ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Imprida 5 mg/80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg of amlodipine (as amlodipine besylate) and 80 mg of valsartan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Dark yellow, round film-coated tablet with bevelled edges, imprinted with “NVR” on one side and “NV” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Imprida is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

4.2 Posology and method of administration

Posology
The recommended dose of Imprida is one tablet per day.

Imprida 5 mg/80 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg or valsartan 80 mg alone.

Imprida can be used with or without food.

Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

For convenience, patients receiving valsartan and amlodipine from separate tablets/capsules may be switched to Imprida containing the same component doses.

Renal impairment
There are no available clinical data in severely renally impaired patients. No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Hepatic impairment
Imprida is contraindicated in patients with severe hepatic impairment (see section 4.3).

Caution should be exercised when administering Imprida to patients with hepatic impairment or biliary obstructive disorders (see section 4.4). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan. Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients (see section 4.1) with hepatic impairment to amlodipine or Imprida, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Elderly (age 65 years or over)
In elderly patients, caution is required when increasing the dosage. When switching eligible elderly hypertensive patients (see section 4.1) to amlodipine or Imprida, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Paediatric population
The safety and efficacy of Imprida in children aged below 18 years have not been established. No data are available.

Method of administration
Oral use.
It is recommended to take Imprida with some water.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Concomitant use of Imprida with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Sodium- and/or volume-depleted patients
Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Imprida in placebo-controlled studies. In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of Imprida or close medical supervision at the start of treatment is recommended.

If hypotension occurs with Imprida, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Hyperkalaemia
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.

Renal artery stenosis
Imprida should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Kidney transplantation
To date there is no experience of the safe use of Imprida in patients who have had a recent kidney transplantation.

Hepatic impairment
Valsartan is mostly eliminated unchanged via the bile. The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Particular caution should be exercised when administering Imprida to patients with mild to moderate hepatic impairment or biliary obstructive disorders.

In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Renal impairment
No dosage adjustment of Imprida is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m^2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.

Angioedema
Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue, has been reported in patients treated with valsartan. Some of these patients previously experienced angioedema with other medicinal products, including ACE - inhibitors. Imprida should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Heart failure/post-myocardial infarction
As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Aortic and mitral valve stenosis
As with all other vasodilators, special caution is indicated in patients suffering from mitral stenosis or significant aortic stenosis that is not high grade.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.

Imprida has not been studied in any patient population other than hypertension.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions common to the combination
No drug-drug interaction studies have been performed with Imprida and other medicinal products.

To be taken into account with concomitant use
Other antihypertensive agents
Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

Interactions linked to amlodipine
Concomitant use not recommended
Grapefruit or grapefruit juice
Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

Caution required with concomitant use
CYP3A4 inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum)
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Simvastatin
Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

Dantrolene (infusion)
In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

To be taken into account with concomitant use
Others
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

Interactions linked to valsartan
Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, including valsartan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diurectic is also used, the risk of lithium toxicity may presumably be increased further with Imprida.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use
Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)
The results of an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren
Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Others
In monotherapy with valsartan, no interactions of clinical significance have been found with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

4.6 Fertility, pregnancy and lactation

Pregnancy

Amlodipine

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Valsartan

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Breast-feeding

No information is available regarding the use of Imprida during breast-feeding, therefore Imprida is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

There are no clinical studies on fertility with Imprida.

Valsartan

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Amlodipine

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients taking Imprida and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.

Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

Summary of the safety profile

The safety of Imprida has been evaluated in five controlled clinical studies with 5,175 patients, 2,613 of whom received valsartan in combination with amlodipine. The following adverse reactions were found to be the most frequently occurring or the most significant or severe: nasopharyngitis, influenza, hypersensitivity, headache, syncope, orthostatic hypotension, oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia and hot flush.

Tabulated list of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: 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).

MedDRA System organ class	**Adverse reactions**	**Frequency**		
		Imprida	**Amlodipine**	**Valsartan**
Infections and infestations	Nasopharyngitis	Common	--	--
	Influenza	Common	--	--
Blood and lymphatic system disorders	Haemoglobin and haematocrit decreased	--	--	Not known
	Leukopenia	--	Very rare	--
	Neutropenia	--	--	Not known
	Thrombocytopenia, sometimes with purpura	--	Very rare	Not known
Immune system disorders	Hypersensitivity	Rare	Very rare	Not known
Metabolism and nutrition disorders	Anorexia	Uncommon	--	--
	Hypercalcaemia	Uncommon	--	--
	Hyperglycaemia	--	Very rare	--
	Hyperlipidaemia	Uncommon	--	--
	Hyperuricaemia	Uncommon	--	--
	Hypokalaemia	Common	--	--
	Hyponatraemia	Uncommon	--	--
Psychiatric disorders	Depression	--	Uncommon	--
	Anxiety	Rare	--	--
	Insomnia/sleep disorders	--	Uncommon	--
	Mood swings	--	Uncommon	--
	Confusion	--	Rare	--

Nervous system disorders	Coordination abnormal	Uncommon	--	--
	Dizziness	Uncommon	Common	--
	Dizziness postural	Uncommon	--	--
	Dysgeusia	--	Uncommon	--
	Extrapyramidal syndrome	--	Not known	--
	Headache	Common	Common	--
	Hypertonia	--	Very rare	--
	Paraesthesia	Uncommon	Uncommon	--
	Peripheral neuropathy, neuropathy	--	Very rare	--
	Somnolence	Uncommon	Common	--
	Syncope	--	Uncommon	--
	Tremor	--	Uncommon	--
	Hypoesthesia	--	Uncommon	--
Eye disorders	Visual disturbance	Rare	Uncommon	--
	Visual impairment	Uncommon	Uncommon	--
Ear and labyrinth disorders	Tinnitus	Rare	Uncommon	--
	Vertigo	Uncommon	--	Uncommon
Cardiac disorders	Palpitations	Uncommon	Common	--
	Syncope	Rare	--	--
	Tachycardia	Uncommon	--	--
	Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	--	Very rare	--
	Myocardial infarction	--	Very rare	--
Vascular disorders	Flushing	--	Common	--
	Hypotension	Rare	Uncommon	--
	Orthostatic hypotension	Uncommon	--	--
	Vasculitis	--	Very rare	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Very rare	Uncommon
	Dyspnoea	--	Uncommon	--
	Pharyngolaryngeal pain	Uncommon	--	--
	Rhinitis	--	Uncommon	--
Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Uncommon	Common	Uncommon
	Change of bowel habit	--	Uncommon	--
	Constipation	Uncommon	--	--
	Diarrhoea	Uncommon	Uncommon	--
	Dry mouth	Uncommon	Uncommon	--
	Dyspepsia	--	Uncommon	--
	Gastritis	--	Very rare	--
	Gingival hyperplasia	--	Very rare	--
	Nausea	Uncommon	Common	--
	Pancreatitis	--	Very rare	--
	Vomiting	--	Uncommon	--

Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	--	Very rare*	Not known
	Hepatitis	--	Very rare	--
	Intrahepatic cholestasis, jaundice	--	Very rare	--
Skin and subcutaneous tissue disorders	Alopecia	--	Uncommon	--
	Angioedema	--	Very rare	Not known
	Dermatitis bullous	--	--	Not known
	Erythema	Uncommon	--	--
	Erythema multiforme	--	Very rare	--
	Exanthema	Rare	Uncommon	--
	Hyperhidrosis	Rare	Uncommon	--
	Photosensitivity reaction	--	Uncommon	--
	Pruritus	Rare	Uncommon	Not known
	Purpura	--	Uncommon	--
	Rash	Uncommon	Uncommon	Not known
	Skin discolouration	--	Uncommon	--
	Urticaria and other forms of rash	--	Very rare	--
	Exfoliative dermatitis	--	Very rare	--
	Stevens-Johnson syndrome	--	Very rare	--
	Quincke oedema	--	Very rare	--
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	Uncommon	--
	Back pain	Uncommon	Uncommon	--
	Joint swelling	Uncommon	--	--
	Muscle spasm	Rare	Uncommon	--
	Myalgia	--	Uncommon	Not known
	Ankle swelling	--	Common	--
	Sensation of heaviness	Rare	--	--
Renal and urinary disorders	Blood creatinine increased	--	--	Not known
	Micturition disorder	--	Uncommon	--
	Nocturia	--	Uncommon	--
	Pollakiuria	Rare	Uncommon	--
	Polyuria	Rare	--	--
	Renal failure and impairment	--	--	Not known
Reproductive system and breast disorders	Impotence	--	Uncommon	--
	Erectile dysfunction	Rare	--	--
	Gynaecomastia	--	Uncommon	--

General disorders and administration site conditions	Asthenia	Common	Uncommon	--
	Discomfort, malaise	--	Uncommon	--
	Fatigue	Common	Common	Uncommon
	Facial oedema	Common	--	--
	Flushing, hot flush	Common	--	--
	Non cardiac chest pain	--	Uncommon	--
	Oedema	Common	Common	--
	Oedema peripheral	Common	--	--
	Pain	--	Uncommon	--
	Pitting oedema	Common	--	--
Investigations	Blood potassium increased	--	--	Not known
	Weight increase	--	Uncommon	--
	Weight decrease	--	Uncommon	--

* Mostly consistent with cholestasis

Additional information on the combination
Peripheral oedema, a recognised side effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone. In double-blind, controlled clinical trials, the incidence of peripheral oedema by dose was as follows:

% of patients who experienced peripheral oedema		**Valsartan (mg)**				
		0	40	80	160	320
Amlodipine (mg)	0	3.0	5.5	2.4	1.6	0.9
	2.5	8.0	2.3	5.4	2.4	3.9
	5	3.1	4.8	2.3	2.1	2.4
	10	10.3	NA	NA	9.0	9.5

The mean incidence of peripheral oedema evenly weighted across all doses was 5.1% with the amlodipine/valsartan combination.

Additional information on the individual components
Adverse reactions previously reported with one of the individual components (amlodipine or valsartan) may be potential adverse reactions with Imprida as well, even if not observed in clinical trials or during the post-marketing period.

Amlodipine

Common Somnolence, dizziness, palpitations, abdominal pain, nausea, ankle swelling.

Uncommon Insomnia, mood changes (including anxiety), depression, tremor, dysgeusia, syncope, hypoesthesia, visual disturbance (including diplopia), tinnitus, hypotension, dyspnoea, rhinitis, vomiting, dyspepsia, alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, exanthema, myalgia, muscle cramps, pain, micturition disorder, increased urinary frequency, impotence, gynaecomastia, chest pain, malaise, weight increase, weight decrease.

