

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan Zentiva 75 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg of irbesartan.

Excipient with known effect: 25.50 mg of lactose monohydrate per film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2871 engraved on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Irbesartan Zentiva is indicated in adults for the treatment of essential hypertension.

It is also indicated for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen (see sections 4.3, 4.4, 4.5 and 5.1).

4.2 Posology and method of administration

Posology

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan Zentiva at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.

In patients insufficiently controlled with 150 mg once daily, the dose of Irbesartan Zentiva can be increased to 300 mg, or other antihypertensive agents can be added (see sections 4.3, 4.4, 4.5 and 5.1). In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect with Irbesartan Zentiva (see section 4.5).

In hypertensive type 2 diabetic patients, therapy should be initiated at 150 mg irbesartan once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease. The demonstration of renal benefit of Irbesartan Zentiva in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see sections 4.3, 4.4, 4.5 and 5.1).

Special Populations

Renal impairment

No dosage adjustment is necessary in patients with impaired renal function. A lower starting dose (75 mg) should be considered for patients undergoing haemodialysis (see section 4.4).

Hepatic impairment

No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment.

Older people

Although consideration should be given to initiating therapy with 75 mg in patients over 75 years of age, dosage adjustment is not usually necessary for older people.

Paediatric population

The safety and efficacy of Irbesartan Zentiva in children aged 0 to 18 has not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of Administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

The concomitant use of Irbesartan Zentiva with aliskiren-containing products 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

Intravascular volume depletion: symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Irbesartan Zentiva.

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 Zentiva, a similar effect should be anticipated with angiotensin-II receptor antagonists.

Renal impairment and kidney transplantation: when Irbesartan Zentiva is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Irbesartan Zentiva in patients with a recent kidney transplantation.

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 Zentiva, 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).

Hypoglycaemia: Irbesartan Zentiva may induce hypoglycaemia, particularly in diabetic patients. In patients treated with insulin or antidiabetics an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated (see section 4.5).

Intestinal angioedema: intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including irbesartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, irbesartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Lithium: the combination of lithium and Irbesartan Zentiva is not recommended (see section 4.5).

Aortic and mitral valve stenosis, obstructive hypertrophic 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 Zentiva is not recommended.

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 black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population (see section 5.1).

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).

Paediatric population: irbesartan has been studied in paediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available (see sections 4.8, 5.1 and 5.2).

Excipients:

Lactose: patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium: 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

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan Zentiva 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 Zentiva (see section 4.4).

Aliskiren-containing products and 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).

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: 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.

Repaglinide: irbesartan has the potential to inhibit OATP1B1. In a clinical study, it was reported that irbesartan increased the C_{max} and AUC of repaglinide (substrate of OATP1B1) by 1.8-fold and 1.3-fold, respectively, when administered 1 hour before repaglinide. In another study, no relevant pharmacokinetic interaction was reported, when the two drugs were co-administered. Therefore, dose adjustment of antidiabetic treatment such as repaglinide may be required (see section 4.4).

Additional information on irbesartan interactions: in clinical studies, the pharmacokinetic 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 coadministered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan

have not been evaluated. The pharmacokinetic of digoxin was not altered by coadministration of irbesartan.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 (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

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

It is unknown whether irbesartan or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk (for details see 5.3).

Fertility

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).

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties, irbesartan is unlikely to affect the ability to drive and use machines. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

4.8 Undesirable effects

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, race, 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 the adverse drug reactions that were 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 frequency of adverse reactions listed below is defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions additionally reported from post-marketing experience are also listed. These adverse reactions are derived from spontaneous reports.

Blood and lymphatic system disorders

Not known: anaemia, thrombocytopenia

Immune system disorders

Not known: hypersensitivity reactions such as angioedema, rash, urticaria, anaphylactic reaction, anaphylactic shock

Metabolism and nutrition disorders

Not known: hyperkalaemia, hypoglycaemia

Nervous system disorders

Common: dizziness, orthostatic dizziness*

Not known: vertigo, headache

Ear and labyrinth disorder

Not known: tinnitus

Cardiac disorders

Uncommon: tachycardia

Vascular disorders

Common: orthostatic hypotension*

Uncommon: flushing

Respiratory, thoracic and mediastinal disorders

Uncommon: cough

Gastrointestinal disorders

Common: nausea/vomiting

Uncommon: diarrhoea, dyspepsia/heartburn

Rare: intestinal angioedema

Not known: dysgeusia

Hepatobiliary disorders

Uncommon: jaundice

Not known: hepatitis, abnormal liver function

Skin and subcutaneous tissue disorders

Not known: leukocytoclastic vasculitis

Musculoskeletal and connective tissue disorders

Common: musculoskeletal pain*

Not known: arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps

Renal and urinary disorders

Not known: impaired renal function including cases of renal failure in patients at risk (see section 4.4)

Reproductive system and breast disorders

Uncommon: sexual dysfunction

General disorders and administration site conditions

Common: fatigue

Uncommon: chest pain

Investigations

Very common: Hyperkalaemia* occurred more often in diabetic patients treated with irbesartan than with placebo. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalaemia (≥ 5.5 mEq/L) occurred in 29.4% of the patients in the irbesartan 300 mg group and 22% of the patients in the placebo group. In diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria, hyperkalaemia (≥ 5.5 mEq/L) occurred in 46.3% of the patients in the irbesartan group and 26.3% of the patients in the placebo group.

Common: significant increases in plasma creatine kinase were commonly observed (1.7%) in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events.
In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed.

Paediatric population

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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. No specific information is available on the treatment of overdose with Irbesartan Zentiva. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin-II antagonists, plain, ATC code: C09C A04.

Mechanism of action

Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT₁) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT₁ receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT₁) 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 mm Hg (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 Zentiva 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 mm Hg (systolic/diastolic).

The efficacy of Irbesartan Zentiva 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 black patients 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-randomized 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 Zentiva, 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 Zentiva 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 Zentiva, 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 $\leq 135/85$ 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, race, age, duration of diabetes, baseline blood pressure, serum creatinine, and albumin excretion rate were assessed for treatment effect. In the female and black 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 hospitalization 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 Zentiva 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 $\leq 135/85$ 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 years period. Regression to normoalbuminuria (< 30 mg/day) was more frequent in the Irbesartan Zentiva 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.

5.2 Pharmacokinetic properties

Absorption

After oral administration, irbesartan is well absorbed: studies of absolute bioavailability gave values of approximately 60-80%. Concomitant food intake does not significantly influence the bioavailability of irbesartan.

Distribution

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

Biotransformation

Following oral or intravenous administration of ¹⁴C 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.

Linearity / non-linearity

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. Peak plasma concentrations are attained at 1.5 - 2 hours after oral administration. The total body and renal clearance are 157 - 176 and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11 - 15 hours. 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. 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. Irbesartan AUC and C_{max} 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.

Elimination

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

Paediatric population

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 C_{max} , 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.

Renal impairment

In patients with renal impairment or those undergoing haemodialysis, the pharmacokinetic parameters of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.

Hepatic impairment

In patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered.

Studies have not been performed in patients with severe hepatic impairment.

5.3 Preclinical safety data

In non-clinical safety studies, high doses of irbesartan caused a reduction of red blood cell parameters. At very high doses degenerative changes in the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced in the rat and the macaque and are considered secondary to the hypotensive effects of irbesartan which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. This finding was considered to be caused by the pharmacological action of irbesartan with little clinical relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Fertility and reproductive performance were not affected in studies of male and female rats. Animal studies with irbesartan showed transient toxic effects (increased renal pelvic cavitation, hydroureter or subcutaneous oedema) in rat foetuses, which were resolved after birth. In rabbits, abortion or early resorption were noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit. Studies in animals indicate that the radiolabelled irbesartan is detected in rat and rabbit foetuses. Irbesartan is excreted in the milk of lactating rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Hypromellose
Silicon dioxide
Magnesium stearate.

