SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan/Amlodipine Besylate Impact 150 mg/5 mg film-coated tablet

Irbesartan/Amlodipine Besylate Impact 300 mg/5 mg film-coated tablet

Irbesartan/Amlodipine Besylate Impact 300 mg/10 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Irbesartan/Amlodipine Besylate Impact 150 mg/5 mg film-coated tablet

Irbesartan ..... 150 mg

Amlodipine (as amlodipine besylate) .....5 mg

For one film-coated tablet.

Irbesartan/Amlodipine Besylate Impact 300 mg/5 mg film-coated tablet

Irbesartan ..... 300 mg

Amlodipine (as amlodipine besylate) ..... 5 mg

For one film-coated tablet.

Irbesartan/Amlodipine Besylate Impact 300 mg/10 mg film-coated tablet

Irbesartan ..... 300 mg

Amlodipine (as amlodipine besylate) ..... 10 mg

For one film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Irbesartan/Amlodipine Besylate Impact 150 mg/5 mg film-coated tablet

White, oval shaped of 12.6 ± 0.3 mm length and 6.6 mm ± 0.3 mm width film-coated tablets with “150/5” debossed on one side.

Irbesartan/Amlodipine Besylate Impact 300 mg/5 mg film-coated tablet

Yellow, oval shaped of 15.7 ± 0.3 mm length and 8.2 mm ± 0.3 mm width film-coated tablets with “300/5” debossed on one side.

Irbesartan/Amlodipine Besylate Impact 300 mg/10 mg film-coated tablet

White, oval shaped film-coated tablet, 15.7 ± 0.3 mm long, and 8.2 mm ± 0.3 mm wide, scored on one side. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Irbesartan/Amlodipine Besylate Impact is indicated as substitution therapy for treatment of essential hypertension in adult patients already controlled with irbesartan and amlodipine given concurrently at

the same dose level as the combination product.

4.2. Posology and method of administration

Posology

Fixed-dose combination is not suitable for initial therapy. Individual dose titration with each component (i.e., amlodipine and irbesartan) must have been performed before changing to the fixed dose combination.

The recommended dose of Irbesartan/Amlodipine Besylate Impact is one tablet (may vary from 150 mg/5 mg to 300 mg/10 mg) per day. Irbesartan/Amlodipine Besylate Impact can be administered with or without food.

The maximum recommended dose is one Irbesartan/Amlodipine Besylate Impact 300 mg/10 mg film-coated tablet per day.

Paediatric population

The safety and efficacy of Irbesartan/Amlodipine Besylate Impact in children aged 0–18 years have not been established.

Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

There are no data available for Irbesartan/Amlodipine Besylate Impact. Currently available data for irbesartan and amlodipine monotherapy are described in section 5.1.

Elderly patients

The use at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but, due to the presence of amlodipine, increase of the dosage should take place with care (see sections 4.4 and 5.2).

Hepatic insufficiency

Due to the presence of amlodipine, Irbesartan/Amlodipine Besylate Impact should be administered with caution in patients with hepatic insufficiency (see sections 4.4 and 5.2).

Renal insufficiency

No dosage adjustment is necessary in patients with impaired renal function (see section 4.4 and 5.2).

Method of administration

Oral use.

4.3. Contraindications

Due to the presence of both irbesartan and amlodipine in the medicinal product, Irbesartan/Amlodipine Besylate Impact is contraindicated in:

- Hypersensitivity to irbesartan, amlodipine, dihydropyridines derivatives or to any of the excipients listed in section 6.1.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe hypotension.
- The concomitant use of Irbesartan/Amlodipine Besylate Impact with aliskiren-containing product is contraindicated in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) <60 mL/min/1.73m2) (see sections 4.5 and 5.1).

4.4. Special warnings and precautions for use

Irbesartan and amlodipine

Hypertensive crisis

The safety and efficacy of the fixed-dose combination of irbesartan/amlodipine in hypertensive crisis has not been established.