Rare Confusion.

Very rare	Leukocytopenia, thrombocytopenia, allergic reactions, hyperglycaemia, hypertonia, peripheral neuropathy, myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), vasculitis, pancreatitis, gastritis, gingival hyperplasia, hepatitis, jaundice, hepatic enzymes increased*, angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity.

* mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

Valsartan

Not known	Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

There is no experience of overdose with Imprida. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to Imprida overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists, combinations; angiotensin II antagonists and calcium channel blockers, ATC code: C09DB01

Imprida combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine/Valsartan

The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Placebo-controlled trials

Over 1,400 hypertensive patients received Imprida once daily in two placebo-controlled trials. Adults with mild to moderate uncomplicated essential hypertension (mean sitting diastolic blood pressure ≥95 and <110 mmHg) were enrolled. Patients with high cardiovascular risks – heart failure, type I and poorly controlled type II diabetes and history of myocardial infarction or stroke within one year – were excluded.

Active-controlled trials in patients who were non-responders to monotherapy

A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <90 mmHg at the end of the trial) in patients not adequately controlled on valsartan 160 mg in 75% of patients treated with amlodipine/valsartan 10 mg/160 mg and 62% of patients treated with amlodipine/valsartan 5 mg/160 mg, compared to 53% of patients remaining on valsartan 160 mg. The addition of amlodipine 10 mg and 5 mg produced an additional reduction in systolic/diastolic blood pressure of 6.0/4.8 mmHg and 3.9/2.9 mmHg, respectively, compared to patients who remained on valsartan 160 mg only.

A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <90 mmHg at the end of the trial) in patients not adequately controlled on amlodipine 10 mg in 78% of patients treated with amlodipine/valsartan 10 mg/160 mg, compared to 67% of patients remaining on amlodipine 10 mg. The addition of valsartan 160 mg produced an additional reduction in systolic/diastolic blood pressure of 2.9/2.1 mmHg compared to patients who remained on amlodipine 10 mg only.

Imprida was also studied in an active-controlled study of 130 hypertensive patients with mean sitting diastolic blood pressure ≥110 mmHg and <120 mmHg. In this study (baseline blood pressure 171/113 mmHg), an Imprida regimen of 5 mg/160 mg titrated to 10 mg/160 mg reduced sitting blood pressure by 36/29 mmHg as compared to 32/28 mmHg with a regimen of lisinopril/hydrochlorothiazide 10 mg/12.5 mg titrated to 20 mg/12.5 mg.

In two long-term follow-up studies the effect of Imprida was maintained for over one year. Abrupt withdrawal of Imprida has not been associated with a rapid increase in blood pressure.

Age, gender, race or body mass index (≥30 kg/m^2, <30 kg/m^2) did not influence the response to Imprida.

Imprida has not been studied in any patient population other than hypertension. Valsartan has been studied in patients with post myocardial infarction and heart failure. Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Amlodipine

The amlodipine component of Imprida inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Use in patients with hypertension

A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% versus 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Valsartan

Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT_1, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked receptor subtype AT_2, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000-fold) greater affinity for the AT_1 receptor than for the AT_2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($p < 0.05$) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9%, respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced coughing, compared to 68.5% of those treated with an ACE inhibitor ($p < 0.05$). Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Administration of valsartan to patients with hypertension results in a drop in blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak drop in blood pressure is achieved within 4–6 hours. The antihypertensive effect persists over 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2–4 weeks and is sustained during long-term therapy. Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Other: dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Two large randomised, controlled trials (ONTARGET [ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial] and VA NEPHRON-D [The Veterans Affairs Nephropathy in Diabetes]) have examined the use of the combination of an ACE inhibitor with an ARB.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and ARBs.

ACE inhibitors and ARBs should therefore not be used concomitantly in patients with diabetic nephropathy (see section 4.4).

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an ARB in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Linearity
Amlodipine and valsartan exhibit linear pharmacokinetics.

Amlodipine/Valsartan
Following oral administration of Imprida, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6–8 hours, respectively. The rate and extent of absorption of Imprida are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets.

Amlodipine
Absorption: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution: Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

Biotransformation: Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.

Elimination: Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Valsartan
Absorption: Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution: The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Biotransformation: Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination: Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Special populations
Paediatric population (age below 18 years)
No pharmacokinetic data are available in the paediatric population.

Elderly (age 65 years or over)
Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young therefore caution is required when increasing the dosage.

Renal impairment
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan.

Hepatic impairment
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC. On average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Caution should be exercised in patients with liver disease (see section 4.2).

5.3 Preclinical safety data

Amlodipine/Valsartan
Adverse reactions observed in animal studies with possible clinical relevance were as follows: Histopathological signs of inflammation of the glandular stomach was seen in male rats at an exposure of about 1.9 (valsartan) and 2.6 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. At higher exposures, there were ulceration and erosion of the stomach mucosa in both females and males. Similar changes were also seen in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

An increased incidence and severity of renal tubular basophilia/hyalinisation, dilation and casts, as well as interstitial lymphocyte inflammation and arteriolar medial hypertrophy were found at an exposure of 8–13 (valsartan) and 7–8 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Similar changes were found in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at exposures of about 12 (valsartan) and 10 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Dilated ureters were also found in the valsartan alone group (exposure 12 times the clinical dose of 160 mg valsartan). There were only modest signs of maternal toxicity (moderate reduction of body weight) in this study. The no-observed-effect-level for developmental effects was observed at 3- (valsartan) and 4- (amlodipine) fold the clinical exposure (based on AUC).

For the single compounds there was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Amlodipine
Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50 kg

Valsartan
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised blood urea nitrogen, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen and creatinine.

Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Crospovidone Type A
Silica, colloidal anhydrous
Magnesium stearate

Coating:
Hypromellose
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Macrogol 4000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 7, 14, 28, 30, 56, 90, 98 or 280 film-coated tablets and multipacks containing 280 (4x70 or 20x14) film-coated tablets.

PVC/PVDC perforated unit dose blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 56, 98 or 280 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/001
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EU/1/06/373/007
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Imprida 5 mg/160 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg of amlodipine (as amlodipine besylate) and 160 mg of valsartan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Dark yellow, oval film-coated tablet, imprinted with “NVR” on one side and “ECE” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Imprida is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

4.2 Posology and method of administration

Posology
The recommended dose of Imprida is one tablet per day.

Imprida 5 mg/160 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg or valsartan 160 mg alone.

Imprida can be used with or without food.

Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

For convenience, patients receiving valsartan and amlodipine from separate tablets/capsules may be switched to Imprida containing the same component doses.

Renal impairment
There are no available clinical data in severely renally impaired patients. No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Hepatic impairment
Imprida is contraindicated in patients with severe hepatic impairment (see section 4.3).

Caution should be exercised when administering Imprida to patients with hepatic impairment or biliary obstructive disorders (see section 4.4). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan. Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients (see section 4.1) with hepatic impairment to amlodipine or Imprida, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Elderly (age 65 years or over)
In elderly patients, caution is required when increasing the dosage. When switching eligible elderly hypertensive patients (see section 4.1) to amlodipine or Imprida, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Paediatric population
The safety and efficacy of Imprida in children aged below 18 years have not been established. No data are available.

Method of administration
Oral use.
It is recommended to take Imprida with some water.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Concomitant use of Imprida with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Sodium- and/or volume-depleted patients
Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Imprida in placebo-controlled studies. In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of Imprida or close medical supervision at the start of treatment is recommended.

If hypotension occurs with Imprida, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Hyperkalaemia
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.

Renal artery stenosis
Imprida should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Kidney transplantation
To date there is no experience of the safe use of Imprida in patients who have had a recent kidney transplantation.

Hepatic impairment
Valsartan is mostly eliminated unchanged via the bile. The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Particular caution should be exercised when administering Imprida to patients with mild to moderate hepatic impairment or biliary obstructive disorders.

In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Renal impairment
No dosage adjustment of Imprida is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m^2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.

Angioedema
Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue, has been reported in patients treated with valsartan. Some of these patients previously experienced angioedema with other medicinal products, including ACE inhibitors. Imprida should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Heart failure/post-myocardial infarction
As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Aortic and mitral valve stenosis
As with all other vasodilators, special caution is indicated in patients suffering from mitral stenosis or significant aortic stenosis that is not high grade.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.

Imprida has not been studied in any patient population other than hypertension.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions common to the combination
No drug-drug interaction studies have been performed with Imprida and other medicinal products.

To be taken into account with concomitant use
Other antihypertensive agents
Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

Interactions linked to amlodipine
Concomitant use not recommended
Grapefruit or grapefruit juice
Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

Caution required with concomitant use
CYP3A4 inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum)
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Simvastatin
Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

Dantrolene (infusion)
In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

To be taken into account with concomitant use
Others
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

Interactions linked to valsartan
Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, including valsartan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diurectic is also used, the risk of lithium toxicity may presumably be increased further with Imprida.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use
Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)
The results of an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren
Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Others
In monotherapy with valsartan, no interactions of clinical significance have been found with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

4.6 Fertility, pregnancy and lactation

Pregnancy

Amlodipine

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Valsartan

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Breast-feeding

No information is available regarding the use of Imprida during breast-feeding, therefore Imprida is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

There are no clinical studies on fertility with Imprida.

Valsartan

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Amlodipine

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients taking Imprida and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.

Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

Summary of the safety profile

The safety of Imprida has been evaluated in five controlled clinical studies with 5,175 patients, 2,613 of whom received valsartan in combination with amlodipine. The following adverse reactions were found to be the most frequently occurring or the most significant or severe: nasopharyngitis, influenza, hypersensitivity, headache, syncope, orthostatic hypotension, oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia and hot flush.

Tabulated list of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: 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).