Film-coating:

Lactose monohydrate
Hypromellose
Titanium dioxide
Macrogol 3000
Carnauba wax.

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

Cartons of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 28 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 30 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 84 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 90 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 98 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 x 1 film-coated tablet in PVC/PVDC/Aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Zentiva k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

8. MARKETING AUTHORISATION NUMBERS

EU/1/06/376/016-021

EU/1/06/376/034-035

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 January 2007

Date of latest renewal: 20 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 <https://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan Zentiva 150 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of irbesartan.

Excipient with known effect: 51.00 mg of lactose monohydrate per film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2872 engraved on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Irbesartan Zentiva is indicated in adults for the treatment of essential hypertension.

It is also indicated for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen (see sections 4.3, 4.4, 4.5 and 5.1).

4.2 Posology and method of administration

Posology

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan Zentiva at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.

In patients insufficiently controlled with 150 mg once daily, the dose of Irbesartan Zentiva can be increased to 300 mg, or other antihypertensive agents can be added (see sections 4.3, 4.4, 4.5 and 5.1). In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect with Irbesartan Zentiva (see section 4.5).

In hypertensive type 2 diabetic patients, therapy should be initiated at 150 mg irbesartan once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease. The demonstration of renal benefit of Irbesartan Zentiva in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see sections 4.3, 4.4, 4.5 and 5.1).

Special Populations

Renal impairment

No dosage adjustment is necessary in patients with impaired renal function. A lower starting dose (75 mg) should be considered for patients undergoing haemodialysis (see section 4.4).

Hepatic impairment

No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment.

Older people

Although consideration should be given to initiating therapy with 75 mg in patients over 75 years of age, dosage adjustment is not usually necessary for older people.

Paediatric population

The safety and efficacy of Irbesartan Zentiva in children aged 0 to 18 has not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of Administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

The concomitant use of Irbesartan Zentiva with aliskiren-containing products 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

Intravascular volume depletion: symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Irbesartan Zentiva.

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 Zentiva, a similar effect should be anticipated with angiotensin-II receptor antagonists.

Renal impairment and kidney transplantation: when Irbesartan Zentiva is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Irbesartan Zentiva in patients with a recent kidney transplantation.

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 Zentiva, 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).

Hypoglycaemia: Irbesartan Zentiva may induce hypoglycaemia, particularly in diabetic patients. In patients treated with insulin or antidiabetics an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated (see section 4.5).

Intestinal angioedema: intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including irbesartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, irbesartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Lithium: the combination of lithium and Irbesartan Zentiva is not recommended (see section 4.5).

Aortic and mitral valve stenosis, obstructive hypertrophic 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 Zentiva is not recommended.

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 black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population (see section 5.1).

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).

Paediatric population: irbesartan has been studied in paediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available (see sections 4.8, 5.1 and 5.2).

Excipients:

Lactose: patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium: 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

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan Zentiva 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 Zentiva (see section 4.4).

Aliskiren-containing products and 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).

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: 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.

Repaglinide: irbesartan has the potential to inhibit OATP1B1. In a clinical study, it was reported that irbesartan increased the C_{max} and AUC of repaglinide (substrate of OATP1B1) by 1.8-fold and 1.3-fold, respectively, when administered 1 hour before repaglinide. In another study, no relevant pharmacokinetic interaction was reported, when the two drugs were co-administered. Therefore, dose adjustment of antidiabetic treatment such as repaglinide may be required (see section 4.4).

Additional information on irbesartan interactions: in clinical studies, the pharmacokinetic 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 coadministered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan

have not been evaluated. The pharmacokinetic of digoxin was not altered by coadministration of irbesartan.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 (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

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

It is unknown whether irbesartan or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of irbesartan or its metabolites in milk (for details see 5.3).

Fertility

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).

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties, irbesartan is unlikely to affect the ability to drive and use machines. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

4.8 Undesirable effects

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, race, 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 the adverse drug reactions that were 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 frequency of adverse reactions listed below is defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions additionally reported from post-marketing experience are also listed. These adverse reactions are derived from spontaneous reports.

Blood and lymphatic system disorders

Not known: anaemia, thrombocytopenia

Immune system disorders

Not known: hypersensitivity reactions such as angioedema, rash, urticaria, anaphylactic reaction, anaphylactic shock

Metabolism and nutrition disorders

Not known: hyperkalaemia, hypoglycaemia

Nervous system disorders

Common: dizziness, orthostatic dizziness*

Not known: vertigo, headache

Ear and labyrinth disorder

Not known: tinnitus

Cardiac disorders

Uncommon: tachycardia

Vascular disorders

Common: orthostatic hypotension*

Uncommon: flushing

Respiratory, thoracic and mediastinal disorders

Uncommon: cough

Gastrointestinal disorders

Common: nausea/vomiting

Uncommon: diarrhoea, dyspepsia/heartburn

Rare: intestinal angioedema

Not known: dysgeusia

Hepatobiliary disorders

Uncommon: jaundice

Not known: hepatitis, abnormal liver function

Skin and subcutaneous tissue disorders

Not known: leukocytoclastic vasculitis

Musculoskeletal and connective tissue disorders

Common: musculoskeletal pain*

Not known: arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps

Renal and urinary disorders

Not known: impaired renal function including cases of renal failure in patients at risk (see section 4.4)

Reproductive system and breast disorders

Uncommon: sexual dysfunction

General disorders and administration site conditions

Common: fatigue

Uncommon: chest pain

Investigations

Very common: Hyperkalaemia* occurred more often in diabetic patients treated with irbesartan than with placebo. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalaemia (≥ 5.5 mEq/L) occurred in 29.4% of the patients in the irbesartan 300 mg group and 22% of the patients in the placebo group. In diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria, hyperkalaemia (≥ 5.5 mEq/L) occurred in 46.3% of the patients in the irbesartan group and 26.3% of the patients in the placebo group.

Common: significant increases in plasma creatine kinase were commonly observed (1.7%) in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events.
In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed.

Paediatric population

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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. No specific information is available on the treatment of overdose with Irbesartan Zentiva. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin-II antagonists, plain, ATC code: C09C A04.

Mechanism of action

Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT₁) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT₁ receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT₁) 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 mm Hg (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 Zentiva 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 mm Hg (systolic/diastolic).

The efficacy of Irbesartan Zentiva 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 black patients 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-randomized

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 Zentiva, 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 Zentiva 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 Zentiva, 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 $\leq 135/85$ 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, race, age, duration of diabetes, baseline blood pressure, serum creatinine, and albumin excretion rate were assessed for treatment effect. In the female and black 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 hospitalization 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 Zentiva 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 $\leq 135/85$ 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 years period. Regression to normoalbuminuria (< 30 mg/day) was more frequent in the Irbesartan Zentiva 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.

5.2 Pharmacokinetic properties

Absorption

After oral administration, irbesartan is well absorbed: studies of absolute bioavailability gave values of approximately 60-80%. Concomitant food intake does not significantly influence the bioavailability of irbesartan.

Distribution

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

Biotransformation

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.

Linearity / non-linearity

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. Peak plasma concentrations are attained at 1.5 - 2 hours after oral administration. The total body and renal clearance are 157 - 176 and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11 - 15 hours. 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. 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. Irbesartan AUC and C_{max} 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.

Elimination

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

Paediatric population

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 C_{max} , 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.

Renal impairment

In patients with renal impairment or those undergoing haemodialysis, the pharmacokinetic parameters of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.

Hepatic impairment

In patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered.

Studies have not been performed in patients with severe hepatic impairment.

5.3 Preclinical safety data

In non-clinical safety studies, high doses of irbesartan caused a reduction of red blood cell parameters. At very high doses degenerative changes in the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced in the rat and the macaque and are considered secondary to the hypotensive effects of irbesartan which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. This finding was considered to be caused by the pharmacological action of irbesartan with little clinical relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Fertility and reproductive performance were not affected in studies of male and female rats. Animal studies with irbesartan showed transient toxic effects (increased renal pelvic cavitation, hydroureter or subcutaneous oedema) in rat foetuses, which were resolved after birth. In rabbits, abortion or early resorption were noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit. Studies in animals indicate that the radiolabelled irbesartan is detected in rat and rabbit foetuses. Irbesartan is excreted in the milk of lactating rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Hypromellose
Silicon dioxide
Magnesium stearate.