Irbesartan

Hypotension - volume-depleted patients

Symptomatic hypotension, as with angiotensin converting enzyme (ACE) inhibitors, may be expected to occur in sodium/volume-depleted patients such as those treated vigorously with diuretics and/or salt restriction, or on haemodialysis. Volume and sodium-depletion should be corrected before initiating therapy with the fixed-dose combination irbesartan/amlodipine.

Hypoglycaemia

Irbesartan/Amlodipine Besylate Impact may cause hypoglycaemia, especially in diabetic patients.

In patients treated with insulin or antidiabetic agents, appropriate blood glucose monitoring should be considered; the dose of insulin or antidiabetic agents may need to be adjusted when indicated (see section 4.5).

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system. While this is not documented with irbesartan, a similar effect should be anticipated with angiotensin-II receptor antagonists.

Hypertensive patients with type 2 diabetes and renal disease

The effects of irbesartan both on renal and cardiovascular events were not uniform across all subgroups, in an analysis carried out in the study with patients with advanced renal disease. In particular, they appeared less favourable in women and non-white subjects (see section 5.1).

Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers 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, angiotensin II receptor blockers 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 angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Hyperkalaemia

As with other medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur during the treatment with irbesartan, especially in the presence of renal impairment, overt proteinuria due to diabetic renal disease, and/or heart failure. Close monitoring of serum potassium in patients at risk is recommended (see section 4.5).

Lithium

The combination of lithium and irbesartan is not recommended (see section 4.5).

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of irbesartan is not recommended.

Foetal/neonatal morbidity and mortality

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 the fixed-dose combination irbesartan/amlodipine should be discontinued as soon as possible, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

General

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or underlying renal

disease, including renal artery stenosis), treatment with angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists that affect this system has been associated with acute hypotension, azotaemia, oliguria, or rarely acute renal failure (see section 4.5). As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

As observed for angiotensin converting enzyme inhibitors, irbesartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in patients identifying with the Black ethnic group, possibly because of higher prevalence of low-renin states in hypertensive Black patients (see section 5.1).

Amlodipine

Patients with cardiac failure

Patients with heart failure should be treated with caution. In a long-term, placebo-controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1). 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.

Patients with hepatic impairment

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function (see section 5.2); dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Patients with renal impairment

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

Elderly patients

In the elderly, increase of the dosage should take place with care due to the presence of amlodipine (see sections 4.2 and 5.2). More frequent monitoring of blood pressure is recommended in elderly patients.

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

4.5. Interaction with other medicinal products and other forms of interaction

Irbesartan and amlodipine

Based on a pharmacokinetic study where irbesartan and amlodipine were given alone or in combination, there is no pharmacokinetic interaction between irbesartan and amlodipine.

No drug interaction studies have been performed with Irbesartan/Amlodipine Besylate Impact and other medicinal products.

Irbesartan

Diuretics and other antihypertensive agents

Other antihypertensive agents may increase the hypotensive effects of irbesartan; however, irbesartan has been safely administered with other antihypertensive agents, such as beta-blockers, long-acting calcium channel blockers, and thiazide diuretics. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with irbesartan (see section 4.4).

Aliskiren-containing products or ACE-inhibitors

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers 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).

Repaglinide

Irbesartan has the potential to inhibit OATP1B1. In a clinical study, irbesartan has been reported to increase the Cmax and the AUC of repaglinide (OATP1B1 substrate) 1.8 times and 1.3 times,

respectively, when administered one hour before repaglinide. In another study, no relevant pharmacokinetic interactions were reported when the two medicinal products were administered together. Therefore, it may be necessary to adjust the dose of antidiabetic treatment, such as repaglinide (see section 4.4).

Potassium supplements and potassium-sparing diuretics

Based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g., heparin) may lead to increases in serum potassium and is, therefore, not recommended (see section 4.4).

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Similar effects have been very rarely reported with irbesartan so far. Therefore, this combination is not recommended (see section 4.4). If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Non-steroidal anti-inflammatory drugs (NSAIDs)

When angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e., selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Additional information on irbesartan interactions

In clinical studies, the pharmacokinetics of irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolised by CYP2C9 and to a lesser extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when irbesartan was co-administered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetics of irbesartan have not been evaluated. The pharmacokinetics of digoxin was not altered by co-administration of irbesartan.