MedDRA System organ class	**Adverse reactions**	**Frequency**		
		Imprida	**Amlodipine**	**Valsartan**
Infections and infestations	Nasopharyngitis	Common	--	--
	Influenza	Common	--	--
Blood and lymphatic system disorders	Haemoglobin and haematocrit decreased	--	--	Not known
	Leukopenia	--	Very rare	--
	Neutropenia	--	--	Not known
	Thrombocytopenia, sometimes with purpura	--	Very rare	Not known
Immune system disorders	Hypersensitivity	Rare	Very rare	Not known
Metabolism and nutrition disorders	Anorexia	Uncommon	--	--
	Hypercalcaemia	Uncommon	--	--
	Hyperglycaemia	--	Very rare	--
	Hyperlipidaemia	Uncommon	--	--
	Hyperuricaemia	Uncommon	--	--
	Hypokalaemia	Common	--	--
	Hyponatraemia	Uncommon	--	--
Psychiatric disorders	Depression	--	Uncommon	--
	Anxiety	Rare	--	--
	Insomnia/sleep disorders	--	Uncommon	--
	Mood swings	--	Uncommon	--
	Confusion	--	Rare	--

Nervous system disorders	Coordination abnormal	Uncommon	--	--
	Dizziness	Uncommon	Common	--
	Dizziness postural	Uncommon	--	--
	Dysgeusia	--	Uncommon	--
	Extrapyramidal syndrome	--	Not known	--
	Headache	Common	Common	--
	Hypertonia	--	Very rare	--
	Paraesthesia	Uncommon	Uncommon	--
	Peripheral neuropathy, neuropathy	--	Very rare	--
	Somnolence	Uncommon	Common	--
	Syncope	--	Uncommon	--
	Tremor	--	Uncommon	--
	Hypoesthesia	--	Uncommon	--
Eye disorders	Visual disturbance	Rare	Uncommon	--
	Visual impairment	Uncommon	Uncommon	--
Ear and labyrinth disorders	Tinnitus	Rare	Uncommon	--
	Vertigo	Uncommon	--	Uncommon
Cardiac disorders	Palpitations	Uncommon	Common	--
	Syncope	Rare	--	--
	Tachycardia	Uncommon	--	--
	Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	--	Very rare	--
	Myocardial infarction	--	Very rare	--
Vascular disorders	Flushing	--	Common	--
	Hypotension	Rare	Uncommon	--
	Orthostatic hypotension	Uncommon	--	--
	Vasculitis	--	Very rare	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Very rare	Uncommon
	Dyspnoea	--	Uncommon	--
	Pharyngolaryngeal pain	Uncommon	--	--
	Rhinitis	--	Uncommon	--
Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Uncommon	Common	Uncommon
	Change of bowel habit	--	Uncommon	--
	Constipation	Uncommon	--	--
	Diarrhoea	Uncommon	Uncommon	--
	Dry mouth	Uncommon	Uncommon	--
	Dyspepsia	--	Uncommon	--
	Gastritis	--	Very rare	--
	Gingival hyperplasia	--	Very rare	--
	Nausea	Uncommon	Common	--
	Pancreatitis	--	Very rare	--
	Vomiting	--	Uncommon	--
Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	--	Very rare*	Not known
	Hepatitis	--	Very rare	--
	Intrahepatic cholestasis, jaundice	--	Very rare	--

Skin and subcutaneous tissue disorders	Alopecia	--	Uncommon	--
	Angioedema	--	Very rare	Not known
	Dermatitis bullous	--	--	Not known
	Erythema	Uncommon	--	--
	Erythema multiforme	--	Very rare	--
	Exanthema	Rare	Uncommon	--
	Hyperhidrosis	Rare	Uncommon	--
	Photosensitivity reaction	--	Uncommon	--
	Pruritus	Rare	Uncommon	Not known
	Purpura	--	Uncommon	--
	Rash	Uncommon	Uncommon	Not known
	Skin discolouration	--	Uncommon	--
	Urticaria and other forms of rash	--	Very rare	--
	Exfoliative dermatitis	--	Very rare	--
	Stevens-Johnson syndrome	--	Very rare	--
	Quincke oedema	--	Very rare	--
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	Uncommon	--
	Back pain	Uncommon	Uncommon	--
	Joint swelling	Uncommon	--	--
	Muscle spasm	Rare	Uncommon	--
	Myalgia	--	Uncommon	Not known
	Ankle swelling	--	Common	--
	Sensation of heaviness	Rare	--	--
Renal and urinary disorders	Blood creatinine increased	--	--	Not known
	Micturition disorder	--	Uncommon	--
	Nocturia	--	Uncommon	--
	Pollakiuria	Rare	Uncommon	--
	Polyuria	Rare	--	--
	Renal failure and impairment	--	--	Not known
Reproductive system and breast disorders	Impotence	--	Uncommon	--
	Erectile dysfunction	Rare	--	--
	Gynaecomastia	--	Uncommon	--
General disorders and administration site conditions	Asthenia	Common	Uncommon	--
	Discomfort, malaise	--	Uncommon	--
	Fatigue	Common	Common	Uncommon
	Facial oedema	Common	--	--
	Flushing, hot flush	Common	--	--
	Non cardiac chest pain	--	Uncommon	--
	Oedema	Common	Common	--
	Oedema peripheral	Common	--	--
	Pain	--	Uncommon	--
	Pitting oedema	Common	--	--
Investigations	Blood potassium increased	--	--	Not known
	Weight increase	--	Uncommon	--
	Weight decrease	--	Uncommon	--

* Mostly consistent with cholestasis

Additional information on the combination
Peripheral oedema, a recognised side effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone. In double-blind, controlled clinical trials, the incidence of peripheral oedema by dose was as follows:

% of patients who experienced peripheral oedema		**Valsartan (mg)**				
		0	40	80	160	320
Amlodipine (mg)	0	3.0	5.5	2.4	1.6	0.9
	2.5	8.0	2.3	5.4	2.4	3.9
	5	3.1	4.8	2.3	2.1	2.4
	10	10.3	NA	NA	9.0	9.5

The mean incidence of peripheral oedema evenly weighted across all doses was 5.1% with the amlodipine/valsartan combination.

Additional information on the individual components
Adverse reactions previously reported with one of the individual components (amlodipine or valsartan) may be potential adverse reactions with Imprida as well, even if not observed in clinical trials or during the post-marketing period.

Amlodipine

Common	Somnolence, dizziness, palpitations, abdominal pain, nausea, ankle swelling.
Uncommon	Insomnia, mood changes (including anxiety), depression, tremor, dysgeusia, syncope, hypoesthesia, visual disturbance (including diplopia), tinnitus, hypotension, dyspnoea, rhinitis, vomiting, dyspepsia, alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, exanthema, myalgia, muscle cramps, pain, micturition disorder, increased urinary frequency, impotence, gynaecomastia, chest pain, malaise, weight increase, weight decrease.
Rare	Confusion.
Very rare	Leukocytopenia, thrombocytopenia, allergic reactions, hyperglycaemia, hypertonia, peripheral neuropathy, myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), vasculitis, pancreatitis, gastritis, gingival hyperplasia, hepatitis, jaundice, hepatic enzymes increased*, angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity.

* mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

Valsartan

Not known	Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
There is no experience of overdose with Imprida. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment
If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to Imprida overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists, combinations; angiotensin II antagonists and calcium channel blockers, ATC code: C09DB01

Imprida combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine/Valsartan
The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Placebo-controlled trials
Over 1,400 hypertensive patients received Imprida once daily in two placebo-controlled trials. Adults with mild to moderate uncomplicated essential hypertension (mean sitting diastolic blood pressure ≥95 and <110 mmHg) were enrolled. Patients with high cardiovascular risks – heart failure, type I and poorly controlled type II diabetes and history of myocardial infarction or stroke within one year – were excluded.

Active-controlled trials in patients who were non-responders to monotherapy
A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <90 mmHg at the end of the trial) in patients not adequately controlled on valsartan 160 mg in 75% of patients treated with amlodipine/valsartan 10 mg/160 mg and 62% of patients treated with amlodipine/valsartan 5 mg/160 mg, compared to 53% of patients remaining on valsartan 160 mg. The addition of amlodipine 10 mg and 5 mg produced an additional reduction in systolic/diastolic blood pressure of 6.0/4.8 mmHg and 3.9/2.9 mmHg, respectively, compared to patients who remained on valsartan 160 mg only.

A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <90 mmHg at the end of the trial) in patients not adequately controlled on amlodipine 10 mg in 78% of patients treated with amlodipine/valsartan 10 mg/160 mg, compared to 67% of patients remaining on amlodipine 10 mg. The addition of valsartan 160 mg produced an additional reduction in systolic/diastolic blood pressure of 2.9/2.1 mmHg compared to patients who remained on amlodipine 10 mg only.

Imprida was also studied in an active-controlled study of 130 hypertensive patients with mean sitting diastolic blood pressure ≥110 mmHg and <120 mmHg. In this study (baseline blood pressure 171/113 mmHg), an Imprida regimen of 5 mg/160 mg titrated to 10 mg/160 mg reduced sitting blood pressure by 36/29 mmHg as compared to 32/28 mmHg with a regimen of lisinopril/hydrochlorothiazide 10 mg/12.5 mg titrated to 20 mg/12.5 mg.

In two long-term follow-up studies the effect of Imprida was maintained for over one year. Abrupt withdrawal of Imprida has not been associated with a rapid increase in blood pressure.

Age, gender, race or body mass index (≥30 kg/m^2, <30 kg/m^2) did not influence the response to Imprida.

Imprida has not been studied in any patient population other than hypertension. Valsartan has been studied in patients with post myocardial infarction and heart failure. Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Amlodipine

The amlodipine component of Imprida inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Use in patients with hypertension
A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% versus 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Valsartan
Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT_1, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked receptor subtype AT_2, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000-fold) greater affinity for the AT_1 receptor than for the AT_2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly (p <0.05) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9%, respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced coughing, compared to 68.5% of those treated with an ACE inhibitor (p <0.05). Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Administration of valsartan to patients with hypertension results in a drop in blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak drop in blood pressure is achieved within 4–6 hours. The antihypertensive effect persists over 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2–4 weeks and is sustained during long-term therapy. Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Other: dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Two large randomised, controlled trials (ONTARGET [ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial] and VA NEPHRON-D [The Veterans Affairs Nephropathy in Diabetes]) have examined the use of the combination of an ACE inhibitor with an ARB.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and ARBs.

ACE inhibitors and ARBs should therefore not be used concomitantly in patients with diabetic nephropathy (see section 4.4).

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an ARB in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Linearity
Amlodipine and valsartan exhibit linear pharmacokinetics.

Amlodipine/Valsartan
Following oral administration of Imprida, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6–8 hours, respectively. The rate and extent of absorption of Imprida are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets.

Amlodipine
Absorption: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution: Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

Biotransformation: Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.

Elimination: Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Valsartan

Absorption: Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution: The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Biotransformation: Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination: Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Special populations

Paediatric population (age below 18 years)

No pharmacokinetic data are available in the paediatric population.

Elderly (age 65 years or over)

Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young therefore caution is required when increasing the dosage.

Renal impairment

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan.