Film-coating:

Lactose monohydrate
Hypromellose
Titanium dioxide
Macrogol 3000
Carnauba wax.

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

Cartons of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 28 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 30 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 84 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 90 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 98 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 x 1 film-coated tablet in PVC/PVDC/Aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Zentiva k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

8. MARKETING AUTHORISATION NUMBERS

EU/1/06/376/022-027

EU/1/06/376/036-037

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 January 2007

Date of latest renewal: 20 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 <https://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan Zentiva 300 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of irbesartan.

Excipient with known effect: 102.00 mg of lactose monohydrate per film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2873 engraved on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Irbesartan Zentiva is indicated in adults for the treatment of essential hypertension.

It is also indicated for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen (see sections 4.3, 4.4, 4.5 and 5.1).

4.2 Posology and method of administration

Posology

The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Irbesartan Zentiva at a dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.

In patients insufficiently controlled with 150 mg once daily, the dose of Irbesartan Zentiva can be increased to 300 mg, or other antihypertensive agents can be added (see sections 4.3, 4.4, 4.5 and 5.1). In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect with Irbesartan Zentiva (see section 4.5).

In hypertensive type 2 diabetic patients, therapy should be initiated at 150 mg irbesartan once daily and titrated up to 300 mg once daily as the preferred maintenance dose for treatment of renal disease. The demonstration of renal benefit of Irbesartan Zentiva in hypertensive type 2 diabetic patients is based on studies where irbesartan was used in addition to other antihypertensive agents, as needed, to reach target blood pressure (see sections 4.3, 4.4, 4.5 and 5.1).

Special Populations

Renal impairment

No dosage adjustment is necessary in patients with impaired renal function. A lower starting dose (75 mg) should be considered for patients undergoing haemodialysis (see section 4.4).

Hepatic impairment

No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment.

Older people

Although consideration should be given to initiating therapy with 75 mg in patients over 75 years of age, dosage adjustment is not usually necessary for older people.

Paediatric population

The safety and efficacy of Irbesartan Zentiva in children aged 0 to 18 has not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of Administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

The concomitant use of Irbesartan Zentiva with aliskiren-containing products 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

Intravascular volume depletion: symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Irbesartan Zentiva.

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 Zentiva, a similar effect should be anticipated with angiotensin-II receptor antagonists.

Renal impairment and kidney transplantation: when Irbesartan Zentiva is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Irbesartan Zentiva in patients with a recent kidney transplantation.

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 Zentiva, 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).

Hypoglycaemia: Irbesartan Zentiva may induce hypoglycaemia, particularly in diabetic patients. In patients treated with insulin or antidiabetics an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated (see section 4.5).

Intestinal angioedema: intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including irbesartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, irbesartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Lithium: the combination of lithium and Irbesartan Zentiva is not recommended (see section 4.5).

Aortic and mitral valve stenosis, obstructive hypertrophic 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 Zentiva is not recommended.

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 black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population (see section 5.1).

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).

Paediatric population: irbesartan has been studied in paediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available (see sections 4.8, 5.1 and 5.2).

Excipients:

Lactose: patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium: 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

Diuretics and other antihypertensive agents: other antihypertensive agents may increase the hypotensive effects of irbesartan; however Irbesartan Zentiva 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 Zentiva (see section 4.4).

Aliskiren-containing products and 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).

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: 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.

Repaglinide: irbesartan has the potential to inhibit OATP1B1. In a clinical study, it was reported that irbesartan increased the C_{max} and AUC of repaglinide (substrate of OATP1B1) by 1.8-fold and 1.3-fold, respectively, when administered 1 hour before repaglinide. In another study, no relevant pharmacokinetic interaction was reported, when the two drugs were co-administered. Therefore, dose adjustment of antidiabetic treatment such as repaglinide may be required (see section 4.4).

Additional information on irbesartan interactions: in clinical studies, the pharmacokinetic 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 coadministered with warfarin, a medicinal product metabolised by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of irbesartan

have not been evaluated. The pharmacokinetic of digoxin was not altered by coadministration of irbesartan.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 (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

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

It is unknown whether irbesartan or its metabolites are excreted in human milk.

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

Fertility

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).

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties, irbesartan is unlikely to affect the ability to drive and use machines. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

4.8 Undesirable effects

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, race, 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 the adverse drug reactions that were 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 frequency of adverse reactions listed below is defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions additionally reported from post-marketing experience are also listed. These adverse reactions are derived from spontaneous reports.

Blood and lymphatic system disorders

Not known: anaemia, thrombocytopenia

Immune system disorders

Not known: hypersensitivity reactions such as angioedema, rash, urticaria, anaphylactic reaction, anaphylactic shock

Metabolism and nutrition disorders

Not known: hyperkalaemia, hypoglycaemia

Nervous system disorders

Common: dizziness, orthostatic dizziness*

Not known: vertigo, headache

Ear and labyrinth disorder

Not known: tinnitus

Cardiac disorders

Uncommon: tachycardia

Vascular disorders

Common: orthostatic hypotension*

Uncommon: flushing

Respiratory, thoracic and mediastinal disorders

Uncommon: cough

Gastrointestinal disorders

Common: nausea/vomiting

Uncommon: diarrhoea, dyspepsia/heartburn

Rare: intestinal angioedema

Not known: dysgeusia

Hepatobiliary disorders

Uncommon: jaundice

Not known: hepatitis, abnormal liver function

Skin and subcutaneous tissue disorders

Not known: leukocytoclastic vasculitis

Musculoskeletal and connective tissue disorders

Common: musculoskeletal pain*

Not known: arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramps

Renal and urinary disorders

Not known: impaired renal function including cases of renal failure in patients at risk (see section 4.4)

Reproductive system and breast disorders

Uncommon: sexual dysfunction

General disorders and administration site conditions

Common: fatigue

Uncommon: chest pain

Investigations

Very common: Hyperkalaemia* occurred more often in diabetic patients treated with irbesartan than with placebo. In diabetic hypertensive patients with microalbuminuria and normal renal function, hyperkalaemia (≥ 5.5 mEq/L) occurred in 29.4% of the patients in the irbesartan 300 mg group and 22% of the patients in the placebo group. In diabetic hypertensive patients with chronic renal insufficiency and overt proteinuria, hyperkalaemia (≥ 5.5 mEq/L) occurred in 46.3% of the patients in the irbesartan group and 26.3% of the patients in the placebo group.

Common: significant increases in plasma creatine kinase were commonly observed (1.7%) in irbesartan treated subjects. None of these increases were associated with identifiable clinical musculoskeletal events.
In 1.7% of hypertensive patients with advanced diabetic renal disease treated with irbesartan, a decrease in haemoglobin*, which was not clinically significant, has been observed.

Paediatric population

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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Experience in adults exposed to doses of up to 900 mg/day for 8 weeks revealed no toxicity. The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. No specific information is available on the treatment of overdose with Irbesartan Zentiva. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin-II antagonists, plain, ATC code: C09C A04.

Mechanism of action

Irbesartan is a potent, orally active, selective angiotensin-II receptor (type AT₁) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT₁ receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT₁) 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 mm Hg (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 Zentiva 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 mm Hg (systolic/diastolic).

The efficacy of Irbesartan Zentiva 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 black patients 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-randomized 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 Zentiva, 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 Zentiva 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 Zentiva, 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 $\leq 135/85$ 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, race, age, duration of diabetes, baseline blood pressure, serum creatinine, and albumin excretion rate were assessed for treatment effect. In the female and black 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 hospitalization 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 Zentiva 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 $\leq 135/85$ 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 years period. Regression to normoalbuminuria (< 30 mg/day) was more frequent in the Irbesartan Zentiva 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.

