Exforge HCT®

Angiotensin II antagonists combinations plain (valsartan) with dihydropyridine derivatives (amlodipine) and thiazide diuretics (HCTZ)

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Film-coated tablets (FCT)

Five strengths are available

- 5 mg of amlodipine (as amlodipine besylate), 160 mg of valsartan and 12.5 mg hydrochlorothiazide, White film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VCL” on the other side
- 10 mg of amlodipine (as amlodipine besylate), 160 mg of valsartan and 12.5 mg hydrochlorothiazide, Pale yellow film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VDL” on the other side
- 5 mg of amlodipine (as amlodipine besylate), 160 mg of valsartan and 25 mg hydrochlorothiazide, Yellow film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VEL” on the other side
- 10 mg of amlodipine (as amlodipine besylate) and 160 mg of valsartan and 25 mg hydrochlorothiazide, Brown-yellow film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VHL” on the other side
- 10 mg of amlodipine (as amlodipine besylate) and 320 mg of valsartan and 25 mg hydrochlorothiazide, Brown-yellow film-coated tablet, ovaloid, biconvex with beveled edge with debossing “NVR” on one side and “VFL” on the other side

Exforge HCT FCT are non-divisible and cannot be divided into equal doses.

Certain dosage strengths and dosage forms may not be available in all countries.

Active substances

Amlodipine besylate

Valsartan

Hydrochlorothiazide

Excipients

5/160/12.5 mg: cellulose microcrystalline; crospovidone; silica, colloidal anhydrous; magnesium stearate; hypromellose, macrogol 4000, talc, titanium dioxide (E171)

10/160/12.5 mg: cellulose microcrystalline; crospovidone; silica, colloidal anhydrous; magnesium stearate; hypromellose, macrogol 4000, talc, titanium dioxide (E171), iron oxide, yellow (E172), iron oxide, red (E 172)

5/160/25 mg: cellulose microcrystalline; crospovidone; silica, colloidal anhydrous, magnesium stearate, hypromellose, macrogol 4000, talc, titanium dioxide (E171), iron oxide, yellow (E172)

10/160/25 mg: cellulose microcrystalline; crospovidone; silica, colloidal anhydrous, magnesium stearate, hypromellose, macrogol 4000, talc, iron oxide, yellow (E172)

10/320/25 mg: cellulose microcrystalline; crospovidone; silica, colloidal anhydrous, magnesium stearate, hypromellose, macrogol 4000, talc, iron oxide, yellow (E172)

Pharmaceutical formulations may vary between countries.

Indications

Treatment of essential hypertension

This fixed combination drug is not indicated for the initial therapy of hypertension (see section DOSAGE AND ADMINISTRATION).

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

The recommended dose is one tablet per day (the 5 strengths are listed in section DESCRIPTION AND COMPOSITION).

A patient whose blood pressure is not adequately controlled on dual therapy may be directly switched to combination therapy with Exforge HCT.

For convenience, patients receiving valsartan, amlodipine and HCTZ from separate tablets may be switched to Exforge HCT containing the same component doses. A patient who experiences dose limiting adverse reactions on any dual combination of the components of Exforge HCT may be switched to Exforge HCT containing a lower dose of that component to achieve similar blood pressure reductions.

Dosage may be increased after two weeks. The maximum antihypertensive effect of Exforge HCT is reached within two weeks after a change in dose. The maximum recommended dose of Exforge HCT is 10/320/25 mg.

Special populations

Geriatric patients (aged 65 years or above)

No dose adjustment of the starting dose is required for elderly patients aged 65 years or above. Starting with the lowest available dose of amlodipine should be considered. The lowest strength of Exforge HCT contains 5 mg of amlodipine. (See section CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years)

Exforge HCT is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Renal impairment

Due to the hydrochlorothiazide component, Exforge HCT is contraindicated in patients with anuria (see section CONTRAINDICATIONS) and should be used with caution in patients with severe kidney disease (GFR <30 mL/min) (see section WARNINGS AND PRECAUTIONS and also section CLINICAL PHARMACOLOGY). Thiazide diuretics are ineffective as monotherapy in severe renal impairment (GFR <30 mL/min) but may be useful in these patients, when used with due caution in combination with a loop diuretic even in patients with GFR <30 mL/min. No dosage adjustment of Exforge HCT is required for patients with mild to moderate renal impairment.

