Valsatens PLUS

Valsartan & Hydrochlorothiazide

Film Coated Tablets

Valsatens Plus 80/12.5 mg, 160/12.5 mg, 160/25 mg
Film coated tablets
Description
Avoid in the second/third pregnancy. As it may cause injury or death to fetus
1. Name of the medicinal product
Valsatens Plus 80/12.5 mg film-coated tablet
Valsatens Plus 160/12.5 mg Film-coated tablet
Valsatens Plus 160/25 mg Film-Coated Tablet
2. Qualitative and quantitative composition
Each Valsatens Plus 80/12.5 mg tablet contains 80 mg of valsartan and 12.5 mg of hydrochlorothiazide.
Each Film-Coated tablet contains 160 mg of valsartan and 12.5 mg of hydrochlorothiazide.
Each Film-Coated tablet contains 160 mg of valsartan and 25 mg of hydrochlorothiazide.
as active ingredients.
Excipients with known effect: Each tablet contains 60 mg lactose monohydrate.
For the full list of excipients, see section 6.1.
3. Pharmaceutical form
Film-coated tablet
4. Clinical particulars
4.1 Therapeutic indications
Essential hypertension in adults.
Valsartan and hydrochlorothiazide fixed-dose combination is indicated in adults whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.
4.2 Posology and method of administration
Posology
The recommended dose of Valsartan and Hydrochlorothiazide 5 mg/5 mg is one film-coated tablet once daily. Dose titration with the individual components is recommended. In such case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotensive and other adverse events. Where clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed. The clinical response to Valsartan/hydrochlorothiazide should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of Valsartan/hydrochlorothiazide 320 mg/25 mg. The antihypertensive effect is substantially present within 2 weeks. In most patients, maximal effects are observed within 4 weeks. However, in some patients 4-8 weeks treatment may be required. The antihypertensive effect is maintained during dose titration.
Method of administration
Valsartan and hydrochlorothiazide can be taken with or without food and should be administered with water.
Special populations
Renal impairment
No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥30 ml/min). Due to the hydrochlorothiazide component, Valsartan/hydrochlorothiazide is contraindicated in patients with severe renal impairment (see sections 4.3, 4.4 and 5.2).
Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg, see sections 4.4), Valsartan/hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).
Elderly
No dose adjustment is required in elderly patients.
Paediatric population
Valsartan/hydrochlorothiazide is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.
4.3 Contraindications
- Hypersensitivity to the substances (valsartan/hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients listed in section 6.1.
- **Not to be used during pregnancy, As it may cause injury or death to fetus** (see sections 4.4 and 4.6).
- The concomitant use of Valsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min. 1.73m2).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Severe renal impairment (creatinine clearance <30 ml/min), anuria.
- Refractory hypokalaemia, hypercalcaemia, symptomatic hyperuricaemia, and symptomatic hyperuricaemia.
4.4 Special warnings and precautions for use
Dual blockade of the renin-angiotensin aldosterone system (RAAS)
Dual blockade of RAAS through the combined 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. 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.
Serum electrolytes changes
Valsartan
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc) is not recommended.
Monitoring of potassium should be undertaken as appropriate.
Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended. Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hypomagnesemia and hyperbicarbonate alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia. As for any patient receiving diuretic treatment, periodic monitoring of electrolytes should be performed at appropriate intervals.
Sodium and/or volume-depleted patients
Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance. In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of treatment with Valsartan/hydrochlorothiazide. Correction of sodium depletion and/or volume depletion should be considered before administering Valsartan/hydrochlorothiazide.
renin-angiotensin- aldosterone-system. In patients whose renal function may depend on the activity of the renin-angiotensin aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia, and in rare cases with acute renal failure. The use of Valsartan/hydrochlorothiazide in patients with severe chronic heart failure has not been established. Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of Valsartan/hydrochlorothiazide as well may be associated with impairment of the renal function. Valsartan/hydrochlorothiazide should not be used in these patients.
Renal artery stenosis
Valsartan/hydrochlorothiazide should not be used to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, since blood urea and serum creatinine may increase in such patients.
Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Valsartan/hydrochlorothiazide as their renin-angiotensin system is not activated.
Acute and subacute obstructive, hypertrophic obstructive cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).
Renal impairment
No change adjustment is required for patients with renal impairment with a creatinine clearance ≥30 ml/min (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Valsartan/hydrochlorothiazide is used in patients with renal impairment.
Hepatic impairment
There is currently no experience on the safe use of Valsartan/hydrochlorothiazide in patients who have recently undergone kidney transplantation.
Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan/hydrochlorothiazide should be used with caution (see sections 4.2 and 5.2).
Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.
Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.
Thiazide diuretics reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a readministration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.
Choroidal effusion, acute myopia
An suspected risk of severe adverse reactions to Valsartan/hydrochlorothiazide should be considered if an adverse reaction occurs. This adverse reaction includes transitory myopia, acute angle-closure glaucoma, choroidal effusion, and choroidal haemorrhage. Untreated acute angle-closure glaucoma may result in permanent vision loss. The primary treatment to reverse the suspected reaction should be as rapid as possible or immediate. If an intraocular pressure remains uncontrolled, immediate medical treatment may be considered. Risk factors for acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.
Cutaneous lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, may induce cutaneous lupus erythematosus like reactions, mechanism of cutaneous lupus erythematosus
4.5 Interaction with other medicinal products and other forms of interaction
Interactions related to both valsartan and hydrochlorothiazide
Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazide, including hydrochlorothiazide. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.
Concomitant use requiring caution
Baclofen, amifostine, lithium
Valsartan/hydrochlorothiazide may increase the effects of other agents with antihypertensive properties (e.g. ACEI, beta blockers, calcium channel blockers).
Pressor amines (e.g. noradrenaline, adrenaline)
Potential interaction with pressor amines which did not sufficient to preclude their use.
Non-steroidal anti-inflammatory medicines (NSAIMs), including selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day), and non-selective NSAIDs
NSAIDs can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Valsartan/hydrochlorothiazide and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.
Interactions related to valsartan
Concomitant use not recommended
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.
No interaction
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indomethacin
Interactions related to hydrochlorothiazide
Concomitant use requiring caution
Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives
If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4).
Interactions related to hydrochlorothiazide
Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazide, including hydrochlorothiazide. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.
Concomitant use requiring caution
Medicinal products affecting the renin-angiotensin system
Valsartan/hydrochlorothiazide may increase the effects of other agents with antihypertensive properties (e.g. ACEI, beta blockers, calcium channel blockers).
Pressor amines (e.g. noradrenaline, adrenaline)
Potential interaction with pressor amines which did not sufficient to preclude their use.
Non-steroidal anti-inflammatory medicines (NSAIMs), including selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day), and non-selective NSAIDs
NSAIDs can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Valsartan/hydrochlorothiazide and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.
Interactions related to valsartan
Concomitant use not recommended
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.
No interaction
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indomethacin
Interactions related to hydrochlorothiazide
Concomitant use requiring caution
Medicinal products affecting the renin-angiotensin system and hyperkalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives
If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4).
Interactions related to hydrochlorothiazide
Concomitant use not recommended
Medicinal products affected by serum potassium disturbances
Recommendations for the combination of potassium-depleting diuretics with other medicinal products with potassium disturbance and toxicity and morbidity are currently unknown.
Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.
Valsartan
Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counteractivate the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity of the AT1 receptor and has much (about 20,000-fold) greater affinity for the AT1 receptor than for the AT2 receptor. Valsartan is not known to bind to or affect other receptors or ion channels known to be important in cardiovascular regulation.
Valsartan does not inhibit ACE, also known as kinkinase II, which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly (P <0.05) lower in patients treated with valsartan than in those treated with an ACE inhibitor. (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and
10.5% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor (P <0.05).
Administration of valsartan to healthy subjects has not produced any clinically relevant adverse effects on blood pressure, heart rate, or ECG. In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. Dating repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2- 4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.
Withdrawal of valsartan in patients with hypertension has not been associated with clinically relevant adverse clinical events.
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing action of HCTZ could act as a possible mechanism for NMSC.
Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UR rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.
Pregnancy
Not to be used during pregnancy, As it may cause injury or death to fetus (see sections 4.3 and 4.6).
Lactation
Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.
4.6 Interaction with other medicinal products and other forms of interaction
Interactions related to both valsartan and hydrochlorothiazide
Concomitant use not recommended
Lithium
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Concomitant use requiring caution
Baclofen, amifostine, lithium