5.2 Pharmacokinetic properties

Absorption

After oral administration, irbesartan is well absorbed: studies of absolute bioavailability gave values of approximately 60-80%. Concomitant food intake does not significantly influence the bioavailability of irbesartan.

Distribution

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

Biotransformation

Following oral or intravenous administration of ¹⁴C 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.

Linearity / non-linearity

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. Peak plasma concentrations are attained at 1.5 - 2 hours after oral administration. The total body and renal clearance are 157 - 176 and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of irbesartan is 11 - 15 hours. 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. 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. Irbesartan AUC and C_{max} 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.

Elimination

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

Paediatric population

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 C_{max} , 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.

Renal impairment

In patients with renal impairment or those undergoing haemodialysis, the pharmacokinetic parameters of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis.

Hepatic impairment

In patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan are not significantly altered.

Studies have not been performed in patients with severe hepatic impairment.

5.3 Preclinical safety data

In non-clinical safety studies, high doses of irbesartan caused a reduction of red blood cell parameters. At very high doses degenerative changes in the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules, increased plasma concentrations of urea and creatinine) were induced in the rat and the macaque and are considered secondary to the hypotensive effects of irbesartan which led to decreased renal perfusion. Furthermore, irbesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. This finding was considered to be caused by the pharmacological action of irbesartan with little clinical relevance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Fertility and reproductive performance were not affected in studies of male and female rats. Animal studies with irbesartan showed transient toxic effects (increased renal pelvic cavitation, hydroureter or subcutaneous oedema) in rat fetuses, which were resolved after birth. In rabbits, abortion or early resorption were noted at doses causing significant maternal toxicity, including mortality. No teratogenic effects were observed in the rat or rabbit. Studies in animals indicate that the radiolabelled irbesartan is detected in rat and rabbit fetuses. Irbesartan is excreted in the milk of lactating rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Hypromellose
Silicon dioxide
Magnesium stearate.

Film-coating:

Lactose monohydrate
Hypromellose
Titanium dioxide
Macrogol 3000
Carnauba wax.

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

Cartons of 14 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 28 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 30 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 84 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 90 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 98 film-coated tablets in PVC/PVDC/Aluminium blisters.
Cartons of 56 x 1 film-coated tablet in PVC/PVDC/Aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Zentiva k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

8. MARKETING AUTHORISATION NUMBERS

EU/1/06/376/028-033

EU/1/06/376/038-039

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 January 2007

Date of latest renewal: 20 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 <https://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURERS 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Sanofi Winthrop Industrie
1 Rue de la vierge
Ambarès et Lagrave
33 565 Carbon Blanc cedex
France

Sanofi Winthrop Industrie
30-36 Avenue Gustave Eiffel
37 100 Tours
France

Zentiva, k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

Sanofi-Aventis, S.A.
Ctra. C-35 (La Batlloria-Hostalric), km. 63.09
17404 Riells i Viabrea (Girona)
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

• Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan Zentiva 75 mg film-coated tablets
irbesartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: irbesartan 75 mg

3. LIST OF EXCIPIENTS

Excipients: also contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 tablets
28 tablets
30 tablets
56 tablets
56 x 1 tablets
84 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before 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.

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**

Zentiva k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/376/016 - 14 tablets
EU/1/06/376/017 - 28 tablets
EU/1/06/376/034 - 30 tablets
EU/1/06/376/018 - 56 tablets
EU/1/06/376/019 - 56 x 1 tablets
EU/1/06/376/020 - 84 tablets
EU/1/06/376/035 - 90 tablets
EU/1/06/376/021 - 98 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Irbesartan Zentiva 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan Zentiva 75 mg tablets
irbesartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Zentiva k.s.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

14 - 28 - 56 - 84 - 98 tablets:

Mon
Tue
Wed
Thu
Fri
Sat
Sun

30 - 56 x 1 - 90 tablets:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan Zentiva 150 mg film-coated tablets
irbesartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: irbesartan 150 mg

3. LIST OF EXCIPIENTS

Excipients: also contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 tablets
28 tablets
30 tablets
56 tablets
56 x 1 tablets
84 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before 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.

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**

Zentiva k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/376/022 - 14 tablets
EU/1/06/376/023 - 28 tablets
EU/1/06/376/036 - 30 tablets
EU/1/06/376/024 - 56 tablets
EU/1/06/376/025 - 56 x 1 tablets
EU/1/06/376/026 - 84 tablets
EU/1/06/376/037 - 90 tablets
EU/1/06/376/027 - 98 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Irbesartan Zentiva 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan Zentiva 150 mg tablets
irbesartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Zentiva k.s.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

14 - 28 - 56 - 84 - 98 tablets:

Mon

Tue

Wed

Thu

Fri

Sat

Sun

30 - 56 x 1 - 90 tablets:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Irbesartan Zentiva 300 mg film-coated tablets
irbesartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains: irbesartan 300 mg

3. LIST OF EXCIPIENTS

Excipients: also contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 tablets
28 tablets
30 tablets
56 tablets
56 x 1 tablets
84 tablets
90 tablets
98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before 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.

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**

Zentiva k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/376/028 - 14 tablets
EU/1/06/376/029 - 28 tablets
EU/1/06/376/038 - 30 tablets
EU/1/06/376/030 - 56 tablets
EU/1/06/376/031 - 56 x 1 tablets
EU/1/06/376/032 - 84 tablets
EU/1/06/376/039 - 90 tablets
EU/1/06/376/033 - 98 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Irbesartan Zentiva 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

1. NAME OF THE MEDICINAL PRODUCT

Irbesartan Zentiva 300 mg tablets
irbesartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Zentiva k.s.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

14 - 28 - 56 - 84 - 98 tablets:

Mon

Tue

Wed

Thu

Fri

Sat

Sun

30 - 56 x 1 - 90 tablets:

B. PACKAGE LEAFLET

Package leaflet: Information for the user
Irbesartan Zentiva 75 mg film-coated tablets
irbesartan

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. See section 4.

What is in this leaflet

1. What Irbesartan Zentiva is and what it is used for
2. What you need to know before you take Irbesartan Zentiva
3. How to take Irbesartan Zentiva
4. Possible side effects
5. How to store Irbesartan Zentiva
6. Contents of the pack and other information

1. What Irbesartan Zentiva is and what it is used for

Irbesartan Zentiva belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body which binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan Zentiva prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower. Irbesartan Zentiva slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes.

Irbesartan Zentiva is used in adult patients

- to treat high blood pressure (*essential hypertension*)
- to protect the kidney in patients with high blood pressure, type 2 diabetes and laboratory evidence of impaired kidney function.

2. What you need to know before you take Irbesartan Zentiva

Do not take Irbesartan Zentiva

- if you are **allergic** to irbesartan or any other ingredients of this medicine (listed in section 6)
- if you are **more than 3 months pregnant**. (It is also better to avoid Irbesartan Zentiva in early pregnancy – see pregnancy section)
- **if you have diabetes or impaired kidney function** and you are treated with a blood pressure lowering medicine containing aliskiren.

Warnings and precautions

Talk to your doctor before taking Irbesartan Zentiva and **if any of the following apply to you:**

- if you get **excessive vomiting or diarrhoea**
- if you suffer from **kidney problems**
- if you suffer from **heart problems**
- if you receive Irbesartan Zentiva for **diabetic kidney disease**. In this case your doctor may perform regular blood tests, especially for measuring blood potassium levels in case of poor kidney function
- if you develop **low blood sugar levels** (symptoms may include sweating, weakness, hunger, dizziness, trembling, headache, flushing or paleness, numbness, having a fast, pounding heartbeat), particularly if you are being treated for diabetes.

- if you are **going to have an operation** (surgery) or **be given anaesthetics**
- 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 Irbesartan Zentiva”.