Amlodipine

Effects of other medicinal products on amlodipine

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 resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers

Upon co-administration of known CYP3A4 inducers, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g., rifampicin, St. John's Wort [*Hypericum perforatum*]).

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.

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.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine add to the blood pressure lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Simvastatin

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

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

4.6. Fertility, pregnancy and lactation

Pregnancy

Irbesartan and amlodipine

There are limited data on the use of Irbesartan/Amlodipine Besylate Impact in pregnant women. Animal reproductive toxicity studies with Irbesartan/Amlodipine Besylate Impact have not been performed.

As for irbesartan (see details below), the use of Irbesartan/Amlodipine Besylate Impact is not recommended during the first trimester of pregnancy (see section 4.4). The use of Irbesartan/Amlodipine Besylate Impact is contraindicated during the second and third trimesters of pregnancy (see section 4.3).

Irbesartan

The use of 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.

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 are no controlled epidemiological studies available on the use of Angiotensin II Receptor Antagonists (AIIRAs) during the first trimester of pregnancy, 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.

Based on the post-marketing experience, AIIRA therapy causes human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) when administered during the 2nd and 3rd trimesters of pregnancy. Studies in animals have shown reproductive toxicity (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.

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 of amlodipine as monotherapy in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding

Irbesartan and amlodipine

No information is available regarding the use Irbesartan/Amlodipine Besylate Impact during breast-feeding. As for irbesartan and amlodipine (see details below) a decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Irbesartan

Because no information is available regarding the use of irbesartan during breast-feeding, this medicinal product is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new-born or preterm infant.

It is not known whether irbesartan or its metabolites are excreted in breast milk.

Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk (see section 5.3).

Amlodipine

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 to 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility

Irbesartan and amlodipine

There are no animal toxicity studies on fertility with Irbesartan/Amlodipine Besylate Impact.

Irbesartan

Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity (see section 5.3).

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

When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

Amlodipine can have minor 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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a medicinal product cannot be directly compared to rates in the clinical trials of another medicinal product and may not reflect the rates observed in practice.

Irbesartan and amlodipine

In the clinical trials comparing the fixed-dose combination irbesartan/amlodipine to either irbesartan or amlodipine monotherapy, the types and incidences of treatment-emergent adverse events (TEAEs) possibly related to study treatment were similar to those observed in the earlier monotherapy clinical trials and post-marketing reports. The most frequently reported adverse event was peripheral oedema, mainly associated with amlodipine.

Irbesartan

In placebo-controlled trials in patients with hypertension, the overall incidence of adverse events did not differ between the irbesartan (56.2%) and the placebo groups (56.5%). Discontinuation due to any clinical or laboratory adverse event was less frequent for irbesartan-treated patients (3.3%) than for placebo-treated patients (4.5%). The incidence of adverse events was not related to dose (in the recommended dose range), gender, age, ethnicity, or duration of treatment.

In diabetic hypertensive patients with microalbuminuria and normal renal function, orthostatic dizziness and orthostatic hypotension were reported in 0.5% of the patients (i.e., uncommon) but in excess of placebo.

The following table presents adverse drug reactions reported in placebo-controlled trials in which 1,965 hypertensive patients received irbesartan. Terms marked with a star (*) refer to the adverse reactions that were additionally reported in >2% of diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria and in excess of placebo.

The following CIOMS frequency rating is used, when applicable: 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).