Hepatic impairment

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC. On average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Caution should be exercised in patients with liver disease (see section 4.2).

5.3 Preclinical safety data

Amlodipine/Valsartan

Adverse reactions observed in animal studies with possible clinical relevance were as follows: Histopathological signs of inflammation of the glandular stomach was seen in male rats at an exposure of about 1.9 (valsartan) and 2.6 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. At higher exposures, there were ulceration and erosion of the stomach mucosa in both females and males. Similar changes were also seen in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

An increased incidence and severity of renal tubular basophilia/hyalinisation, dilation and casts, as well as interstitial lymphocyte inflammation and arteriolar medial hypertrophy were found at an exposure of 8–13 (valsartan) and 7–8 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Similar changes were found in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at exposures of about 12 (valsartan) and 10 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Dilated ureters were also found in the valsartan alone group (exposure 12 times the clinical dose of 160 mg valsartan). There were only modest signs of maternal toxicity (moderate reduction of body weight) in this study. The no-observed-effect-level for developmental effects was observed at 3- (valsartan) and 4- (amlodipine) fold the clinical exposure (based on AUC).

For the single compounds there was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Amlodipine

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50 kg

Valsartan

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised blood urea nitrogen, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen and creatinine.

Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Crospovidone Type A
Silica, colloidal anhydrous
Magnesium stearate

Coating:
Hypromellose
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Macrogol 4000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 7, 14, 28, 30, 56, 90, 98 or 280 film-coated tablets and multipacks containing 280 (4x70 or 20x14) film-coated tablets.

PVC/PVDC perforated unit dose blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 56, 98 or 280 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/009
EU/1/06/373/010
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EU/1/06/373/013
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EU/1/06/373/029
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EU/1/06/373/038

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Imprida 10 mg/160 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of amlodipine (as amlodipine besylate) and 160 mg of valsartan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Light yellow, oval film-coated tablet, imprinted with “NVR” on one side and “UIC” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Imprida is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

4.2 Posology and method of administration

Posology
The recommended dose of Imprida is one tablet per day.

Imprida 10 mg/160 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10 mg or valsartan 160 mg alone or with Imprida 5 mg/160 mg.

Imprida can be used with or without food.

Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

For convenience, patients receiving valsartan and amlodipine from separate tablets/capsules may be switched to Imprida containing the same component doses.

Renal impairment
There are no available clinical data in severely renally impaired patients. No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Hepatic impairment
Imprida is contraindicated in patients with severe hepatic impairment (see section 4.3).

Caution should be exercised when administering Imprida to patients with hepatic impairment or biliary obstructive disorders (see section 4.4). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan. Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients (see section 4.1) with hepatic impairment to amlodipine or Imprida, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Elderly (age 65 years or over)
In elderly patients, caution is required when increasing the dosage. When switching eligible elderly hypertensive patients (see section 4.1) to amlodipine or Imprida, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Paediatric population
The safety and efficacy of Imprida in children aged below 18 years have not been established. No data are available.

Method of administration
Oral use.
It is recommended to take Imprida with some water.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Concomitant use of Imprida with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Sodium- and/or volume-depleted patients
Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Imprida in placebo-controlled studies. In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of Imprida or close medical supervision at the start of treatment is recommended.

If hypotension occurs with Imprida, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Hyperkalaemia
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.

Renal artery stenosis
Imprida should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Kidney transplantation
To date there is no experience of the safe use of Imprida in patients who have had a recent kidney transplantation.

Hepatic impairment
Valsartan is mostly eliminated unchanged via the bile. The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Particular caution should be exercised when administering Imprida to patients with mild to moderate hepatic impairment or biliary obstructive disorders.

In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Renal impairment
No dosage adjustment of Imprida is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m^2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.

Angioedema
Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue, has been reported in patients treated with valsartan. Some of these patients previously experienced angioedema with other medicinal products, including ACE inhibitors. Imprida should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Heart failure/post-myocardial infarction
As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Aortic and mitral valve stenosis
As with all other vasodilators, special caution is indicated in patients suffering from mitral stenosis or significant aortic stenosis that is not high grade.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.

Imprida has not been studied in any patient population other than hypertension.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions common to the combination
No drug-drug interaction studies have been performed with Imprida and other medicinal products.

To be taken into account with concomitant use
Other antihypertensive agents
Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

Interactions linked to amlodipine
Concomitant use not recommended
Grapefruit or grapefruit juice
Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

Caution required with concomitant use
CYP3A4 inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum)
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Simvastatin
Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

Dantrolene (infusion)
In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

To be taken into account with concomitant use
Others
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

Interactions linked to valsartan
Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, including valsartan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diurectic is also used, the risk of lithium toxicity may presumably be increased further with Imprida.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use
Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)
The results of an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren
Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Others
In monotherapy with valsartan, no interactions of clinical significance have been found with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

4.6 Fertility, pregnancy and lactation

Pregnancy

Amlodipine

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Valsartan

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Breast-feeding

No information is available regarding the use of Imprida during breast-feeding, therefore Imprida is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

There are no clinical studies on fertility with Imprida.

Valsartan

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Amlodipine

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients taking Imprida and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.

Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

Summary of the safety profile

The safety of Imprida has been evaluated in five controlled clinical studies with 5,175 patients, 2,613 of whom received valsartan in combination with amlodipine. The following adverse reactions were found to be the most frequently occurring or the most significant or severe: nasopharyngitis, influenza, hypersensitivity, headache, syncope, orthostatic hypotension, oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia and hot flush.

Tabulated list of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: 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).

MedDRA System organ class	**Adverse reactions**	**Frequency**		
		Imprida	**Amlodipine**	**Valsartan**
Infections and infestations	Nasopharyngitis	Common	--	--
	Influenza	Common	--	--
Blood and lymphatic system disorders	Haemoglobin and haematocrit decreased	--	--	Not known
	Leukopenia	--	Very rare	--
	Neutropenia	--	--	Not known
	Thrombocytopenia, sometimes with purpura	--	Very rare	Not known
Immune system disorders	Hypersensitivity	Rare	Very rare	Not known
Metabolism and nutrition disorders	Anorexia	Uncommon	--	--
	Hypercalcaemia	Uncommon	--	--
	Hyperglycaemia	--	Very rare	--
	Hyperlipidaemia	Uncommon	--	--
	Hyperuricaemia	Uncommon	--	--
	Hypokalaemia	Common	--	--
	Hyponatraemia	Uncommon	--	--
Psychiatric disorders	Depression	--	Uncommon	--
	Anxiety	Rare	--	--
	Insomnia/sleep disorders	--	Uncommon	--
	Mood swings	--	Uncommon	--
	Confusion	--	Rare	--

Nervous system disorders	Coordination abnormal	Uncommon	--	--
	Dizziness	Uncommon	Common	--
	Dizziness postural	Uncommon	--	--
	Dysgeusia	--	Uncommon	--
	Extrapyramidal syndrome	--	Not known	--
	Headache	Common	Common	--
	Hypertonia	--	Very rare	--
	Paraesthesia	Uncommon	Uncommon	--
	Peripheral neuropathy, neuropathy	--	Very rare	--
	Somnolence	Uncommon	Common	--
	Syncope	--	Uncommon	--
	Tremor	--	Uncommon	--
	Hypoesthesia	--	Uncommon	--
Eye disorders	Visual disturbance	Rare	Uncommon	--
	Visual impairment	Uncommon	Uncommon	--
Ear and labyrinth disorders	Tinnitus	Rare	Uncommon	--
	Vertigo	Uncommon	--	Uncommon
Cardiac disorders	Palpitations	Uncommon	Common	--
	Syncope	Rare	--	--
	Tachycardia	Uncommon	--	--
	Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	--	Very rare	--
	Myocardial infarction	--	Very rare	--
Vascular disorders	Flushing	--	Common	--
	Hypotension	Rare	Uncommon	--
	Orthostatic hypotension	Uncommon	--	--
	Vasculitis	--	Very rare	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Very rare	Uncommon
	Dyspnoea	--	Uncommon	--
	Pharyngolaryngeal pain	Uncommon	--	--
	Rhinitis	--	Uncommon	--
Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Uncommon	Common	Uncommon
	Change of bowel habit	--	Uncommon	--
	Constipation	Uncommon	--	--
	Diarrhoea	Uncommon	Uncommon	--
	Dry mouth	Uncommon	Uncommon	--
	Dyspepsia	--	Uncommon	--
	Gastritis	--	Very rare	--
	Gingival hyperplasia	--	Very rare	--
	Nausea	Uncommon	Common	--
	Pancreatitis	--	Very rare	--
	Vomiting	--	Uncommon	--

Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	--	Very rare*	Not known
	Hepatitis	--	Very rare	--
	Intrahepatic cholestasis, jaundice	--	Very rare	--
Skin and subcutaneous tissue disorders	Alopecia	--	Uncommon	--
	Angioedema	--	Very rare	Not known
	Dermatitis bullous	--	--	Not known
	Erythema	Uncommon	--	--
	Erythema multiforme	--	Very rare	--
	Exanthema	Rare	Uncommon	--
	Hyperhidrosis	Rare	Uncommon	--
	Photosensitivity reaction	--	Uncommon	--
	Pruritus	Rare	Uncommon	Not known
	Purpura	--	Uncommon	--
	Rash	Uncommon	Uncommon	Not known
	Skin discolouration	--	Uncommon	--
	Urticaria and other forms of rash	--	Very rare	--
	Exfoliative dermatitis	--	Very rare	--
	Stevens-Johnson syndrome	--	Very rare	--
	Quincke oedema	--	Very rare	--
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	Uncommon	--
	Back pain	Uncommon	Uncommon	--
	Joint swelling	Uncommon	--	--
	Muscle spasm	Rare	Uncommon	--
	Myalgia	--	Uncommon	Not known
	Ankle swelling	--	Common	--
	Sensation of heaviness	Rare	--	--
Renal and urinary disorders	Blood creatinine increased	--	--	Not known
	Micturition disorder	--	Uncommon	--
	Nocturia	--	Uncommon	--
	Pollakiuria	Rare	Uncommon	--
	Polyuria	Rare	--	--
	Renal failure and impairment	--	--	Not known
Reproductive system and breast disorders	Impotence	--	Uncommon	--
	Erectile dysfunction	Rare	--	--
	Gynaecomastia	--	Uncommon	--

General disorders and administration site conditions	Asthenia	Common	Uncommon	--
	Discomfort, malaise	--	Uncommon	--
	Fatigue	Common	Common	Uncommon
	Facial oedema	Common	--	--
	Flushing, hot flush	Common	--	--
	Non cardiac chest pain	--	Uncommon	--
	Oedema	Common	Common	--
	Oedema peripheral	Common	--	--
	Pain	--	Uncommon	--
	Pitting oedema	Common	--	--
Investigations	Blood potassium increased	--	--	Not known
	Weight increase	--	Uncommon	--
	Weight decrease	--	Uncommon	--

* Mostly consistent with cholestasis

Additional information on the combination
Peripheral oedema, a recognised side effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone. In double-blind, controlled clinical trials, the incidence of peripheral oedema by dose was as follows:

% of patients who experienced peripheral oedema		**Valsartan (mg)**				
		0	40	80	160	320
Amlodipine (mg)	0	3.0	5.5	2.4	1.6	0.9
	2.5	8.0	2.3	5.4	2.4	3.9
	5	3.1	4.8	2.3	2.1	2.4
	10	10.3	NA	NA	9.0	9.5

The mean incidence of peripheral oedema evenly weighted across all doses was 5.1% with the amlodipine/valsartan combination.

