction studies have been carried out between nifedipine and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore the potential for an increase of nifedipine plasma

concentrations upon co-administration of macrolide antibiotics and NIF-TEN cannot be excluded
Azithromycin, although structurally related to the class of macrolide antibiotics is void of CYP3A4 inhibition.

Anti-HIV protease inhibitors (e.g., ritonavir)
A clinical study investigating the potential of a drug interaction between nifedipine and certain anti-HIV protease inhibitors has not yet been performed. Drugs of this class are known to inhibit the cytochrome P450 3A4 system. In addition, drugs of this class have been shown to inhibit in vitro the cytochrome P450 3A4 mediated metabolism of nifedipine. When administered together with NIF-TEN, a substantial increase in plasma concentrations of nifedipine due to a decreased first pass metabolism and a decreased elimination cannot be excluded.

Azole anti-mycotics (e.g., ketoconazole)
A formal interaction study investigating the potential of a drug interaction between nifedipine and certain azole anti-mycotics has not yet been performed. Drugs of this class are known to inhibit the cytochrome P450 3A4 system. When administered orally together with NIF-TEN, a substantial increase in systemic bioavailability of nifedipine due to a decreased first pass metabolism cannot be excluded.

Fluoxetine
A clinical study investigating the potential of a drug interaction between nifedipine and fluoxetine has not yet been performed. Fluoxetine has been shown to inhibit in vitro the cytochrome P450 3A4 mediated metabolism of nifedipine. Therefore an increase of nifedipine plasma concentrations upon co-administration of fluoxetine and NIF-TEN cannot be excluded.

Nefazodone
A clinical study investigating the potential of a drug interaction between nifedipine and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore an increase of nifedipine plasma concentrations upon co-administration of nefazodone and NIF-TEN cannot be excluded.

Quinupristin / Dalfopristin
Simultaneous administration of quinupristin / dalfopristin and NIF-TEN may lead to increased plasma concentrations of nifedipine.

Valproic acid
No formal studies have been performed to investigate the potential interaction between nifedipine and valproic acid. As valproic acid has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, an increase in nifedipine plasma concentrations and hence an increase in efficacy cannot be excluded upon co-administration of valproic acid and NIF-TEN.

Cimetidine

Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the antihypertensive effect of NIF-TEN.

Further studies

Cisapride

Simultaneous administration of cisapride and NIF-TEN may lead to increased plasma concentrations of nifedipine.

Cytochrome P450 3A4 system-inducing anti-epileptic drugs, such as phenytoin, carbamazepine and phenobarbitone.

Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of nifedipine is reduced and thus its efficacy weakened. When phenytoin and NIF-TEN are concomitantly administered, the clinical response to NIF-TEN should be monitored and, if necessary, an increase of the NIF-TEN dose considered. If the dose of NIF-TEN is increased during co-administration of both drugs, a reduction of the NIF-TEN dose should be considered when the treatment with phenytoin is discontinued.

No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazepine or phenobarbitone. As both drugs have been shown to reduce the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme induction, a decrease in nifedipine plasma concentrations and hence a decrease in efficacy is possible following co-administration of carbamazepine or phenobarbital with NIF-TEN.

Effects of NIF-TEN on other drugs

Blood pressure lowering drugs

NIF-TEN may increase the blood pressure lowering and heart rate modulating effects of concomitant applied antihypertensives, such as:

- diuretics,
- beta-blockers,
- ACE-inhibitors,
- Angiotensin 1 (AT1) receptor-antagonists,
- other calcium antagonists,
- α-adrenergic blocking agents,
- PDE5 inhibitors,
- anti-sympathomimetics

Quinidine

When nifedipine and quinidine have been administered simultaneously, lowered quinidine or, after discontinuation of nifedipine, distinct increase in plasma concentrations of quinidine have been observed in individual cases. For this reason, when NIF-TEN is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and, if necessary, adjustment of the quinidine dose are recommended. Some authors reported increased plasma concentrations of nifedipine upon co-administration of nifedipine and quinidine, while others did not observe an alteration in the pharmacokinetics of nifedipine.

Therefore, the blood pressure should be carefully monitored, if quinidine is added to an existing therapy with NIF-TEN if necessary, the dose of NIF-TEN should be decreased.

Digoxin
The simultaneous administration of NIF-TEN and digoxin may lead to reduced digoxin clearance and hence an increase in plasma concentrations of digoxin. The patient should therefore be checked for symptoms of digoxin overdosage as a precaution and, if necessary, the glycoside dose should be reduced taking account of the plasma concentration of digoxin.

Tacrolimus
Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. Data recently published indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of tacrolimus and NIF-TEN, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Drug-food interactions
Grapefruit juice
NIF-TEN should not be taken with grapefruit juice because its metabolism may be inhibited. Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of NIF-TEN together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect may be increased. After regular intake of grapefruit juice this effect may last for at least 3 days after the last ingestion of grapefruit juice.