Table 1 Adverse events reported in irbesartan clinical trials or post-marketing reports

System organ class	Common	Uncommon	Not known
Blood and lymphatic system disorders			Anaemia, thrombocytopenia
Immune system disorders			Hypersensitivity reactions such as angioedema, rash, urticaria, anaphylactic reaction, anaphylactic shock
Metabolism and nutrition disorders			Hyperkalaemia, hypoglycaemia
Nervous system disorders	Dizziness, orthostatic dizziness		Vertigo, headache
Ear and labyrinth disorders			Tinnitus
Cardiac disorders		Tachycardia	
Vascular disorders	Orthostatic hypotension*	Flushing	
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders	Nausea/vomiting	Diarrhoea, dyspepsia/heartburn	Dysgeusia
Hepatobiliary disorders		Jaundice	Hepatitis, abnormal liver function
Skin and subcutaneous tissue disorders			Leukocytoclastic vasculitis
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*		Arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps
Renal and urinary disorders			Impaired renal function including renal failure in patients at risk
Reproductive system and breast disorders		Sexual dysfunction	
General disorders and administration site conditions	Fatigue	Chest pain	
Investigations	Increases in plasma creatine kinase		

Amlodipine

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders					Leukocytopenia, thrombocytopenia	
Immune system disorders					Allergic reactions	
Metabolism and nutrition disorders					Hyperglycaemia	
Psychiatric disorders			Depression, mood changes (including anxiety), insomnia	Confusion		
Nervous system disorders		Somnolence, dizziness, headache (especially at the beginning of the treatment)	Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia		Hypertonia, peripheral neuropathy	Extrapyramidal disorder
Eye disorders		Visual disturbance (including diplopia)				
Ear and labyrinth disorders			Tinnitus			
Cardiac disorders		Palpitations	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)		Myocardial infarction	
Vascular disorders		Flushing	Hypotension		Vasculitis	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Cough, rhinitis			
Gastrointestinal disorders		Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)	Vomiting, dry mouth		Pancreatitis, gastritis, gingival hyperplasia	
Hepatobiliary disorders					Hepatitis, jaundice, liver enzymes increased*	
Skin and subcutaneous tissue disorders			Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria		Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke's oedema, photosensitivity	Toxic epidermal necrolysis

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Musculoskeletal and connective tissue disorders		Ankle swelling, muscle cramps	Arthralgia, myalgia, back pain			
Renal and urinary disorders			Micturition disorder, nocturia, increased urinary frequency			
Reproductive system and breast disorders			Impotence, gynaecomastia			
General disorders and administration site conditions	Oedema	Fatigue, asthenia	Chest pain, pain, malaise			
Investigations			Weight increased, weight decreased			

* Mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

Paediatric population

Irbesartan and amlodipine

The safety of Irbesartan/Amlodipine Besylate Impact in children 0 to 18 years of age has not been established (see section 4.2).

Irbesartan:

In a randomised trial of 318 hypertensive children and adolescents aged 6 to 16 years, the following adverse reactions occurred in the 3-week double-blind phase: headache (7.9%), hypotension (2.2%), dizziness (1.9%), cough (0.9%). In the 26-week open-label period of this trial the most frequent laboratory abnormalities observed were creatinine increases (6.5%) and elevated CK values in 2% of child recipients.

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.

4.9. Overdose

Irbesartan

Experience in adults exposed to doses of up to 900 mg/day irbesartan for 8 weeks revealed no toxicity.

Symptoms

The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose.

Treatment

No specific information is available on the treatment of overdose with irbesartan. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Irbesartan is not removed by haemodialysis.

Amlodipine

In humans, experience with intentional overdose is limited.

Symptoms

Available data suggest that gross overdose could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Cases of non-cardiogenic pulmonary oedema have been reported rarely following an overdose of amlodipine which may appear delayed (24-48 hours after ingestion) and require ventilatory support. Early resuscitation measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment

Clinically significant hypotension due to amlodipine 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.

Gastric lavage may be worthwhile in some cases. In healthy volunteers, the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

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: C09DB05.

Irbesartan and amlodipine

Irbesartan/Amlodipine Besylate Impact combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor antagonist, irbesartan, and a dihydropyridinic calcium channel blocker, amlodipine.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Irbesartan/Amlodipine Besylate Impact film-coated tablets, in all subsets of the paediatric population in treatment of hypertension. See section 4.2 for information on paediatric use.