Additional information on the individual components
Adverse reactions previously reported with one of the individual components (amlodipine or valsartan) may be potential adverse reactions with Imprida as well, even if not observed in clinical trials or during the post-marketing period.

Amlodipine

Common Somnolence, dizziness, palpitations, abdominal pain, nausea, ankle swelling.

Uncommon Insomnia, mood changes (including anxiety), depression, tremor, dysgeusia, syncope, hypoesthesia, visual disturbance (including diplopia), tinnitus, hypotension, dyspnoea, rhinitis, vomiting, dyspepsia, alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, exanthema, myalgia, muscle cramps, pain, micturition disorder, increased urinary frequency, impotence, gynaecomastia, chest pain, malaise, weight increase, weight decrease.

Rare Confusion.

Very rare	Leukocytopenia, thrombocytopenia, allergic reactions, hyperglycaemia, hypertonia, peripheral neuropathy, myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), vasculitis, pancreatitis, gastritis, gingival hyperplasia, hepatitis, jaundice, hepatic enzymes increased*, angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity.

* mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

Valsartan

Not known	Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

There is no experience of overdose with Imprida. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to Imprida overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists, combinations; angiotensin II antagonists and calcium channel blockers, ATC code: C09DB01

Imprida combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine/Valsartan

The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours.

Placebo-controlled trials

Over 1,400 hypertensive patients received Imprida once daily in two placebo-controlled trials. Adults with mild to moderate uncomplicated essential hypertension (mean sitting diastolic blood pressure ≥95 and <110 mmHg) were enrolled. Patients with high cardiovascular risks – heart failure, type I and poorly controlled type II diabetes and history of myocardial infarction or stroke within one year – were excluded.

Active-controlled trials in patients who were non-responders to monotherapy

A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <90 mmHg at the end of the trial) in patients not adequately controlled on valsartan 160 mg in 75% of patients treated with amlodipine/valsartan 10 mg/160 mg and 62% of patients treated with amlodipine/valsartan 5 mg/160 mg, compared to 53% of patients remaining on valsartan 160 mg. The addition of amlodipine 10 mg and 5 mg produced an additional reduction in systolic/diastolic blood pressure of 6.0/4.8 mmHg and 3.9/2.9 mmHg, respectively, compared to patients who remained on valsartan 160 mg only.

A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure <90 mmHg at the end of the trial) in patients not adequately controlled on amlodipine 10 mg in 78% of patients treated with amlodipine/valsartan 10 mg/160 mg, compared to 67% of patients remaining on amlodipine 10 mg. The addition of valsartan 160 mg produced an additional reduction in systolic/diastolic blood pressure of 2.9/2.1 mmHg compared to patients who remained on amlodipine 10 mg only.

Imprida was also studied in an active-controlled study of 130 hypertensive patients with mean sitting diastolic blood pressure ≥110 mmHg and <120 mmHg. In this study (baseline blood pressure 171/113 mmHg), an Imprida regimen of 5 mg/160 mg titrated to 10 mg/160 mg reduced sitting blood pressure by 36/29 mmHg as compared to 32/28 mmHg with a regimen of lisinopril/hydrochlorothiazide 10 mg/12.5 mg titrated to 20 mg/12.5 mg.

In two long-term follow-up studies the effect of Imprida was maintained for over one year. Abrupt withdrawal of Imprida has not been associated with a rapid increase in blood pressure.

Age, gender, race or body mass index (≥30 kg/m^2, <30 kg/m^2) did not influence the response to Imprida.

Imprida has not been studied in any patient population other than hypertension. Valsartan has been studied in patients with post myocardial infarction and heart failure. Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Amlodipine

The amlodipine component of Imprida inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Use in patients with hypertension

A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% versus 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Valsartan

Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT_1, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked receptor subtype AT_2, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000-fold) greater affinity for the AT_1 receptor than for the AT_2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($p < 0.05$) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9%, respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced coughing, compared to 68.5% of those treated with an ACE inhibitor ($p < 0.05$). Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Administration of valsartan to patients with hypertension results in a drop in blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak drop in blood pressure is achieved within 4–6 hours. The antihypertensive effect persists over 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2–4 weeks and is sustained during long-term therapy. Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Other: dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Two large randomised, controlled trials (ONTARGET [ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial] and VA NEPHRON-D [The Veterans Affairs Nephropathy in Diabetes]) have examined the use of the combination of an ACE inhibitor with an ARB.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and ARBs.

ACE inhibitors and ARBs should therefore not be used concomitantly in patients with diabetic nephropathy (see section 4.4).

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an ARB in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Linearity
Amlodipine and valsartan exhibit linear pharmacokinetics.

Amlodipine/Valsartan
Following oral administration of Imprida, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6–8 hours, respectively. The rate and extent of absorption of Imprida are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets.

Amlodipine
Absorption: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution: Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

Biotransformation: Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.

Elimination: Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Valsartan
Absorption: Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution: The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Biotransformation: Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination: Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Special populations
Paediatric population (age below 18 years)
No pharmacokinetic data are available in the paediatric population.

Elderly (age 65 years or over)
Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young therefore caution is required when increasing the dosage.

Renal impairment
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan.

Hepatic impairment
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC. On average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Caution should be exercised in patients with liver disease (see section 4.2).

5.3 Preclinical safety data

Amlodipine/Valsartan
Adverse reactions observed in animal studies with possible clinical relevance were as follows: Histopathological signs of inflammation of the glandular stomach was seen in male rats at an exposure of about 1.9 (valsartan) and 2.6 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. At higher exposures, there were ulceration and erosion of the stomach mucosa in both females and males. Similar changes were also seen in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

An increased incidence and severity of renal tubular basophilia/hyalinisation, dilation and casts, as well as interstitial lymphocyte inflammation and arteriolar medial hypertrophy were found at an exposure of 8–13 (valsartan) and 7–8 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Similar changes were found in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan).

In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at exposures of about 12 (valsartan) and 10 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Dilated ureters were also found in the valsartan alone group (exposure 12 times the clinical dose of 160 mg valsartan). There were only modest signs of maternal toxicity (moderate reduction of body weight) in this study. The no-observed-effect-level for developmental effects was observed at 3- (valsartan) and 4- (amlodipine) fold the clinical exposure (based on AUC).

For the single compounds there was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Amlodipine
Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50 kg

Valsartan
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised blood urea nitrogen, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen and creatinine.

Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Crospovidone Type A
Silica, colloidal anhydrous
Magnesium stearate

Coating:
Hypromellose
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Iron oxide, red (E172)
Macrogol 4000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 7, 14, 28, 30, 56, 90, 98 or 280 film-coated tablets and multipacks containing 280 (4x70 or 20x14) film-coated tablets.

PVC/PVDC perforated unit dose blisters. One blister contains 7, 10 or 14 film-coated tablets.
Pack sizes: 56, 98 or 280 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/017
EU/1/06/373/018
EU/1/06/373/019
EU/1/06/373/020
EU/1/06/373/021
EU/1/06/373/022
EU/1/06/373/023
EU/1/06/373/024
EU/1/06/373/031
EU/1/06/373/032
EU/1/06/373/033
EU/1/06/373/036
EU/1/06/373/039

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 January 2007
Date of latest renewal: 17 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Imprida 5 mg/80 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 80 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets
280 film-coated tablets
56x1 film-coated tablet (unit dose)
98x1 film-coated tablet (unit dose)
280x1 film-coated tablet (unit dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/001	7 film-coated tablets
EU/1/06/373/002	14 film-coated tablets
EU/1/06/373/003	28 film-coated tablets
EU/1/06/373/004	30 film-coated tablets
EU/1/06/373/005	56 film-coated tablets
EU/1/06/373/006	90 film-coated tablets
EU/1/06/373/007	98 film-coated tablets
EU/1/06/373/008	280 film-coated tablets
EU/1/06/373/025	56x1 film-coated tablet (unit dose)
EU/1/06/373/026	98x1 film-coated tablet (unit dose)
EU/1/06/373/027	280x1 film-coated tablet (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imprida 5 mg/80 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Imprida 5 mg/80 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 80 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

70 film-coated tablets. Component of a multipack, not to be sold separately.
14 film-coated tablets. Component of a multipack, not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/034	280 film-coated tablets (4x70)
EU/1/06/373/037	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imprida 5 mg/80 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Imprida 5 mg/80 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 80 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 280 (4 packs of 70) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/034	280 film-coated tablets (4x70)
EU/1/06/373/037	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imprida 5 mg/80 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Imprida 5 mg/80 mg film-coated tablets
amlodipine/valsartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Imprida 5 mg/160 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets
280 film-coated tablets
56x1 film-coated tablet (unit dose)
98x1 film-coated tablet (unit dose)
280x1 film-coated tablet (unit dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/009	7 film-coated tablets
EU/1/06/373/010	14 film-coated tablets
EU/1/06/373/011	28 film-coated tablets
EU/1/06/373/012	30 film-coated tablets
EU/1/06/373/013	56 film-coated tablets
EU/1/06/373/014	90 film-coated tablets
EU/1/06/373/015	98 film-coated tablets
EU/1/06/373/016	280 film-coated tablets
EU/1/06/373/028	56x1 film-coated tablet (unit dose)
EU/1/06/373/029	98x1 film-coated tablet (unit dose)
EU/1/06/373/030	280x1 film-coated tablet (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imprida 5 mg/160 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Imprida 5 mg/160 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