Talk to your doctor if you experience abdominal pain, nausea, vomiting or diarrhoea after taking Irbesartan Zentiva. Your doctor will decide on further treatment. Do not stop taking Irbesartan Zentiva on your own.

You must tell your doctor if you think you are (or might become) pregnant. Irbesartan Zentiva is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

Children and adolescents

This medicinal product should not be used in children and adolescents because the safety and efficacy have not yet been fully established.

Other medicines and Irbesartan Zentiva

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:

If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not take Irbesartan Zentiva” and “Warnings and precautions”).

You may need to have blood checks if you take:

- potassium supplements
- salt substitutes containing potassium
- potassium-sparing medicines (such as certain diuretics)
- medicines containing lithium
- repaglinide (medication used for lowering blood sugar levels)

If you take certain painkillers, called non-steroidal anti-inflammatory drugs, the effect of irbesartan may be reduced.

Irbesartan Zentiva with food and drink

Irbesartan Zentiva can be taken with or without food.

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 Irbesartan Zentiva before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Irbesartan Zentiva. Irbesartan Zentiva is not recommended in early pregnancy, 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. Irbesartan Zentiva 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.

Driving and using machines

Irbesartan Zentiva is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

Irbesartan Zentiva contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Irbesartan Zentiva contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Irbesartan Zentiva

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Method of administration

Irbesartan Zentiva is for **oral use**. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan Zentiva with or without food. Try to take your daily dose at about the same time each day. It is important that you continue to take Irbesartan Zentiva until your doctor tells you otherwise.

- **Patients with high blood pressure**

The usual dose is 150 mg once a day (two tablets a day). The dose may later be increased to 300 mg (four tablets a day) once daily depending on blood pressure response.

- **Patients with high blood pressure and type 2 diabetes with kidney disease**

In patients with high blood pressure and type 2 diabetes, 300 mg (four tablets a day) once daily is the preferred maintenance dose for the treatment of associated kidney disease.

The doctor may advise a lower dose, especially when starting treatment in certain patients such as those on **haemodialysis**, or those **over the age of 75 years**.

The maximal blood pressure lowering effect should be reached 4-6 weeks after beginning treatment.

Use in children and adolescents

Irbesartan Zentiva should not be given to children under 18 years of age. If a child swallows some tablets, contact your doctor immediately.

If you take more Irbesartan Zentiva than you should:

If you accidentally take too many tablets, contact your doctor immediately.

If you forget to take Irbesartan Zentiva:

If you accidentally miss a daily dose, just take the next dose as normal. Do not take a double dose to make up for a forgotten dose.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these effects may be serious and may require medical attention.

As with similar medicines, rare cases of allergic skin reactions (rash, urticaria), as well as localised swelling of the face, lips and/or tongue have been reported in patients taking irbesartan. If you get any

of these symptoms or get short of breath, **stop taking Irbesartan Zentiva and contact your doctor immediately.**

The frequency of the side effects listed below is defined using the following convention:

Very common: may affect more than 1 in 10 people

Common: may affect up to 1 in 10 people

Uncommon: may affect up to 1 in 100 people

Rare: may affect up to 1 in 1,000 people

Side effects reported in clinical studies for patients treated with Irbesartan Zentiva were:

- Very common (may affect more than 1 in 10 people): if you suffer from high blood pressure and type 2 diabetes with kidney disease, blood tests may show an increased level of potassium.
- Common (may affect up to 1 in 10 people): dizziness, feeling sick/vomiting, fatigue and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatinine kinase enzyme). In patients with high blood pressure and type 2 diabetes with kidney disease, dizziness when getting up from a lying or sitting position, low blood pressure when getting up from a lying or sitting position, pain in joints or muscles and decreased levels of a protein in the red blood cells (haemoglobin) were also reported.
- Uncommon (may affect up to 1 in 100 people): heart rate increased, flushing, cough, diarrhoea, indigestion/heartburn, sexual dysfunction (problems with sexual performance), chest pain.
- Rare (may affect up to 1 in 1,000 people): intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea.

Some undesirable effects have been reported since marketing of Irbesartan Zentiva. Undesirable effects where the frequency is not known are: feeling of spinning, headache, taste disturbance, ringing in the ears, muscle cramps, pain in joints and muscles, decreased number of red blood cells (anaemia – symptoms may include tiredness, headaches, being short of breath when exercising, dizziness and looking pale), reduced number of platelets, abnormal liver function, increased blood potassium levels, impaired kidney function, inflammation of small blood vessels mainly affecting the skin (a condition known as leukocytoclastic vasculitis), severe allergic reactions (anaphylactic shock) and low blood sugar levels. Uncommon cases of jaundice (yellowing of the skin and/or whites of the eyes) have also been reported.

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 Irbesartan Zentiva

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 on the blister after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Irbesartan Zentiva contains

- The active substance is irbesartan. Each tablet of Irbesartan Zentiva 75 mg contains 75 mg irbesartan.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, silicon dioxide, magnesium stearate, titanium dioxide, macrogol 3000, carnauba wax. Please see section 2 “Irbesartan Zentiva contains lactose”.

What Irbesartan Zentiva looks like and contents of the pack

Irbesartan Zentiva 75 mg film-coated tablets are white to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2871 engraved on the other side.

Irbesartan Zentiva 75 mg film-coated tablets are supplied in blister packs of 14, 28, 30, 56, 84, 90 or 98 film-coated tablets. Unidose blister packs of 56 x 1 film-coated tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Zentiva k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

Manufacturer:

Sanofi Winthrop Industrie
1 Rue de la vierge
Ambarès et Lagrave
33 565 Carbon Blanc cedex
France

Sanofi Winthrop Industrie
30-36 Avenue Gustave Eiffel
37 100 Tours
France

Zentiva, k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien

Zentiva, k.s.
Tél/Tel: +32 (78) 700 112
PV-Belgium@zentiva.com

Lietuva

Zentiva, k.s.
Tel: +370 52152025
PV-Lithuania@zentiva.com

България

Zentiva, k.s.
Тел: +35924417136
PV-Bulgaria@zentiva.com

Luxembourg/Luxemburg

Zentiva, k.s.
Tél/Tel: +352 208 82330
PV-Luxembourg@zentiva.com

Česká republika

Zentiva, k.s.
Tel: +420 267 241 111
PV-Czech-Republic@zentiva.com

Danmark

Zentiva Denmark ApS
Tlf: +45 787 68 400
PV-Denmark@zentiva.com

Deutschland

Zentiva Pharma GmbH
Tel: +49 (0) 800 53 53 010
PV-Germany@zentiva.com

Eesti

Zentiva, k.s.
Tel: +372 52 70308
PV-Estonia@zentiva.com

Ελλάδα

Zentiva, k.s.
Τηλ: +30 211 198 7510
PV-Greece@zentiva.com

España

Zentiva Spain S.L.U.
Tel: +34 671 365 828
PV-Spain@zentiva.com

France

Zentiva France
Tél: +33 (0) 800 089 219
PV-France@zentiva.com

Hrvatska

Zentiva d.o.o.
Tel: +385 1 6641 830
PV-Croatia@zentiva.com

Ireland

Zentiva, k.s.
Tel: +353 818 882 243
PV-Ireland@zentiva.com

Ísland

Zentiva Denmark ApS
Sími: +354 539 5025
PV-Iceland@zentiva.com

Italia

Zentiva Italia S.r.l.
Tel: +39 800081631
PV-Italy@zentiva.com

Magyarország

Zentiva Pharma Kft.
Tel.: +36 1 299 1058
PV-Hungary@zentiva.com

Malta

Zentiva, k.s.
Tel: +356 2034 1796
PV-Malta@zentiva.com

Nederland

Zentiva, k.s.
Tel: +31 202 253 638
PV-Netherlands@zentiva.com

Norge

Zentiva Denmark ApS
Tlf: +45 787 68 400
PV-Norway@zentiva.com

Österreich

Zentiva, k.s.
Tel: +43 720 778 877
PV-Austria@zentiva.com

Polska

Zentiva Polska Sp. z o.o.
Tel: + 48 22 375 92 00
PV-Poland@zentiva.com

Portugal

Zentiva Portugal, Lda
Tel: +351210601360
PV-Portugal@zentiva.com

România

ZENTIVA S.A.
Tel: +4 021 304 7597
PV-Romania@zentiva.com

Slovenija

Zentiva, k.s.
Tel: +386 360 00 408
PV-Slovenia@zentiva.com

Slovenská republika

Zentiva, a.s.
Tel: +421 2 3918 3010
PV-Slovakia@zentiva.com

Suomi/Finland

Zentiva Denmark ApS
Puh/Tel: +358 942 598 648
PV-Finland@zentiva.com

Κύπρος

Zentiva, k.s.