Irbesartan

Mechanism of action

Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT_1) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT_1 receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT_1) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

Clinical efficacy

Hypertension

Irbesartan lowers blood pressure with minimal change in heart rate. The decrease in blood pressure is dose-related for once a day doses with a tendency towards plateau at doses above 300 mg. Doses of 150-300 mg once daily lower supine or seated blood pressures at trough (i.e., 24 hours after dosing) by an average of 8-13/5-8 mmHg (systolic/diastolic), greater than those associated with placebo.

Peak reduction of blood pressure is achieved within 3-6 hours after administration and the blood pressure lowering effect is maintained for at least 24 hours. At 24 hours the reduction of blood pressure was 60-70% of the corresponding peak diastolic and systolic responses at the recommended doses. Once daily dosing with 150 mg produced trough and mean 24-hour responses similar to twice daily dosing on the same total dose.

The blood pressure lowering effect of irbesartan is evident within 1-2 weeks, with the maximal effect occurring by 4-6 weeks after start of therapy. The antihypertensive effects are maintained during long term therapy. After withdrawal of therapy, blood pressure gradually returns toward baseline. Rebound hypertension has not been observed.

The blood pressure lowering effects of irbesartan and thiazide-type diuretics are additive. In patients not adequately controlled by irbesartan alone, the addition of a low dose of hydrochlorothiazide (12.5 mg) to irbesartan once daily results in a further placebo-adjusted blood pressure reduction at trough of 7-10/3-6 mmHg (systolic/diastolic).

The efficacy of irbesartan is not influenced by age or gender. As is the case with other medicinal products that affect the renin-angiotensin system, black hypertensive patients have notably less response to irbesartan monotherapy. When irbesartan is administered concomitantly with a low dose of hydrochlorothiazide (e.g., 12.5 mg daily), the antihypertensive response in patients identifying with the Black ethnic group approaches that of White patients.

There is no clinically important effect on serum uric acid or urinary uric acid secretion.

Paediatric population

Reduction of blood pressure with 0.5 mg/kg (low), 1.5 mg/kg (medium) and 4.5 mg/kg (high) target titrated doses of irbesartan was evaluated in 318 hypertensive or at risk (diabetic, family history of hypertension) children and adolescents aged 6 to 16 years over a three-week period. At the end of the three weeks the mean reduction from baseline in the primary efficacy variable, trough seated systolic blood pressure (SeSBP) was 11.7 mmHg (low dose), 9.3 mmHg (medium dose), 13.2 mmHg (high dose). No significant difference was apparent between these doses. Adjusted mean change of trough seated diastolic blood pressure (SeDBP) was as follows: 3.8 mmHg (low dose), 3.2 mmHg (medium dose), 5.6 mmHg (high dose). Over a subsequent two-week period where patients were re-randomised to either active medicinal product or placebo, patients on placebo had increases of 2.4 and 2.0 mmHg in SeSBP and SeDBP compared to +0.1 and -0.3 mmHg changes respectively in those on all doses of irbesartan (see section 4.2).

Hypertension and type 2 diabetes with renal disease

The “Irbesartan Diabetic Nephropathy Trial (IDNT)” shows that irbesartan decreases the progression of renal disease in patients with chronic renal insufficiency and overt proteinuria. IDNT was a double blind, controlled, morbidity and mortality trial comparing irbesartan, amlodipine and placebo. In 1,715 hypertensive patients with type 2 diabetes, proteinuria ≥900 mg/day and serum creatinine ranging from 1.0-3.0 mg/dL, the long-term effects (mean 2.6 years) of irbesartan on the progression of renal disease and all-cause mortality were examined. Patients were titrated from 75 mg to a maintenance dose of 300 mg irbesartan, from 2.5 mg to 10 mg amlodipine, or placebo as tolerated. Patients in all treatment groups typically received between 2 and 4 antihypertensive agents (e.g., diuretics, beta blockers, alpha blockers) to reach a predefined blood pressure goal of ≤135/85 mmHg or a 10 mmHg reduction in systolic pressure if baseline was >160 mmHg. Sixty per cent (60%) of patients in the placebo group reached this target blood pressure whereas this figure was 76% and 78% in the irbesartan and amlodipine groups respectively. Irbesartan significantly reduced the relative risk in the primary combined endpoint of doubling serum creatinine, end-stage renal disease (ESRD) or all-cause mortality. Approximately 33% of patients in the irbesartan group reached the primary renal composite endpoint compared to 39% and 41% in the placebo and amlodipine groups [20% relative risk reduction versus placebo ($p = 0.024$) and 23% relative risk reduction compared to amlodipine ($p = 0.006$)]. When the individual components of the primary endpoint were analysed, no effect in all-cause mortality was observed, while a positive trend in the reduction in ESRD and a significant reduction in doubling of serum creatinine were observed.