Hepatic impairment

Due to the valsartan, hydrochlorothiazide and amlodipine components, particular caution should be exercised when administering Exforge HCT in patients with hepatic impairment or biliary obstructive disorders. Starting with the lowest avaliable dose of amlodipine should be considered. The lowest strength of Exforge HCT contains 5 mg of amlodipine. (See section WARNINGS AND PRECAUTIONS and also section CLINICAL PHARMACOLOGY).

Method of administration

Exforge HCT can be taken with or without food. It is recommended to take Exforge HCT with some water.

CONTRAINDICATIONS

Known hypersensitivity to amlodipine, valsartan, HCTZ, other sulfonamide derived medicinal products or to any of the excipients

Pregnancy (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL)

Because of hydrochlorothiazide, Exforge HCT is contraindicated in patients with anuria

Concomitant use of angiotensin receptor antagonists (ARBs) - including valsartan - or of angiotensin-converting enzyme inhibitors (ACEIs) with aliskiren in patients with Type 2 diabetes (see section INTERACTIONS, subsection dual blockade of the RAS)

WARNINGS AND PRECAUTIONS

Patients with sodium- and/or volume depletion

Excessive hypotension, including orthostatic hypotension was seen in 1.7% of patients treated with the maximum dose of Exforge HCT (10/320/25 mg) compared to 1.8% of valsartan/HCTZ (320/25 mg) patients, 0.4% of amlodipine/valsartan (10/320 mg) patients, and 0.2% of HCTZ/amlodipine (25/10 mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension.

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 therapy with Exforge HCT. Exforge HCT should be used only after correction of any pre-existing sodium and/or volume depletion otherwise the treatment should start under close medical supervision.

If excessive hypotension occurs with Exforge HCT, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once blood pressure has been stabilized.

Patients with renal impairment

Due to the hydrochlorothiazide component, use Exforge HCT with caution in patients with severe renal impairment (GFR < 30 mL/min). Thiazide diuretics may precipitate azotemia in patients with chronic kidney disease. Thiazides diuretics are ineffective as monotherapy in severe renal impairment (GFR <30 mL/min) but may be useful, when used with due caution in combination with loop diuretics even in patients with GFR <30 mL/min (see section WARNINGS AND PRECAUTIONS and also section CLINICAL PHARMACOLOGY). No dosage adjustment of Exforge HCT is required for patients with mild to moderate renal impairment.

The use of ARBs - including valsartan- or of ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section INTERACTIONS, subsection dual blockade of the RAS).

Patients with renal artery stenosis

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

Patients with kidney transplantation

There is no experience with the use of Exforge HCT in patients with recent kidney transplantation.

Patients with hepatic impairment

Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolized by the liver. Due to the valsartan, hydrochlorothiazide and amlodipine components, particular caution should be exercised when administering Exforge HCT to patients with hepatic impairment or biliary obstructive disorders. (see section DOSAGE REGIMEN AND ADMINISTRATION and also section CLINICAL PHARMACOLOGY).

Angioedema

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

Patients with heart failure/post-myocardial Infarction

In general, calcium channel blockers including amlodipine should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV).

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 or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia, and in rare cases with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

Patients with acute myocardial infarction

Worsening angina pectoris and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

Patients with aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with all other vasodilators, special caution is required when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Serum electrolyte changes

Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) could lead to hyperkalaemia and should be used with caution.

Thiazide diuretics can precipitate new onset hypokalemia or exacerbate pre-existing hypokalemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalemia is accompanied by clinical signs (e.g. muscular weakness, paresis, or ECG alterations), Exforge HCT should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides. Potassium and magnesium serum concentrations should be checked periodically. All patients receiving thiazide diuretics should be monitored for imbalances in electrolytes, particularly potassium.

Thiazide diuretics can precipitate new onset hyponatremia and hypochloremic alkalosis or exacerbate pre-existing hyponatremia. Hyponatremia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed in isolated cases. Regular monitoring of serum sodium concentrations is recommended.

Amlodipine -Valsartan – Hydrochlorothiazide

In the controlled trial of Exforge HCT in moderate to severe hypertensive patients, the incidence of hypokalemia (serum potassium <3.5 mEq/L) at any time post-baseline with the maximum dose of Exforge HCT (10/320/25 mg) was 9.9% compared to 24.5% with HCTZ/amlodipine (25/10 mg), 6.6% with valsartan/HCTZ (320/25 mg), and 2.7% with amlodipine/valsartan (10/320 mg). One patient (0.2%) discontinued therapy due to an adverse event of hypokalemia in each of the Exforge HCT and HCTZ/amlodipine groups. The incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% with Exforge HCT compared to 0.2-0.7% with the dual therapies.