70 film-coated tablets. Component of a multipack, not to be sold separately.
14 film-coated tablets. Component of a multipack, not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/035	280 film-coated tablets (4x70)
EU/1/06/373/038	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imprida 5 mg/160 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Imprida 5 mg/160 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 280 (4 packs of 70) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/035	280 film-coated tablets (4x70)
EU/1/06/373/038	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imprida 5 mg/160 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Imprida 5 mg/160 mg film-coated tablets
amlodipine/valsartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Imprida 10 mg/160 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets
280 film-coated tablets
56x1 film-coated tablet (unit dose)
98x1 film-coated tablet (unit dose)
280x1 film-coated tablet (unit dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/017	7 film-coated tablets
EU/1/06/373/018	14 film-coated tablets
EU/1/06/373/019	28 film-coated tablets
EU/1/06/373/020	30 film-coated tablets
EU/1/06/373/021	56 film-coated tablets
EU/1/06/373/022	90 film-coated tablets
EU/1/06/373/023	98 film-coated tablets
EU/1/06/373/024	280 film-coated tablets
EU/1/06/373/031	56x1 film-coated tablet (unit dose)
EU/1/06/373/032	98x1 film-coated tablet (unit dose)
EU/1/06/373/033	280x1 film-coated tablet (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imprida 10 mg/160 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Imprida 10 mg/160 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

70 film-coated tablets. Component of a multipack, not to be sold separately.
14 film-coated tablets. Component of a multipack, not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/036	280 film-coated tablets (4x70)
EU/1/06/373/039	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imprida 10 mg/160 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Imprida 10 mg/160 mg film-coated tablets
amlodipine/valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg amlodipine (as amlodipine besylate) and 160 mg valsartan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 280 (4 packs of 70) film-coated tablets
Multipack: 280 (20 packs of 14) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/373/036	280 film-coated tablets (4x70)
EU/1/06/373/039	280 film-coated tablets (20x14)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imprida 10 mg/160 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Imprida 10 mg/160 mg film-coated tablets
amlodipine/valsartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: information for the user

Imprida 5 mg/80 mg film-coated tablets
amlodipine/valsartan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Imprida is and what it is used for

Imprida tablets contain two substances called amlodipine and valsartan. Both of these substances help to control high blood pressure.
- Amlodipine belongs to a group of substances called "calcium channel blockers". Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening.
- Valsartan belongs to a group of substances called "angiotensin-II receptor antagonists". Angiotensin II is produced by the body and makes the blood vessels tighten, thus increasing the blood pressure. Valsartan works by blocking the effect of angiotensin II.

This means that both of these substances help to stop the blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

Imprida is used to treat high blood pressure in adults whose blood pressure is not controlled enough with either amlodipine or valsartan on its own.

2. What you need to know before you take Imprida

Do not take Imprida
- if you are allergic to amlodipine or to any other calcium channel blockers. This may involve itching, reddening of the skin or difficulty in breathing.
- if you are allergic to valsartan or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, talk to your doctor before taking Imprida.
- if you have severe liver problems or bile problems such as biliary cirrhosis or cholestasis.
- if you are more than 3 months pregnant. (It is also better to avoid Imprida in early pregnancy, see Pregnancy section).
- if you have severe low blood pressure (hypotension).
- if you have narrowing of the aortic valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- if you suffer from heart failure after a heart attack.

- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

If any of the above applies to you, do not take Imprida and talk to your doctor.

Warnings and precautions
Talk to your doctor before taking Imprida:
- if you have been sick (vomiting or diarrhoea).
- if you have liver or kidney problems.
- if you have had a kidney transplant or if you had been told that you have a narrowing of your kidney arteries.
- if you have a condition affecting the renal glands called "primary hyperaldosteronism".
- if you have had heart failure or have experienced a heart attack. Follow your doctor's instructions for the starting dose carefully. Your doctor may also check your kidney function.
- if your doctor has told you that you have a narrowing of the valves in your heart (called "aortic or mitral stenosis") or that the thickness of your heart muscle is abnormally increased (called "obstructive hypertrophic cardiomyopathy").
- if you have experienced swelling, particularly of the face and throat, while taking other medicines (including angiotensin converting enzyme inhibitors). If you get these symptoms, stop taking Imprida and contact your doctor straight away. You should never take Imprida again.
- if you are taking any of the following medicines used to treat high blood pressure:
  - an ACE inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
  - aliskiren.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading "Do not take Imprida".

If any of these apply to you, tell your doctor before taking Imprida.

Children and adolescents
The use of Imprida in children and adolescents is not recommended (aged below 18 years old).

Other medicines and Imprida
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may need to change your dose and/or to take other precautions. In some cases you may have to stop taking one of the medicines. This applies especially to the medicines listed below:
- ACE inhibitors or aliskiren (see also information under the headings "Do not take Imprida" and "Warnings and precautions");
- diuretics (a type of medicine also called "water tablets" which increases the amount of urine you produce);
- lithium (a medicine used to treat some types of depression);
- potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels;
- certain types of painkillers called non-steroidal anti-inflammatory medicines (NSAIDs) or selective cyclooxygenase-2 inhibitors (COX-2 inhibitors). Your doctor may also check your kidney function;
- anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone);
- St. John's wort;
- nitroglycerin and other nitrates, or other substances called "vasodilators";
- medicines used for HIV/AIDS (e.g. ritonavir, indinavir, nelfinavir);
- medicines used to treat fungal infections (e.g. ketoconazole, itraconazole);

- medicines used to treat bacterial infections (such as rifampicin, erythromycin, clarithromycin, talithromycin);
- verapamil, diltiazem (heart medicines);
- simvastatin (a medicine used to control high cholesterol levels);
- dantrolene (infusion for severe body temperature abnormalities);
- medicines used to protect against transplant rejection (ciclosporin).

Imprida with food and drink
Grapefruit and grapefruit juice should not be consumed by people who are taking Imprida. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active substance amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Imprida.

Pregnancy and breast-feeding
Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Imprida before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Imprida. Imprida is not recommended in early pregnancy (first 3 months), and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Imprida is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine may make you feel dizzy. This can affect how well you can concentrate. So, if you are not sure how this medicine will affect you, do not drive, use machinery, or do other activities that you need to concentrate on.

3. How to take Imprida

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. This will help you get the best results and lower the risk of side effects.

The usual dose of Imprida is one tablet per day.
- It is preferable to take your medicine at the same time each day.
- Swallow the tablets with a glass of water.
- You can take Imprida with or without food. Do not take Imprida with grapefruit or grapefruit juice.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

Do not exceed the prescribed dose.

Imprida and older people (age 65 years or over)
Your doctor should exercise caution when increasing your dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you take more Imprida than you should
If you have taken too many tablets of Imprida, or if someone else has taken your tablets, consult a doctor immediately.

If you forget to take Imprida
If you forget to take this medicine, take it as soon as you remember. Then take your next dose at its usual time. However, if it is almost time for your next dose, skip the dose you missed. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Imprida
Stopping your treatment with Imprida may cause your disease to get worse. Do not stop taking your medicine unless your doctor tells you to.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious and need immediate medical attention:
A few patients have experienced these serious side effects *(may affect up to 1 in 1,000 people)*. **If any of the following happen, tell your doctor straight away:**
Allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, low blood pressure (feeling of faintness, light-headedness).

Other possible side effects of Imprida:
Common (may affect up to 1 in 10 people): Influenza (flu); blocked nose, sore throat and discomfort when swallowing; headache; swelling of arms, hands, legs, ankles or feet; tiredness; asthenia (weakness); redness and warm feeling of the face and/or neck.
Uncommon (may affect up to 1 in 100 people): Dizziness; nausea and abdominal pain; dry mouth; drowsiness, tingling or numbness of the hands or feet; vertigo; fast heart beat including palpitations; dizziness on standing up; cough; diarrhoea; constipation; skin rash, redness of the skin; joint swelling, back pain; pain in joints.
Rare (may affect up to 1 in 1,000 people): Feeling anxious; ringing in the ears (tinnitus); fainting; passing more urine than normal or feeling more of an urge to pass urine; inability to get or maintain an erection; sensation of heaviness; low blood pressure with symptoms such as dizziness, light-headedness; excessive sweating; skin rash all over your body; itching; muscle spasm.
If any of these affect you severely, tell your doctor.

Side effects reported with amlodipine or valsartan alone and either not observed with Imprida or observed with a higher frequency than with Imprida:

<u>Amlodipine</u>
Consult a doctor immediately if you experience any of the following very rare, severe side effects after taking this medicine:
- Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing.
- Swelling of eyelids, face or lips.
- Swelling of the tongue and throat which causes great difficulty breathing.
- Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of the mucous membranes (Stevens-Johnson Syndrome) or other allergic reactions.
- Heart attack, abnormal heart beat.
- Inflamed pancreas, which may cause severe abdominal and back pain accompanied with feeling of being very unwell.

The following side effects have been reported. If any of these cause you problems or if they last for more than one week, you should contact your doctor.

Common (may affect up to 1 in 10 people): Dizziness, sleepiness; palpitations (awareness of your heart beat); flushing, ankle swelling (oedema); abdominal pain, feeling sick (nausea).
Uncommon (may affect up to 1 in 100 people): Mood changes, anxiety, depression, sleeplessness, trembling, taste abnormalities, fainting, loss of pain sensation; visual disturbances, visual impairment, ringing in the ears; low blood pressure; sneezing/runny nose caused by inflammation of the lining of the nose (rhinitis); indigestion, vomiting (being sick); hair loss, increased sweating, itchy skin, skin discolouration; disorder in passing urine, increased need to urinate at night, increased number of times of passing urine; inability to obtain an erection, discomfort or enlargement of the breasts in men, pain, feeling unwell, muscle pain, muscle cramps; weight increase or decrease.
Rare (may affect up to 1 in 1,000 people): Confusion.
Very rare (may affect up to 1 in 10,000 people): Decreased number of white blood cells, decrease in blood platelets which may result in unusual brusing or easy bleeding (red blood cell damage); excess sugar in blood (hyperglycaemia); swelling of the gums, abdominal bloating (gastritis); abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests; increased muscle tension; inflammation of blood vessels often with skin rash, sensitivity to light; disorders combining rigidity, tremor and/or movement disorders.

Valsartan
Not known (frequency cannot be estimated from the available data): Decrease in red blood cells, fever, sore throat or mouth sores due to infections; spontaneous bleeding or bruising; high level of potassium in the blood; abnormal liver test results; decreased renal functions and severely decreased renal functions; swelling mainly of the face and the throat; muscle pain; rash, purplish-red spots; fever; itching; allergic reaction; blistering skin (sign of a condition called dermatitis bullous).