Subgroups consisting of gender, ethnicity, age, duration of diabetes, baseline blood pressure, serum creatinine, and albumin excretion rate were assessed for treatment effect. In the female and black ethnic group subgroups, which represented 32% and 26% of the overall study population respectively, a renal benefit was not evident, although the confidence intervals do not exclude it. As for the secondary endpoint of fatal and non-fatal cardiovascular events, there was no difference among the three groups in the overall population, although an increased incidence of non-fatal MI was seen for women and a decreased incidence of non-fatal MI was seen in males in the irbesartan group versus the placebo-based regimen. An increased incidence of non-fatal MI and stroke was seen in females in the

irbesartan-based regimen versus the amlodipine-based regimen, while hospitalisation due to heart failure was reduced in the overall population. However, no proper explanation for these findings in women has been identified.

The study of the "Effects of Irbesartan on Microalbuminuria in Hypertensive Patients with type 2 Diabetes Mellitus (IRMA 2)" shows that irbesartan 300 mg delays progression to overt proteinuria in patients with microalbuminuria. IRMA 2 was a placebo-controlled double-blind morbidity study in 590 patients with type 2 diabetes, microalbuminuria (30-300 mg/day) and normal renal function (serum creatinine ≤1.5 mg/dL in males and <1.1 mg/dL in females). The study examined the long-term effects (2 years) of irbesartan on the progression to clinical (overt) proteinuria (urinary albumin excretion rate (UAER) >300 mg/day, and an increase in UAER of at least 30% from baseline). The predefined blood pressure goal was ≤135/85 mmHg. Additional antihypertensive agents (excluding ACE inhibitors, angiotensin II receptor antagonists and dihydropyridine calcium blockers) were added as needed to help achieve the blood pressure goal. While similar blood pressure was achieved in all treatment groups, fewer subjects in the irbesartan 300 mg group (5.2%) than in the placebo (14.9%) or in the irbesartan 150 mg group (9.7%) reached the endpoint of overt proteinuria, demonstrating a 70% relative risk reduction versus placebo ($p = 0.0004$) for the higher dose. An accompanying improvement in the glomerular filtration rate (GFR) was not observed during the first three months of treatment. The slowing in the progression to clinical proteinuria was evident as early as three months and continued over the 2-year period. Regression to normal albuminuria (<30 mg/day) was more frequent in the irbesartan 300 mg group (34%) than in the placebo group (21%).

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 angiotensin II receptor blocker. 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 angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

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 angiotensin II receptor blocker 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.

Amlodipine

Mechanism of action

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx 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. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Pharmacodynamic effects

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration. Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Clinical efficacy and safety

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 drug therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40mg/day (ACE-inhibitor) as first-line therapies to that of the thiazidediuretic, 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 CHD risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrolment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C <35 mg/dL (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 CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: 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% vs. 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.

Use in patients with heart failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo-controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure. In a follow-up, long term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema.

Paediatric population

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant. The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

5.2. Pharmacokinetic properties

Absorption

Irbesartan and amlodipine

Concurrent administration of irbesartan and amlodipine, whether in a fixed dose combination tablet or the free combination, has no influence on the bioavailability of the individual components.

The two fixed dose combinations of irbesartan and amlodipine (150 mg/10 mg and 300 mg/10 mg) are bioequivalent to the free dose combinations (150 mg/10 mg and 300 mg/10 mg) both in terms of rate and extent of absorption.