Concomitant intake of grapefruit juice with nifedipine inhibits the oxidative metabolism of nifedipine, resulting in increased AUC and C_{max} by 103% (SD 73, Range 48 to 265%) and 94% (SD 83, Range 23 to 259%) respectively. This may result in increased reduction in blood pressure.

Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking NIF-TEN.

Other forms of interaction
Nifedipine may cause falsely increased spectrophotometric values of urinary vanillylmandellic acid. However, measurement with HPLC is unaffected.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding
NIF-TEN is contraindicated in women capable of childbearing or during pregnancy or during breast-feeding (see section 4.3).

Fertility
In-vitro fertilisation

In single cases of in vitro fertilisation calcium antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by in vitro fertilization, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

4.7 Effects on ability to drive and use machines

NIF-TEN 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

Tabulated list of adverse reactions

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); Not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable event
Blood and lymphatic system disorders	Rare	Thrombocytopenia*
	Not known	Agranulocytosis**, Leucopenia**, Purpura
Immune system disorders	Uncommon	Allergic reaction**, Allergic oedema (including larynx oedema)**
	Not known	Anaphylactic/anaphylactoid reaction**
Metabolism and nutrition disorders	Not known	Hyperglycaemia**
Psychiatric disorders	Uncommon	Sleep disturbances of the type noted with other beta-blockers*, Anxiety reactions**, Sleep disorders**
	Rare	Mood changes (including depression)*, Nightmares*, Confusion*, Psychoses and hallucinations*
Nervous system disorders	Common	Headache**
	Uncommon	Vertigo**, Migraine**, Dizziness**, Tremor**, Syncope**
	Rare	Dizziness*, Headache*, Paraesthesia*, Par-/dysaestesia**
	Not known	Hypoaesthesia**, Somnolence** , Dizziness, Headache
Eye disorders	Uncommon	Visual disturbances**
	Rare	Dry eyes*, Visual disturbances*

	Not known	Eye pain**
Cardiac disorders	Common	Bradycardia*
	Uncommon	Tachycardia**, Palpitations**
	Rare	Heart failure deterioration*, Precipitation of heart block*
	Not known	Chest pain (angina pectoris)**, Flushing, Oedema
Vascular disorders	Common	Cold extremities*, Vasodilation**
	Uncommon	Hypotension**
	Rare	Postural hypotension which may be associated with syncope*, Intermittent claudication may be increased if already present in susceptible patients to Raynaud's phenomenon*
Respiratory, thoracic and mediastinal disorders	Uncommon	Nosebleed**, Nasal congestion**
	Rare	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints*
	Not known	Dyspnoea**
Gastrointestinal disorders	Common	Gastrointestinal disturbances*, Constipation**
	Uncommon	Gastrointestinal and abdominal pain**, Nausea**, Dyspepsia**, Flatulence**, Dry mouth**
	Rare	Gingival hyperplasia**, Dry mouth*,
	Not known	Vomiting**, Gastro-oesophageal sphincter insufficiency**, Constipation*, Gastrointestinal disturbance
Hepatobiliary disorders	Rare	Hepatic toxicity including hepatitis and intrahepatic cholestasis*
	Uncommon	Transient increases in liver enzymes**
	Not known	Jaundice**
Skin and subcutaneous tissue disorders	Uncommon	Angioedema**, Erythema**
	Rare	Alopecia*, Psoriasiform skin reaction*, Exacerbation of psoriasis*, Skin rashes*, Pruritus**, Urticaria**, Rash**
	Not known	Toxic epidermal necrosis**, Photosensitivity allergic reaction**, Palpable purpura**, Exfoliative dermatitis**
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps**, Joint swelling**
	Not known	Arthralgia**, Myalgia**, Lupus-like syndrome
Renal and urinary disorders	Uncommon	Polyuria**, Dysuria**
Reproductive system and breast disorders	Uncommon	Erectile dysfunction**
	Rare	Impotence*

	Not known	Impotence
General disorders and administration site conditions	Common	Fatigue*, Feeling unwell**, Oedema**
	Uncommon	Unspecific pains**, Chills**
Investigations	Uncommon	Elevations of transaminase levels*
	Very rare	An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear*

** Frequency reported for the mono component atenolol*
*** Frequency reported for the mono component nifedipine*

Discontinuance of NIF-TEN 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. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Toxicity
The toxicity of both components is potentiated by the other.

The toxicity of nifedipine varies between individuals. The risk for severe effects in the presence of simultaneous beta-blocker overdosing should be noted, though. Atenolol has in doses of 300-350 mg been associated with mild intoxication in adults, while 500 mg, in a 15 year old, resulted in moderate to severe intoxication.