Τηλ: +30 211 198 7510

PV-Cyprus@zentiva.com

Sverige

Zentiva Denmark ApS

Tel: +46 840 838 822

PV-Sweden@zentiva.com

Latvija

Zentiva, k.s.

Tel: +371 67893939

PV-Latvia@zentiva.com

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:

<https://www.ema.europa.eu/>

Package leaflet: Information for the user
Irbesartan Zentiva 150 mg film-coated tablets
irbesartan

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. See section 4.

What is in this leaflet

1. What Irbesartan Zentiva is and what it is used for
2. What you need to know before you take Irbesartan Zentiva
3. How to take Irbesartan Zentiva
4. Possible side effects
5. How to store Irbesartan Zentiva
6. Contents of the pack and other information

1. What Irbesartan Zentiva is and what it is used for

Irbesartan Zentiva belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body which binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan Zentiva prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower. Irbesartan Zentiva slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes.

Irbesartan Zentiva is used in adult patients

- to treat high blood pressure (*essential hypertension*)
- to protect the kidney in patients with high blood pressure, type 2 diabetes and laboratory evidence of impaired kidney function.

2. What you need to know before you take Irbesartan Zentiva

Do not take Irbesartan Zentiva

- if you are **allergic** to irbesartan or any other ingredients of this medicine (listed in section 6)
- if you are **more than 3 months pregnant**. (It is also better to avoid Irbesartan Zentiva in early pregnancy – see pregnancy section)
- **if you have diabetes or impaired kidney function** and you are treated with a blood pressure lowering medicine containing aliskiren.

Warnings and precautions

Talk to your doctor before taking Irbesartan Zentiva and **if any of the following apply to you:**

- if you get **excessive vomiting or diarrhoea**
- if you suffer from **kidney problems**
- if you suffer from **heart problems**
- if you receive Irbesartan Zentiva for **diabetic kidney disease**. In this case your doctor may perform regular blood tests, especially for measuring blood potassium levels in case of poor kidney function
- if you develop **low blood sugar levels** (symptoms may include sweating, weakness, hunger, dizziness, trembling, headache, flushing or paleness, numbness, having a fast, pounding heartbeat), particularly if you are being treated for diabetes.

- if you are **going to have an operation** (surgery) or **be given anaesthetics**
- 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 Irbesartan Zentiva”.

Talk to your doctor if you experience abdominal pain, nausea, vomiting or diarrhoea after taking Irbesartan Zentiva. Your doctor will decide on further treatment. Do not stop taking Irbesartan Zentiva on your own.

You must tell your doctor if you think you are (or might become) pregnant. Irbesartan Zentiva is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

Children and adolescents

This medicinal product should not be used in children and adolescents because the safety and efficacy have not yet been fully established.

Other medicines and Irbesartan Zentiva

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:

If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not take Irbesartan Zentiva” and “Warnings and precautions”).

You may need to have blood checks if you take:

- potassium supplements
- salt substitutes containing potassium
- potassium-sparing medicines (such as certain diuretics)
- medicines containing lithium
- repaglinide (medication used for lowering blood sugar levels)

If you take certain painkillers, called non-steroidal anti-inflammatory drugs, the effect of irbesartan may be reduced.

Irbesartan Zentiva with food and drink

Irbesartan Zentiva can be taken with or without food.

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 Irbesartan Zentiva before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Irbesartan Zentiva. Irbesartan Zentiva is not recommended in early pregnancy, 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. Irbesartan Zentiva 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.

Driving and using machines

Irbesartan Zentiva is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

Irbesartan Zentiva contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Irbesartan Zentiva contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Irbesartan Zentiva

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Method of administration

Irbesartan Zentiva is for **oral use**. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan Zentiva with or without food. Try to take your daily dose at about the same time each day. It is important that you continue to take Irbesartan Zentiva until your doctor tells you otherwise.

- **Patients with high blood pressure**

The usual dose is 150 mg once a day. The dose may later be increased to 300 mg (two tablets a day) once daily depending on blood pressure response.

- **Patients with high blood pressure and type 2 diabetes with kidney disease**

In patients with high blood pressure and type 2 diabetes, 300 mg (two tablets a day) once daily is the preferred maintenance dose for the treatment of associated kidney disease.

The doctor may advise a lower dose, especially when starting treatment in certain patients such as those on **haemodialysis**, or those **over the age of 75 years**.

The maximal blood pressure lowering effect should be reached 4-6 weeks after beginning treatment.

Use in children and adolescents

Irbesartan Zentiva should not be given to children under 18 years of age. If a child swallows some tablets, contact your doctor immediately.

If you take more Irbesartan Zentiva than you should:

If you accidentally take too many tablets, contact your doctor immediately.

If you forget to take Irbesartan Zentiva:

If you accidentally miss a daily dose, just take the next dose as normal. Do not take a double dose to make up for a forgotten dose.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these effects may be serious and may require medical attention.

As with similar medicines, rare cases of allergic skin reactions (rash, urticaria), as well as localised swelling of the face, lips and/or tongue have been reported in patients taking irbesartan. If you get any

of these symptoms or get short of breath, **stop taking Irbesartan Zentiva and contact your doctor immediately.**

The frequency of the side effects listed below is defined using the following convention:

Very common: may affect more than 1 in 10 people

Common: may affect up to 1 in 10 people

Uncommon: may affect up to 1 in 100 people

Rare: may affect up to 1 in 1,000 people

Side effects reported in clinical studies for patients treated with Irbesartan Zentiva were:

- Very common (may affect more than 1 in 10 people): if you suffer from high blood pressure and type 2 diabetes with kidney disease, blood tests may show an increased level of potassium.
- Common (may affect up to 1 in 10 people): dizziness, feeling sick/vomiting, fatigue and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatinine kinase enzyme). In patients with high blood pressure and type 2 diabetes with kidney disease, dizziness when getting up from a lying or sitting position, low blood pressure when getting up from a lying or sitting position, pain in joints or muscles and decreased levels of a protein in the red blood cells (haemoglobin) were also reported.
- Uncommon (may affect up to 1 in 100 people): heart rate increased, flushing, cough, diarrhoea, indigestion/heartburn, sexual dysfunction (problems with sexual performance), chest pain.
- Rare (may affect up to 1 in 1,000 people): intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea.

Some undesirable effects have been reported since marketing of Irbesartan Zentiva. Undesirable effects where the frequency is not known are: feeling of spinning, headache, taste disturbance, ringing in the ears, muscle cramps, pain in joints and muscles, decreased number of red blood cells (anaemia – symptoms may include tiredness, headaches, being short of breath when exercising, dizziness and looking pale), reduced number of platelets, abnormal liver function, increased blood potassium levels, impaired kidney function, inflammation of small blood vessels mainly affecting the skin (a condition known as leukocytoclastic vasculitis), severe allergic reactions (anaphylactic shock) and low blood sugar levels. Uncommon cases of jaundice (yellowing of the skin and/or whites of the eyes) have also been reported.

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 Irbesartan Zentiva

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 on the blister after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Irbesartan Zentiva contains

- The active substance is irbesartan. Each tablet of Irbesartan Zentiva 150 mg contains 150 mg irbesartan.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, silicon dioxide, magnesium stearate, titanium dioxide, macrogol 3000, carnauba wax. Please see section 2 “Irbesartan Zentiva contains lactose”.

