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BEZARTAN TABLET

Irbesartan 150mg, 300mg

DESCRIPTION
Bezartan Tablet 150mg - White to off white, biconvex, oval-shaped, with marking '150' on one side and film coated tablet

Bezartan Tablet 300mg - White, oval shape, with scored on one side and film coated tablet

CLINICAL PARTICULARS
Therapeutic indications
Treatment of essential hypertension.
Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension. In this population, Bezartan reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end-stage renal disease (need for dialysis or renal transplantation).

Posology and method of administration
The usual recommended initial and maintenance dose is 150 mg once daily, with or without food. Bezartan 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 Bezartan can be increased to 300 mg, or other antihypertensive agents can be added. In particular, the addition of a diuretic such as hydrochlorothiazide has been shown to have an additive effect.

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.

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.

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 Bezartan in children aged 0 to 18 has not been established.

Contraindications
Hypersensitivity to the active substance, or to any of the excipients *(see List of Excipients)*. Second and third trimesters of pregnancy *(see Special warnings and precautions for use/Pregnancy and Lactation).*

Concomitant use of irbesartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2)

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 Bezartan.

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 reninangiotensin-aldosterone system. While this is not documented with Bezartan, a similar effect should be anticipated with angiotensin-II receptor antagonists.

Renal impairment and kidney transplantation:
when Bezartan 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 Bezartan in patients with a recent kidney transplantation.

Dual blockade of the renin-angiotensinaldosterone 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 ACEinhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. 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-angiotensinaldosterone system, hyperkalaemia may occur during the treatment with Bezartan, 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 Interaction with other medicinal products and other forms of interaction).*

Lithium: the combination of lithium and Bezartan is not recommended.

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 Bezartan 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. 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 that in non-black, possibly because of higher prevalence of low-renin stated in the black hypertensive population (see Pharmacodynamic properties).

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 Contraindication and Pregnancy and Lactation).*

Lactose: this medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 Bezartan has been safely administered with other antihypertensive agents, such as betablockers, 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 Bezartan *(see Special warnings and precautions for use).*

Aliskiren-containing products and ACEinhibitors:
Data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACEinhibitors, 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.

ACE inhibitors: The use of irbesartan with an ACE inhibitor may increase the risk of hyperkalaemia, hypotension, and syncope, particularly in patients with atherosclerotic disease or heart failure, or in diabetics who have end-organ damage. Such combinations should be reserved for selected cases with close monitoring of renal function.

Potassium supplements and potassium-sparing diuretics:
based on experience with the use of other medicinal products that affect the reninangiotensin 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 Special warnings and precautions for use).*

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 Special warnings and precautions for use).* 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 antiinflammatory 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.

Pregnancy and lactation
Pregnancy:

> The use of AIIRAs is not recommended during the first trimester of pregnancy (see Special warnings and precautions for use). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see Contraindications and Special warnings and precautions for use).

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 fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

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 Contraindications and Special warnings and precautions for use).*

Lactation:
Because no information is available regarding the use of Bezartan during breastfeeding, Bezartan is not recommended and alternative treatments with

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better established safety profiles during breastfeeding 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.

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. Effects on ability to drive and use machines No studies on the effects on the ability to drive and use machines have been performed. Based on its pharmacodynamics properties, irbesartan is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. Based on its pharmacodynamics properties, irbesartan is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.

Undesirable Effects

Blood and lymphatic system disorders	
Not known:	thrombocytopenia
Immune system disorders:	
Not known:	hypersensitivity reactions such as angioedema, rash, urticaria
Metabolism and nutrition disorders:	
Not known:	hyperkalaemia
Nervous system disorders:	
Common: Not known:	dizziness, orthostatic dizziness vertigo, headache
Ear and labyrinth disorder:	
Not known:	tinnitus
Cardiac disorders:	
Not known:	tachycardia
Vascular disorders:	
Common: Uncommon:	orthostatic hypotension flushing
Respiratory, thoracic and mediastinal disorders:	
Uncommon:	Cough
Gastrointestinal disorders:	
Common: Uncommon: Not known:	nausea/vomiting diarrhoea, dyspepsia/heartburn dysgeusia
Hepatobiliary disorders:	
Uncommon: Not known:	jaundice hepatitis, abnormal liver function
Skin and subcutaneous tissue disorders:	
Not known:	leukocytoclastic vasculitis
Musculoskeletal and connective tissue disorders:	
Common: Not known:	musculoskeletal pain arthralgia, myalgia (in some cases associated with increased plasma creatine kinase levels), muscle cramp
Renal and urinary disorders:	
Not known:	impaired renal function including cases of renal failure in patients at risk
Reproductive system and breast disorders:	
Uncommon:	sexual dysfunction
General disorders and administration site conditions:	
Common: Uncommon:	fatigue chest pain
Investigations:	
Very common:	Hyperkalaemia
Common:	Significant increases in plasma creatine kinase

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 Bezartan. 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.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics 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.

Pharmacokinetic properties
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. Plasma protein binding is approximately 96%, with negligible binding to cellular blood components. The volume of distribution is 53 - 93 litres. Irbesartan is metabolised by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (approximately 6%).

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

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.

ROUTE OF ADMINISTRATION
Oral

PHARMACEUTICAL PARTICULARS
Shelf life
As indicated on the outer package

Dosage forms and packaging available
Bezartan Tablet 150mg: Box of 30 tablets
Bezartan Tablet 300mg: Box of 30 tablets

Storage Conditions
Store in a dry place below 30ºC.
Protect from light.

Keep out of reach of children.
Jauhkan daripada kanak-kanak.

PRODUCT REGISTRATION HOLDER:
DUOPHARMA MARKETING SDN. BHD.
Lot No. 2,4,6,8,10, Jalan P/7, Section 13,
Bangi Industrial Estate, 43650,
Bandar Baru Bangi, Selangor, Malaysia.

MANUFACTURER:
DUOPHARMA MANUFACTURING (BANGI) SDN. BHD.
Lot No. 2&4, Jalan P/7, Section 13,
Bangi Industrial Estate, 43650,
Bandar Baru Bangi, Selangor, Malaysia.

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