Symptoms
Due to the properties of being a modified release formulation with long effect duration, the symptoms from nifedipine-atenolol intoxication may emerge 12-18 hours after intake and severe effects can appear after several days.

Circulatory effects are the main risks from

Heart failure including pulmonary oedema and shock, brady as well as tachyarrhythmias (including both asystole and ventricular fibrillation), cardiac conduction disturbances such as AV-dissociations and AV-blocks, low blood pressure.

Neurologic effects
Depressed consciousness, Seizures, Coma, Headache, Flush with hypothermia.

Metabolic and respiratory effects have been observed
Bronchospasm, Dyspnoea with non-cardiac pulmonary oedema, ARDS, acidosis, hypokalaemia, hyperglycaemia, hypocalcaemia, impaired renal function, rhabdomyolysis, nausea and emesis.

Management
Gastric lavage which can be justified also late after intake (clumping of modified release tablets occur: consider gastroscopy). Charcoal can be considered. Atropine should be given prior to lavage to counteract the risks from potential vagal stimulation. Use of haemodialysis and plasmapheresis (nifedipine) may be considered.

The patient's condition, including cardiac rhythm, should be monitored. Mechanical ventilation should be considered on wide indications.

Acid base and electrolyte imbalances are to be corrected.

Bradyarrhythmias can be treated with atropine (repeated doses may become necessary). Pacemaker should be employed early in cases with more severe bradyarrhythmias. Cases with circulatory failure should have their haemodynamics monitored to guide therapy and fluid substitution.

Vasoconstricting therapy may commence with noradrenaline or phenylephrine. Calcium glubonate combined with metaraminol can be given as repeated injections or infusion. Cases not responding to the above measures can be given glucagon, potentially followed by a phosphodiesterase inhibitor (milrinone or amrinone) or dobutamine. Insulin-glucose infusion can also be used. It can be expected that dose escalation of sympathomimetic drugs will be necessary to overcome the β blocking effects.

Bronchospasm can usually be reversed by bronchodilators.

Protracted – over several hours – resuscitation can be justified.

Seizures can be treated with benzodiazepines.

Symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents and other antihypertensives, ATC code: C07 FB.

Atenolol is a beta-blocker which is $beta_1$-selective (i.e. acts preferentially on $beta_1$- 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, atenolol has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure).

As with other beta-blockers, its mode of action 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.

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

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.

Nifedipine is a calcium channel blocker. It is a powerful coronary and peripheral vasodilator which increases myocardial oxygen supply and reduces blood pressure (afterload) and peripheral resistance.

Concomitant use of atenolol, therefore, ameliorates the reflex sympathetic response to nifedipine monotherapy by blocking the rise in heart rate, while atenolol's tendency to increase peripheral resistance is balanced by the vasodilation and increased sympathetic tone induced by the calcium antagonist.

Consequently, greater antihypertensive or antianginal efficacy is achieved by the concomitant use of nifedipine and atenolol than either drug alone. This beneficial pharmacodynamic interaction also results in fewer side effects when lower dosages of the two drugs are used in combination.

5.2 Pharmacokinetic properties

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. 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. 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%).

Absorption of nifedipine following oral dosing is complete with peak plasma concentrations occurring about every 3 hours after dosing. Nifedipine is >90% plasma protein bound. There is significant hepatic metabolism of nifedipine. The plasma half-life is between 6 and 11 hours for the sustained formulation of nifedipine.

Co-administration of atenolol and nifedipine has little effect on the pharmacokinetics of either. In the elderly, the systemic bioavailability and elimination half-life of both components are increased.

NIF-TEN is effective when given either once or twice daily. This simplicity of dosing facilitates compliance by its acceptability to patients.

5.3 Preclinical safety data

Atenolol and nifedipine are drugs on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Granule
Maize starch
Heavy magnesium carbonate
Sodium laurilsulfate
Gelatine
Magnesium stearate

Tablet core
Microcrystalline cellulose
Maize starch
Lactose monohydrate
Polysorbate 80
Magnesium stearate

Tablet coating
Hypromellose
Macrogol 4000
Titanium dioxide (E171)

Iron oxide red (E172)

Capsule shell
Iron oxide red (E172)
Titanium dioxide (E171)
Gelatine

Printing ink
Ink 1
Titanium dioxide (E171)
Shellac

Ink 2
Titanium dioxide (E171)
Shellac
Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

4 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package. Keep the container in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

PVC/PVDC/AL blister strips (box of 28 capsules).

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85

Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

PA 1019/013/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th September 1988
Date of latest renewal: 31 July 2009

10. DATE OF REVISION OF THE TEXT

07th Jan 2019