If you experience any of these, tell your doctor straight away.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Imprida

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister.
Do not store above 30°C.
Store in the original package in order to protect from moisture.
Do not use any Imprida pack that is damaged or shows signs of tampering.

6. Contents of the pack and other information

What Imprida contains
- The active substances of Imprida are amlodipine (as amlodipine besylate) and valsartan. Each tablet contains 5 mg amlodipine and 80 mg valsartan.
- The other ingredients are cellulose microcrystalline; crospovidone type A; silica, colloidal anhydrous; magnesium stearate; hypromellose; macrogol 4000; talc, titanium dioxide (E171); iron oxide, yellow (E172).

What Imprida looks like and contents of the pack
Imprida 5 mg/80 mg tablets are round and dark yellow with “NVR” on one side and “NV” on the other side.

Imprida is available in packs containing 7, 14, 28, 30, 56, 90, 98 or 280 tablets and in multipacks comprising 4 cartons, each containing 70 tablets, or 20 cartons, each containing 14 tablets. All packs are available with standard blisters; the 56, 98 and 280 tablet packs are additionally available with perforated unit dose blisters. Not all pack sizes may be available in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

Manufacturer
Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: information for the user

Imprida 5 mg/160 mg film-coated tablets
amlodipine/valsartan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Imprida is and what it is used for

Imprida tablets contain two substances called amlodipine and valsartan. Both of these substances help to control high blood pressure.
- Amlodipine belongs to a group of substances called "calcium channel blockers". Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening.
- Valsartan belongs to a group of substances called "angiotensin-II receptor antagonists". Angiotensin II is produced by the body and makes the blood vessels tighten, thus increasing the blood pressure. Valsartan works by blocking the effect of angiotensin II.

This means that both of these substances help to stop the blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

Imprida is used to treat high blood pressure in adults whose blood pressure is not controlled enough with either amlodipine or valsartan on its own.

2. What you need to know before you take Imprida

Do not take Imprida
- if you are allergic to amlodipine or to any other calcium channel blockers. This may involve itching, reddening of the skin or difficulty in breathing.
- if you are allergic to valsartan or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, talk to your doctor before taking Imprida.
- if you have severe liver problems or bile problems such as biliary cirrhosis or cholestasis.
- if you are more than 3 months pregnant. (It is also better to avoid Imprida in early pregnancy, see Pregnancy section).
- if you have severe low blood pressure (hypotension).
- if you have narrowing of the aortic valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- if you suffer from heart failure after a heart attack.

- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

If any of the above applies to you, do not take Imprida and talk to your doctor.

Warnings and precautions
Talk to your doctor before taking Imprida:
- if you have been sick (vomiting or diarrhoea).
- if you have liver or kidney problems.
- if you have had a kidney transplant or if you had been told that you have a narrowing of your kidney arteries.
- if you have a condition affecting the renal glands called "primary hyperaldosteronism".
- if you have had heart failure or have experienced a heart attack. Follow your doctor's instructions for the starting dose carefully. Your doctor may also check your kidney function.
- if your doctor has told you that you have a narrowing of the valves in your heart (called "aortic or mitral stenosis") or that the thickness of your heart muscle is abnormally increased (called "obstructive hypertrophic cardiomyopathy").
- if you have experienced swelling, particularly of the face and throat, while taking other medicines (including angiotensin converting enzyme inhibitors). If you get these symptoms, stop taking Imprida and contact your doctor straight away. You should never take Imprida again.
- if you are taking any of the following medicines used to treat high blood pressure:
  - an ACE inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
  - aliskiren.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading "Do not take Imprida".

If any of these apply to you, tell your doctor before taking Imprida.

Children and adolescents
The use of Imprida in children and adolescents is not recommended (aged below 18 years old).

Other medicines and Imprida
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may need to change your dose and/or to take other precautions. In some cases you may have to stop taking one of the medicines. This applies especially to the medicines listed below:
- ACE inhibitors or aliskiren (see also information under the headings "Do not take Imprida" and "Warnings and precautions");
- diuretics (a type of medicine also called "water tablets" which increases the amount of urine you produce);
- lithium (a medicine used to treat some types of depression);
- potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels;
- certain types of painkillers called non-steroidal anti-inflammatory medicines (NSAIDs) or selective cyclooxygenase-2 inhibitors (COX-2 inhibitors). Your doctor may also check your kidney function;
- anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone);
- St. John's wort;
- nitroglycerin and other nitrates, or other substances called "vasodilators";
- medicines used for HIV/AIDS (e.g. ritonavir, indinavir, nelfinavir);

- medicines used to treat fungal infections (e.g. ketoconazole, itraconazole);
- medicines used to treat bacterial infections (such as rifampicin, erythromycin, clarithromycin, talithromycin);
- verapamil, diltiazem (heart medicines);
- simvastatin (a medicine used to control high cholesterol levels);
- dantrolene (infusion for severe body temperature abnormalities);
- medicines used to protect against transplant rejection (ciclosporin).

Imprida with food and drink
Grapefruit and grapefruit juice should not be consumed by people who are taking Imprida. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active substance amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Imprida.

Pregnancy and breast-feeding
Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Imprida before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Imprida. Imprida is not recommended in early pregnancy (first 3 months), and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Imprida is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine may make you feel dizzy. This can affect how well you can concentrate. So, if you are not sure how this medicine will affect you, do not drive, use machinery, or do other activities that you need to concentrate on.

3. How to take Imprida

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. This will help you get the best results and lower the risk of side effects.

The usual dose of Imprida is one tablet per day.
- It is preferable to take your medicine at the same time each day.
- Swallow the tablets with a glass of water.
- You can take Imprida with or without food. Do not take Imprida with grapefruit or grapefruit juice.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

Do not exceed the prescribed dose.

Imprida and older people (age 65 years or over)
Your doctor should exercise caution when increasing your dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you take more Imprida than you should
If you have taken too many tablets of Imprida, or if someone else has taken your tablets, consult a doctor immediately.

If you forget to take Imprida
If you forget to take this medicine, take it as soon as you remember. Then take your next dose at its usual time. However, if it is almost time for your next dose, skip the dose you missed. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Imprida
Stopping your treatment with Imprida may cause your disease to get worse. Do not stop taking your medicine unless your doctor tells you to.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious and need immediate medical attention:
A few patients have experienced these serious side effects *(may affect up to 1 in 1,000 people)*. **If any of the following happen, tell your doctor straight away:**
Allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, low blood pressure (feeling of faintness, light-headedness).

Other possible side effects of Imprida:
Common (may affect up to 1 in 10 people): Influenza (flu); blocked nose, sore throat and discomfort when swallowing; headache; swelling of arms, hands, legs, ankles or feet; tiredness; asthenia (weakness); redness and warm feeling of the face and/or neck.
Uncommon (may affect up to 1 in 100 people): Dizziness; nausea and abdominal pain; dry mouth; drowsiness, tingling or numbness of the hands or feet; vertigo; fast heart beat including palpitations; dizziness on standing up; cough; diarrhoea; constipation; skin rash, redness of the skin; joint swelling, back pain; pain in joints.
Rare (may affect up to 1 in 1,000 people): Feeling anxious; ringing in the ears (tinnitus); fainting; passing more urine than normal or feeling more of an urge to pass urine; inability to get or maintain an erection; sensation of heaviness; low blood pressure with symptoms such as dizziness, light-headedness; excessive sweating; skin rash all over your body; itching; muscle spasm.
If any of these affect you severely, tell your doctor.

Side effects reported with amlodipine or valsartan alone and either not observed with Imprida or observed with a higher frequency than with Imprida:

<u>Amlodipine</u>
Consult a doctor immediately if you experience any of the following very rare, severe side effects after taking this medicine:
- Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing.
- Swelling of eyelids, face or lips.
- Swelling of the tongue and throat which causes great difficulty breathing.
- Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of the mucous membranes (Stevens-Johnson Syndrome) or other allergic reactions.
- Heart attack, abnormal heart beat.
- Inflamed pancreas, which may cause severe abdominal and back pain accompanied with feeling of being very unwell.

The following side effects have been reported. If any of these cause you problems or if they last for more than one week, you should contact your doctor.

Common (may affect up to 1 in 10 people): Dizziness, sleepiness; palpitations (awareness of your heart beat); flushing, ankle swelling (oedema); abdominal pain, feeling sick (nausea).
Uncommon (may affect up to 1 in 100 people): Mood changes, anxiety, depression, sleeplessness, trembling, taste abnormalities, fainting, loss of pain sensation; visual disturbances, visual impairment, ringing in the ears; low blood pressure; sneezing/runny nose caused by inflammation of the lining of the nose (rhinitis); indigestion, vomiting (being sick); hair loss, increased sweating, itchy skin, skin discolouration; disorder in passing urine, increased need to urinate at night, increased number of times of passing urine; inability to obtain an erection, discomfort or enlargement of the breasts in men, pain, feeling unwell, muscle pain, muscle cramps; weight increase or decrease.
Rare (may affect up to 1 in 1,000 people): Confusion.
Very rare (may affect up to 1 in 10,000 people): Decreased number of white blood cells, decrease in blood platelets which may result in unusual brusing or easy bleeding (red blood cell damage); excess sugar in blood (hyperglycaemia); swelling of the gums, abdominal bloating (gastritis); abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests; increased muscle tension; inflammation of blood vessels often with skin rash, sensitivity to light; disorders combining rigidity, tremor and/or movement disorders.

Valsartan
Not known (frequency cannot be estimated from the available data): Decrease in red blood cells, fever, sore throat or mouth sores due to infections; spontaneous bleeding or bruising; high level of potassium in the blood; abnormal liver test results; decreased renal functions and severely decreased renal functions; swelling mainly of the face and the throat; muscle pain; rash, purplish-red spots; fever; itching; allergic reaction; blistering skin (sign of a condition called dermatitis bullous).

If you experience any of these, tell your doctor straight away.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Imprida

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister.
Do not store above 30°C.
Store in the original package in order to protect from moisture.
Do not use any Imprida pack that is damaged or shows signs of tampering.

6. Contents of the pack and other information

What Imprida contains
- The active substances of Imprida are amlodipine (as amlodipine besylate) and valsartan. Each tablet contains 5 mg amlodipine and 160 mg valsartan.
- The other ingredients are cellulose microcrystalline; crospovidone type A; silica, colloidal anhydrous; magnesium stearate; hypromellose; macrogol 4000; talc, titanium dioxide (E171); iron oxide, yellow (E172).