What Irbesartan Zentiva looks like and contents of the pack

Irbesartan Zentiva 150 mg film-coated tablets are white to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2872 engraved on the other side.

Irbesartan Zentiva 150 mg film-coated tablets are supplied in blister packs of 14, 28, 30, 56, 84, 90 or 98 film-coated tablets. Unidose blister packs of 56 x 1 film-coated tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Zentiva k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

Manufacturer:

Sanofi Winthrop Industrie
1 Rue de la vierge
Ambarès et Lagrave
33 565 Carbon Blanc cedex
France

Sanofi Winthrop Industrie
30-36 Avenue Gustave Eiffel
37 100 Tours
France

Zentiva, k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

Sanofi-Aventis, S.A.
Ctra. C-35 (La Batlloria-Hostalric), km. 63.09
17404 Riells i Viabrea (Girona)
Spain

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien

Zentiva, k.s.
Tél/Tel: +32 (78) 700 112
PV-Belgium@zentiva.com

Lietuva

Zentiva, k.s.
Tel: +370 52152025
PV-Lithuania@zentiva.com

България

Zentiva, k.s.
Тел: +35924417136
PV-Bulgaria@zentiva.com

Česká republika

Zentiva, k.s.
Tel: +420 267 241 111
PV-Czech-Republic@zentiva.com

Danmark

Zentiva Denmark ApS
Tlf: +45 787 68 400
PV-Denmark@zentiva.com

Deutschland

Zentiva Pharma GmbH
Tel: +49 (0) 800 53 53 010
PV-Germany@zentiva.com

Eesti

Zentiva, k.s.
Tel: +372 52 70308
PV-Estonia@zentiva.com

Ελλάδα

Zentiva, k.s.
Τηλ: +30 211 198 7510
PV-Greece@zentiva.com

España

Zentiva Spain S.L.U.
Tel: +34 671 365 828
PV-Spain@zentiva.com

France

Zentiva France
Tél: +33 (0) 800 089 219
PV-France@zentiva.com

Hrvatska

Zentiva d.o.o.
Tel: +385 1 6641 830
PV-Croatia@zentiva.com

Ireland

Zentiva, k.s.
Tel: +353 818 882 243
PV-Ireland@zentiva.com

Ísland

Zentiva Denmark ApS
Sími: +354 539 5025
PV-Iceland@zentiva.com

Luxembourg/Luxemburg

Zentiva, k.s.
Tél/Tel: +352 208 82330
PV-Luxembourg@zentiva.com

Magyarország

Zentiva Pharma Kft.
Tel.: +36 1 299 1058
PV-Hungary@zentiva.com

Malta

Zentiva, k.s.
Tel: +356 2034 1796
PV-Malta@zentiva.com

Nederland

Zentiva, k.s.
Tel: +31 202 253 638
PV-Netherlands@zentiva.com

Norge

Zentiva Denmark ApS
Tlf: +45 787 68 400
PV-Norway@zentiva.com

Österreich

Zentiva, k.s.
Tel: +43 720 778 877
PV-Austria@zentiva.com

Polska

Zentiva Polska Sp. z o.o.
Tel: + 48 22 375 92 00
PV-Poland@zentiva.com

Portugal

Zentiva Portugal, Lda
Tel: +351210601360
PV-Portugal@zentiva.com

România

ZENTIVA S.A.
Tel: +4 021 304 7597
PV-Romania@zentiva.com

Slovenija

Zentiva, k.s.
Tel: +386 360 00 408
PV-Slovenia@zentiva.com

Slovenská republika

Zentiva, a.s.
Tel: +421 2 3918 3010
PV-Slovakia@zentiva.com

Italia

Zentiva Italia S.r.l.
Tel: +39 800081631
PV-Italy@zentiva.com

Κύπρος

Zentiva, k.s.
Τηλ: +30 211 198 7510
PV-Cyprus@zentiva.com

Latvija

Zentiva, k.s.
Tel: +371 67893939
PV-Latvia@zentiva.com

Suomi/Finland

Zentiva Denmark ApS
Puh/Tel: +358 942 598 648
PV-Finland@zentiva.com

Sverige

Zentiva Denmark ApS
Tel: +46 840 838 822
PV-Sweden@zentiva.com

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<https://www.ema.europa.eu/>

Package leaflet: Information for the user
Irbesartan Zentiva 300 mg film-coated tablets
irbesartan

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. See section 4.

What is in this leaflet

1. What Irbesartan Zentiva is and what it is used for
2. What you need to know before you take Irbesartan Zentiva
3. How to take Irbesartan Zentiva
4. Possible side effects
5. How to store Irbesartan Zentiva
6. Contents of the pack and other information

1. What Irbesartan Zentiva is and what it is used for

Irbesartan Zentiva belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body which binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan Zentiva prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower. Irbesartan Zentiva slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes.

Irbesartan Zentiva is used in adult patients

- to treat high blood pressure (*essential hypertension*)
- to protect the kidney in patients with high blood pressure, type 2 diabetes and laboratory evidence of impaired kidney function.

2. What you need to know before you take Irbesartan Zentiva

Do not take Irbesartan Zentiva

- if you are **allergic** to irbesartan or any other ingredients of this medicine (listed in section 6)
- if you are **more than 3 months pregnant**. (It is also better to avoid Irbesartan Zentiva in early pregnancy – see pregnancy section)
- **if you have diabetes or impaired kidney function** and you are treated with a blood pressure lowering medicine containing aliskiren.

Warnings and precautions

Talk to your doctor before taking Irbesartan Zentiva and **if any of the following apply to you:**

- if you get **excessive vomiting or diarrhoea**
- if you suffer from **kidney problems**
- if you suffer from **heart problems**
- if you receive Irbesartan Zentiva for **diabetic kidney disease**. In this case your doctor may perform regular blood tests, especially for measuring blood potassium levels in case of poor kidney function
- if you develop **low blood sugar levels** (symptoms may include sweating, weakness, hunger, dizziness, trembling, headache, flushing or paleness, numbness, having a fast, pounding heartbeat), particularly if you are being treated for diabetes.

- if you are **going to have an operation** (surgery) or **be given anaesthetics**
- 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.

ně

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 Irbesartan Zentiva”.

Talk to your doctor if you experience abdominal pain, nausea, vomiting or diarrhoea after taking Irbesartan Zentiva. Your doctor will decide on further treatment. Do not stop taking Irbesartan Zentiva on your own.

You must tell your doctor if you think you are (or might become) pregnant. Irbesartan Zentiva is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

Children and adolescents

This medicinal product should not be used in children and adolescents because the safety and efficacy have not yet been fully established.

Other medicines and Irbesartan Zentiva

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:

If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not take Irbesartan Zentiva” and “Warnings and precautions”).

You may need to have blood checks if you take:

- potassium supplements
- salt substitutes containing potassium
- potassium-sparing medicines (such as certain diuretics)
- medicines containing lithium
- repaglinide (medication used for lowering blood sugar levels)

If you take certain painkillers, called non-steroidal anti-inflammatory drugs, the effect of irbesartan may be reduced.

Irbesartan Zentiva with food and drink

Irbesartan Zentiva can be taken with or without food.

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 Irbesartan Zentiva before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Irbesartan Zentiva. Irbesartan Zentiva is not recommended in early pregnancy, 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. Irbesartan Zentiva 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.

Driving and using machines

Irbesartan Zentiva is unlikely to affect your ability to drive or use machines. However, occasionally dizziness or weariness may occur during treatment of high blood pressure. If you experience these, talk to your doctor before attempting to drive or use machines.

Irbesartan Zentiva contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Irbesartan Zentiva contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Irbesartan Zentiva

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Method of administration

Irbesartan Zentiva is for **oral use**. Swallow the tablets with a sufficient amount of fluid (e.g. one glass of water). You can take Irbesartan Zentiva with or without food. Try to take your daily dose at about the same time each day. It is important that you continue to take Irbesartan Zentiva until your doctor tells you otherwise.