When given separately or concomitantly at 300 mg and 10 mg dose levels, time to median peak plasma concentrations of irbesartan and amlodipine remain unchanged, i.e., 0.75-1 hour and 5 hours respectively after administration. Similarly, Cmax and AUCs are in the same range resulting in a relative bioavailability of 95% for irbesartan and 98% for amlodipine when they are co-administered.

Irbesartan

After oral administration, irbesartan is well absorbed: studies of absolute bioavailability gave values of approximately 60-80%. Peak plasma concentrations are attained at 1.5 to 2 hours after oral administration. Concomitant food intake does not significantly influence the bioavailability of irbesartan.

Amlodipine

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6 and 12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%.

The bioavailability of amlodipine is not affected by food intake.

Distribution

Irbesartan

Plasma protein binding is approximately 96%, with negligible binding to cellular blood components. The volume of distribution is 53-93 L.

Amlodipine

The volume of distribution of amlodipine is approximately 21 L/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Metabolism

Irbesartan

Following oral or intravenous administration of ^{14}C irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged irbesartan. Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%). In vitro studies indicate that irbesartan is primarily oxidised by the cytochrome P450 enzyme CYP2C9; isoenzyme CYP3A4 has negligible effect. It is not metabolised by, nor does it substantially induce or inhibit most isoenzymes commonly associated with drug metabolism (i.e., CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, or CYP2E1). Irbesartan does not induce nor inhibit isoenzyme CYP3A4.

Irbesartan does not affect the pharmacokinetics of simvastatin (metabolised by CYP3A4) or digoxin (substrate of P-glycoprotein efflux transporter). The pharmacokinetic parameters of irbesartan are not affected by the co-administration with nifedipine or hydrochlorothiazide.

Amlodipine

Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Elimination

Irbesartan and amlodipine

When given separately or concomitantly at 300 mg and 10 mg, dose levels, the mean half-life values for irbesartan and amlodipine, given alone or in combination, are similar: 17.6 hours versus 17.7 hours for irbesartan, and 52.1 hours versus 58.5 hours for amlodipine. Elimination of irbesartan and amlodipine is comparable when the medicinal products are administered alone or concomitantly.

Irbesartan

Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or intravenous administration of ^{14}C irbesartan, about 20% of the radioactivity is recovered in urine, and the remainder in the faeces. Less than 2% of the dose is excreted in urine as unchanged irbesartan.

The total body and renal clearance are 157-176 mL/min and 3-3.5 mL/min, respectively. The terminal elimination half-life of irbesartan is 11-15 hours.

Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg.

A less than proportional increase in oral absorption at doses beyond 600 mg (twice the maximal recommended dose) was observed; the mechanism for this is unknown.

Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing

regimen. Limited accumulation of irbesartan (<20%) is observed in plasma upon repeated once-daily dosing.

Amlodipine

The terminal plasma elimination half-life is about 35–50 hours and is consistent with once-daily dosing.

Special populations

Ethnicity

Irbesartan

In normotensive black and white patients, the plasma AUC and $t_{1/2}$ of irbesartan are approximately 20-25% greater in the black ethnic group than in the white ethic group; the peak plasma concentrations (Cmax) of irbesartan are essentially equivalent.

Gender

Irbesartan

In a study, somewhat higher plasma concentrations of irbesartan were observed in female hypertensive patients. However, there was no difference in the half-life and accumulation of irbesartan. No dosage adjustment is necessary in female patients.

Elderly patients

Irbesartan

Irbesartan AUC and Cmax values were also somewhat greater in older subjects (≥65 years) than those of young subjects (18-40 years). However, the terminal half-life was not significantly altered. No dosage adjustment is necessary in older people.

Amlodipine

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients.

Paediatric population

Irbesartan

The pharmacokinetics of irbesartan were evaluated in 23 hypertensive children after the administration of single and multiple daily doses of irbesartan (2 mg/kg) up to a maximum daily dose of 150 mg for four weeks. Of those 23 children, 21 were evaluable for comparison of pharmacokinetics with adults (twelve children over 12 years, nine children between 6 and 12 years). Results showed that Cmax, AUC and clearance rates were comparable to those observed in adult patients receiving 150 mg irbesartan daily. A limited accumulation of irbesartan (18%) in plasma was observed upon repeated once-daily dosing.