What Imprida looks like and contents of the pack
Imprida 5 mg/160 mg tablets are oval and dark yellow “NVR” on one side and “ECE” on the other side.

Imprida is available in packs containing 7, 14, 28, 30, 56, 90, 98 or 280 tablets and in multipacks comprising 4 cartons, each containing 70 tablets, or 20 cartons, each containing 14 tablets. All packs are available with standard blisters; the 56, 98 and 280 tablet packs are additionally available with perforated unit dose blisters. Not all pack sizes may be available in your country.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

Package leaflet: information for the user

Imprida 10 mg/160 mg film-coated tablets
amlodipine/valsartan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Imprida is and what it is used for

Imprida tablets contain two substances called amlodipine and valsartan. Both of these substances help to control high blood pressure.
- Amlodipine belongs to a group of substances called "calcium channel blockers". Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening.
- Valsartan belongs to a group of substances called "angiotensin-II receptor antagonists". Angiotensin II is produced by the body and makes the blood vessels tighten, thus increasing the blood pressure. Valsartan works by blocking the effect of angiotensin II.

This means that both of these substances help to stop the blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

Imprida is used to treat high blood pressure in adults whose blood pressure is not controlled enough with either amlodipine or valsartan on its own.

2. What you need to know before you take Imprida

Do not take Imprida
- if you are allergic to amlodipine or to any other calcium channel blockers. This may involve itching, reddening of the skin or difficulty in breathing.
- if you are allergic to valsartan or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, talk to your doctor before taking Imprida.
- if you have severe liver problems or bile problems such as biliary cirrhosis or cholestasis.
- if you are more than 3 months pregnant. (It is also better to avoid Imprida in early pregnancy, see Pregnancy section).
- if you have severe low blood pressure (hypotension).
- if you have narrowing of the aortic valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- if you suffer from heart failure after a heart attack.

- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

If any of the above applies to you, do not take Imprida and talk to your doctor.

Warnings and precautions
Talk to your doctor before taking Imprida:
- if you have been sick (vomiting or diarrhoea).
- if you have liver or kidney problems.
- if you have had a kidney transplant or if you had been told that you have a narrowing of your kidney arteries.
- if you have a condition affecting the renal glands called "primary hyperaldosteronism".
- if you have had heart failure or have experienced a heart attack. Follow your doctor's instructions for the starting dose carefully. Your doctor may also check your kidney function.
- if your doctor has told you that you have a narrowing of the valves in your heart (called "aortic or mitral stenosis") or that the thickness of your heart muscle is abnormally increased (called "obstructive hypertrophic cardiomyopathy").
- if you have experienced swelling, particularly of the face and throat, while taking other medicines (including angiotensin converting enzyme inhibitors). If you get these symptoms, stop taking Imprida and contact your doctor straight away. You should never take Imprida again.
- if you are taking any of the following medicines used to treat high blood pressure:
  - an ACE inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
  - aliskiren.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading "Do not take Imprida".

If any of these apply to you, tell your doctor before taking Imprida.

Children and adolescents
The use of Imprida in children and adolescents is not recommended (aged below 18 years old).

Other medicines and Imprida
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may need to change your dose and/or to take other precautions. In some cases you may have to stop taking one of the medicines. This applies especially to the medicines listed below:
- ACE inhibitors or aliskiren (see also information under the headings "Do not take Imprida" and "Warnings and precautions");
- diuretics (a type of medicine also called "water tablets" which increases the amount of urine you produce);
- lithium (a medicine used to treat some types of depression);
- potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels;
- certain types of painkillers called non-steroidal anti-inflammatory medicines (NSAIDs) or selective cyclooxygenase-2 inhibitors (COX-2 inhibitors). Your doctor may also check your kidney function;
- anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone);
- St. John's wort;
- nitroglycerin and other nitrates, or other substances called "vasodilators";
- medicines used for HIV/AIDS (e.g. ritonavir, indinavir, nelfinavir);

- medicines used to treat fungal infections (e.g. ketoconazole, itraconazole);
- medicines used to treat bacterial infections (such as rifampicin, erythromycin, clarithromycin, talithromycin);
- verapamil, diltiazem (heart medicines);
- simvastatin (a medicine used to control high cholesterol levels);
- dantrolene (infusion for severe body temperature abnormalities);
- medicines used to protect against transplant rejection (ciclosporin).

Imprida with food and drink
Grapefruit and grapefruit juice should not be consumed by people who are taking Imprida. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active substance amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Imprida.

Pregnancy and breast-feeding
Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Imprida before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Imprida. Imprida is not recommended in early pregnancy (first 3 months), and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Imprida is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine may make you feel dizzy. This can affect how well you can concentrate. So, if you are not sure how this medicine will affect you, do not drive, use machinery, or do other activities that you need to concentrate on.

3. How to take Imprida

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. This will help you get the best results and lower the risk of side effects.

The usual dose of Imprida is one tablet per day.
- It is preferable to take your medicine at the same time each day.
- Swallow the tablets with a glass of water.
- You can take Imprida with or without food. Do not take Imprida with grapefruit or grapefruit juice.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

Do not exceed the prescribed dose.

Imprida and older people (age 65 years or over)
Your doctor should exercise caution when increasing your dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you take more Imprida than you should
If you have taken too many tablets of Imprida, or if someone else has taken your tablets, consult a doctor immediately.

If you forget to take Imprida
If you forget to take this medicine, take it as soon as you remember. Then take your next dose at its usual time. However, if it is almost time for your next dose, skip the dose you missed. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Imprida
Stopping your treatment with Imprida may cause your disease to get worse. Do not stop taking your medicine unless your doctor tells you to.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious and need immediate medical attention:
A few patients have experienced these serious side effects *(may affect up to 1 in 1,000 people)*. **If any of the following happen, tell your doctor straight away:**
Allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, low blood pressure (feeling of faintness, light-headedness).

Other possible side effects of Imprida:
Common (may affect up to 1 in 10 people): Influenza (flu); blocked nose, sore throat and discomfort when swallowing; headache; swelling of arms, hands, legs, ankles or feet; tiredness; asthenia (weakness); redness and warm feeling of the face and/or neck.
Uncommon (may affect up to 1 in 100 people): Dizziness; nausea and abdominal pain; dry mouth; drowsiness, tingling or numbness of the hands or feet; vertigo; fast heart beat including palpitations; dizziness on standing up; cough; diarrhoea; constipation; skin rash, redness of the skin; joint swelling, back pain; pain in joints.
Rare (may affect up to 1 in 1,000 people): Feeling anxious; ringing in the ears (tinnitus); fainting; passing more urine than normal or feeling more of an urge to pass urine; inability to get or maintain an erection; sensation of heaviness; low blood pressure with symptoms such as dizziness, light-headedness; excessive sweating; skin rash all over your body; itching; muscle spasm.
If any of these affect you severely, tell your doctor.

Side effects reported with amlodipine or valsartan alone and either not observed with Imprida or observed with a higher frequency than with Imprida:

<u>Amlodipine</u>
Consult a doctor immediately if you experience any of the following very rare, severe side effects after taking this medicine:
- Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing.
- Swelling of eyelids, face or lips.
- Swelling of the tongue and throat which causes great difficulty breathing.
- Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of the mucous membranes (Stevens-Johnson Syndrome) or other allergic reactions.
- Heart attack, abnormal heart beat.
- Inflamed pancreas, which may cause severe abdominal and back pain accompanied with feeling of being very unwell.

The following side effects have been reported. If any of these cause you problems or if they last for more than one week, you should contact your doctor.

Common (may affect up to 1 in 10 people): Dizziness, sleepiness; palpitations (awareness of your heart beat); flushing, ankle swelling (oedema); abdominal pain, feeling sick (nausea).
Uncommon (may affect up to 1 in 100 people): Mood changes, anxiety, depression, sleeplessness, trembling, taste abnormalities, fainting, loss of pain sensation; visual disturbances, visual impairment, ringing in the ears; low blood pressure; sneezing/runny nose caused by inflammation of the lining of the nose (rhinitis); indigestion, vomiting (being sick); hair loss, increased sweating, itchy skin, skin discolouration; disorder in passing urine, increased need to urinate at night, increased number of times of passing urine; inability to obtain an erection, discomfort or enlargement of the breasts in men, pain, feeling unwell, muscle pain, muscle cramps; weight increase or decrease.
Rare (may affect up to 1 in 1,000 people): Confusion.
Very rare (may affect up to 1 in 10,000 people): Decreased number of white blood cells, decrease in blood platelets which may result in unusual brusing or easy bleeding (red blood cell damage); excess sugar in blood (hyperglycaemia); swelling of the gums, abdominal bloating (gastritis); abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests; increased muscle tension; inflammation of blood vessels often with skin rash, sensitivity to light; disorders combining rigidity, tremor and/or movement disorders.

Valsartan
Not known (frequency cannot be estimated from the available data): Decrease in red blood cells, fever, sore throat or mouth sores due to infections; spontaneous bleeding or bruising; high level of potassium in the blood; abnormal liver test results; decreased renal functions and severely decreased renal functions; swelling mainly of the face and the throat; muscle pain; rash, purplish-red spots; fever; itching; allergic reaction; blistering skin (sign of a condition called dermatitis bullous).

If you experience any of these, tell your doctor straight away.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Imprida

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister.
Do not store above 30°C.
Store in the original package in order to protect from moisture.
Do not use any Imprida pack that is damaged or shows signs of tampering.

6. Contents of the pack and other information

What Imprida contains
- The active substances of Imprida are amlodipine (as amlodipine besylate) and valsartan. Each tablet contains 10 mg amlodipine and 160 mg valsartan.
- The other ingredients are cellulose microcrystalline; crospovidone type A; silica, colloidal anhydrous; magnesium stearate; hypromellose; macrogol 4000; talc, titanium dioxide (E171); iron oxide, yellow (E172), iron oxide, red (E172).

What Imprida looks like and contents of the pack
Imprida 10 mg/160 mg tablets are oval and light yellow with “NVR” on one side and “UIC” on the other side.

Imprida is available in packs containing 7, 14, 28, 30, 56, 90, 98 or 280 tablets and in multipacks comprising 4 cartons, each containing 70 tablets, or 20 cartons, each containing 14 tablets. All packs are available with standard blisters; the 56, 98 and 280 tablet packs are additionally available with perforated unit dose blisters. Not all pack sizes may be available in your country.

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