- **Patients with high blood pressure**

The usual dose is 150 mg once a day. The dose may later be increased to 300 mg once daily depending on blood pressure response.

- **Patients with high blood pressure and type 2 diabetes with kidney disease**

In patients with high blood pressure and type 2 diabetes, 300 mg once daily is the preferred maintenance dose for the treatment of associated kidney disease.

The doctor may advise a lower dose, especially when starting treatment in certain patients such as those on **haemodialysis**, or those **over the age of 75 years**.

The maximal blood pressure lowering effect should be reached 4-6 weeks after beginning treatment.

Use in children and adolescents

Irbesartan Zentiva should not be given to children under 18 years of age. If a child swallows some tablets, contact your doctor immediately.

If you take more Irbesartan Zentiva than you should:

If you accidentally take too many tablets, contact your doctor immediately.

If you forget to take Irbesartan Zentiva:

If you accidentally miss a daily dose, just take the next dose as normal. Do not take a double dose to make up for a forgotten dose.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these effects may be serious and may require medical attention.

As with similar medicines, rare cases of allergic skin reactions (rash, urticaria), as well as localised swelling of the face, lips and/or tongue have been reported in patients taking irbesartan. If you get any

of these symptoms or get short of breath, **stop taking Irbesartan Zentiva and contact your doctor immediately.**

The frequency of the side effects listed below is defined using the following convention:

Very common: may affect more than 1 in 10 people

Common: may affect up to 1 in 10 people

Uncommon: may affect up to 1 in 100 people

Rare: may affect up to 1 in 1,000 people

Side effects reported in clinical studies for patients treated with Irbesartan Zentiva were:

- Very common (may affect more than 1 in 10 people): if you suffer from high blood pressure and type 2 diabetes with kidney disease, blood tests may show an increased level of potassium.
- Common (may affect up to 1 in 10 people): dizziness, feeling sick/vomiting, fatigue and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatinine kinase enzyme). In patients with high blood pressure and type 2 diabetes with kidney disease, dizziness when getting up from a lying or sitting position, low blood pressure when getting up from a lying or sitting position, pain in joints or muscles and decreased levels of a protein in the red blood cells (haemoglobin) were also reported.
- Uncommon (may affect up to 1 in 100 people): heart rate increased, flushing, cough, diarrhoea, indigestion/heartburn, sexual dysfunction (problems with sexual performance), chest pain.
- Rare (may affect up to 1 in 1,000 people): intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea.

Some undesirable effects have been reported since marketing of Irbesartan Zentiva. Undesirable effects where the frequency is not known are: feeling of spinning, headache, taste disturbance, ringing in the ears, muscle cramps, pain in joints and muscles, decreased number of red blood cells (anaemia – symptoms may include tiredness, headaches, being short of breath when exercising, dizziness and looking pale), reduced number of platelets, abnormal liver function, increased blood potassium levels, impaired kidney function, inflammation of small blood vessels mainly affecting the skin (a condition known as leukocytoclastic vasculitis), severe allergic reactions (anaphylactic shock) and low blood sugar levels. Uncommon cases of jaundice (yellowing of the skin and/or whites of the eyes) have also been reported.

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 Irbesartan Zentiva

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 on the blister after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Irbesartan Zentiva contains

- The active substance is irbesartan. Each tablet of Irbesartan Zentiva 300 mg contains 300 mg irbesartan.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, silicon dioxide, magnesium stearate, titanium dioxide, macrogol 3000, carnauba wax. Please see section 2 “Irbesartan Zentiva contains lactose”.

What Irbesartan Zentiva looks like and contents of the pack

Irbesartan Zentiva 300 mg film-coated tablets are white to off-white, biconvex, and oval-shaped with a heart debossed on one side and the number 2873 engraved on the other side.

Irbesartan Zentiva 300 mg film-coated tablets are supplied in blister packs of 14, 28, 30, 56, 84, 90 or 98 film-coated tablets. Unidose blister packs of 56 x 1 film-coated tablet for delivery in hospitals are also available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Zentiva k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

Manufacturer:

Sanofi Winthrop Industrie
1 Rue de la vierge
Ambarès et Lagrave
33 565 Carbon Blanc cedex
France

Sanofi Winthrop Industrie
30-36 Avenue Gustave Eiffel
37 100 Tours
France

Zentiva, k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

Sanofi-Aventis, S.A.
Ctra. C-35 (La Batlloria-Hostalric), km. 63.09
17404 Riells i Viabrea (Girona)
Spain

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien

Zentiva, k.s.
Tél/Tel: +32 (78) 700 112
PV-Belgium@zentiva.com

Lietuva

Zentiva, k.s.
Tel: +370 52152025
PV-Lithuania@zentiva.com

България

Zentiva, k.s.
Тел: +35924417136
PV-Bulgaria@zentiva.com

Česká republika

Zentiva, k.s.
Tel: +420 267 241 111
PV-Czech-Republic@zentiva.com

Danmark

Zentiva Denmark ApS
Tlf: +45 787 68 400
PV-Denmark@zentiva.com

Deutschland

Zentiva Pharma GmbH
Tel: +49 (0) 800 53 53 010
PV-Germany@zentiva.com

Eesti

Zentiva, k.s.
Tel: +372 52 70308
PV-Estonia@zentiva.com

Ελλάδα

Zentiva, k.s.
Τηλ: +30 211 198 7510
PV-Greece@zentiva.com

España

Zentiva Spain S.L.U.
Tel: +34 671 365 828
PV-Spain@zentiva.com

France

Zentiva France
Tél: +33 (0) 800 089 219
PV-France@zentiva.com

Hrvatska

Zentiva d.o.o.
Tel: +385 1 6641 830
PV-Croatia@zentiva.com

Ireland

Zentiva, k.s.
Tel: +353 818 882 243
PV-Ireland@zentiva.com

Ísland

Zentiva Denmark ApS
Sími: +354 539 5025
PV-Iceland@zentiva.com

Luxembourg/Luxemburg

Zentiva, k.s.
Tél/Tel: +352 208 82330
PV-Luxembourg@zentiva.com

Magyarország

Zentiva Pharma Kft.
Tel.: +36 1 299 1058
PV-Hungary@zentiva.com

Malta

Zentiva, k.s.
Tel: +356 2034 1796
PV-Malta@zentiva.com

Nederland

Zentiva, k.s.
Tel: +31 202 253 638
PV-Netherlands@zentiva.com

Norge

Zentiva Denmark ApS
Tlf: +45 787 68 400
PV-Norway@zentiva.com

Österreich

Zentiva, k.s.
Tel: +43 720 778 877
PV-Austria@zentiva.com

Polska

Zentiva Polska Sp. z o.o.
Tel: + 48 22 375 92 00
PV-Poland@zentiva.com

Portugal

Zentiva Portugal, Lda
Tel: +351210601360
PV-Portugal@zentiva.com

România

ZENTIVA S.A.
Tel: +4 021 304 7597
PV-Romania@zentiva.com

Slovenija

Zentiva, k.s.
Tel: +386 360 00 408
PV-Slovenia@zentiva.com

Slovenská republika

Zentiva, a.s.
Tel: +421 2 3918 3010
PV-Slovakia@zentiva.com

Italia

Zentiva Italia S.r.l.
Tel: +39 800081631
PV-Italy@zentiva.com

Κύπρος

Zentiva, k.s.
Τηλ: +30 211 198 7510
PV-Cyprus@zentiva.com

Latvija

Zentiva, k.s.
Tel: +371 67893939
PV-Latvia@zentiva.com

Suomi/Finland

Zentiva Denmark ApS
Puh/Tel: +358 942 598 648
PV-Finland@zentiva.com

Sverige

Zentiva Denmark ApS
Tel: +46 840 838 822
PV-Sweden@zentiva.com

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