Amlodipine

A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13 to 17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years are limited.

Hepatic impairment

Irbesartan

In patients with hepatic insufficiency due to mild to moderate cirrhosis, the pharmacokinetics of irbesartan is not significantly altered.

Amlodipine

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60% (see section 4.4).

Renal impairment

Irbesartan

In patients with renal impairment (regardless of degree) and in haemodialysis patients, the pharmacokinetics of irbesartan is not significantly altered. Irbesartan is not removed by haemodialysis.

Other

Amlodipine

Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

5.3. Preclinical safety data

Irbesartan and amlodipine

Repeated dose toxicity study in rats demonstrated that the combined administration of irbesartan and amlodipine neither augmented any of the previously reported and existing toxicities of the individual agents, nor induced any new toxicity, and no toxicologically synergistic effects were observed.

Irbesartan

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Repeated dose toxicology

Irbesartan caused changes in haematology (decreased haemoglobin, haematocrit and erythrocyte count) at doses equivalent or greater than 5 times the maximum recommended human dose of 300 mg*, and in blood chemistry (decreased total protein, increased urea, creatinine and potassium) at doses equivalent to 0.2 or 4 times the maximum recommended human dose of 300 mg*. In rats but not in macaques, irbesartan induced a dose-dependent increase in blood glucose at doses equivalent to 0.8-fold the maximum recommended human dose of 300 mg*. Irbesartan reduced heart weight in both species at doses equivalent to 2 times the maximum recommended human dose of 300 mg*.

Reproductive toxicology

At doses of 50 mg/kg/day (equivalent to the maximum recommended human dose of 300 mg*) and higher of irbesartan, transient effects (increased renal pelvic cavitation, hydroureter or subcutaneous oedema) were noted in rat foetuses, which were resolved after birth. In rabbits at doses of 30 mg/kg/day (1.6 times the maximum recommended human dose of 300 mg*), maternal mortality, abortion and early foetal resorption were noted. No teratogenic effects were observed in the rat or rabbit. Irbesartan is detected in rat and rabbit foetuses and it is excreted in the milk of lactating rats. Fertility and reproductive performance were not affected in studies of male and female rats even at oral doses of irbesartan causing some parental toxicity (up to 650 mg/kg/day equivalent to 17 times the maximum recommended human dose of 300 mg*).

Amlodipine

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

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*). In another rat study in which male rats were treated with amlodipine besylate 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.

* Based on patient weighing 50 kg.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Irbesartan/Amlodipine Besylate Impact 150 mg/5 mg film-coated tablet

Irbesartan/Amlodipine Besylate Impact 300 mg/10 mg film-coated tablet

Tablet core

Microcrystalline cellulose

Sodium croscarmellose

Hypromellose

Anhydrous colloidal silica

Magnesium stearate

Film-coating

Hypromellose

Macrogol

Titanium dioxide (E171)

Irbesartan/Amlodipine Besylate Impact 300 mg/5 mg film-coated tablet

Tablet core

Microcrystalline cellulose

Sodium croscarmellose

Hypromellose

Anhydrous colloidal silica

Magnesium stearate

Film-coating

Hypromellose

Macrogol

Titanium dioxide (E171)

Yellow iron oxide (E172)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Do not store above 30°C.

6.5. Nature and contents of container

White opaque (PVC/PE/PVDC/Aluminium) blister pack.

Pack sizes: 15, 28, 30, 90 and 98 film-coated tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

7. MANUFACTURER

Sanofi Ilac Sanayi ve Ticaret Anonim Sirketi
Küçükkarıştıran, Mahallesi Merkez Sok. No: 223/A
39780 Büyükkarıştıran Lüleburgaz Kırklareli
Turkey

8. DATE OF REVISION OF THE TEXT

July 2023