In the controlled trial of Exforge HCT, the opposite effects of valsartan 320 mg and hydrochlorothiazide 25 mg on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

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 and triglycerides.

Like other diuretics, hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia as well as precipitate gout in susceptible patients.

Thiazides decrease urinary calcium excretion and may cause mild elevation of serum calcium in the absence of known disorders of calcium metabolism. Since hydrochlorothiazide can increase serum calcium concentrations, it should be used with caution in patients with hypercalcemia. Marked hypercalcemia unresponsive to thiazide withdrawal or ≥ 12 mg/dL may be evidence of an underlying thiazide independent hypercalcemic process. Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic clarification is necessary.

General

Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Acute Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of a drug initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulfonamide or penicillin allergy.

Dual Blockade of the Renin-Angiotensin System (RAS)

Caution is required while co-administering ARBs, including valsartan, with other agents blocking the RAS such as ACEIs or aliskiren (see section INTERACTIONS, subsection dual blockade of the RAS).

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies based on Danish National cancer registry. The risk for NMSC appears to increase with long-term use (see section CLINICAL PHARMACOLOGY). Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide 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 adequate protection when exposed to sunlight 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 examination of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have previously experienced NMSC (see section ADVERSE DRUG REACTIONS)

ADVERSE DRUG REACTIONS

The presentation of the safety profile of Exforge HCT is based on the experience with Exforge HCT and the individual components.

Information on Exforge HCT

The safety of Exforge HCT has been evaluated at its maximum dose of 10/320/25 mg for safety in one controlled clinical study with 2271 patients, 582 of whom received valsartan in combination with amlodipine and HCTZ. There were no new adverse reactions which occurred specifically with Exforge HCT in addition to those known to be associated with the individual monotherapies. No additional risks other than those previously identified were observed with long-term treatment. Exforge HCT was generally well-tolerated regardless of gender, age, or race. Changes in laboratory parameters observed with the combination of Exforge HCT were minor and consistent with the pharmacologic mechanism of action of the monotherapy agents. The presence of valsartan in both the triple combination and the dual combination with HCTZ attenuated the hypokalemic effect of HCTZ.

Additional information on individual components

Adverse reactions previously reported with one of the individual components may occur with Exforge HCT even if not observed in the pivotal clinical trial.

Amlodipine

Because amlodipine clinical trials were conducted under widely varying conditions, adverse experience rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse experiences reported with amlodipine monotherapy, irrespective of their causal association with the study drug, were as follows:

Table 1 Adverse experiences with amlodipine

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leucocytopenia
Immune system disorders	
Very rare	Allergic reactions

Metabolism and nutrition disorders	
Very rare	Hyperglycaemia
Psychiatric disorders	
Uncommon	Insomnia, mood changes including anxiety
Nervous system disorders	
Common	Headache, somnolence, dizziness
Uncommon	Tremor, hypoesthesia, dysgeusia, paresthesia, syncope
Very rare	Peripheral neuropathy, hypertonia
Eye disorders	
Uncommon	Visual impairment, diplopia
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Common	Palpitations
Very rare	Arrhythmia, bradycardia, atrial fibrillation, ventricular tachycardia, myocardial infarction
Vascular disorders	
Common	Flushing
Uncommon	Hypotension
Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnea, rhinitis
Very rare	Cough
Gastrointestinal disorders	
Common	Abdominal pain, nausea
Uncommon	Vomiting, dyspepsia, dry mouth, constipation, diarrhoea
Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	
Very rare	Hepatitis, jaundice
Skin and subcutaneous tissue disorders	
Uncommon	Alopecia, hyperhidrosis, pruritus, rash, purpura, skin discoloration, photosensitivity
Very rare	Angioedema, urticaria, erythema multiforme, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	
Uncommon	Back pain, muscle spasms, myalgia, arthralgia
Renal and urinary disorders	
Uncommon	Micturition disorder, nocturia, pollakiuria
Reproductive system and breast disorders	
Uncommon	Gynecomastia, erectile dysfunction
General disorders and administration site conditions	
Common	Oedema, fatigue
Uncommon	Asthenia, pain, malaise, chest pain
Investigations	
Uncommon	Weight decreased, weight increased
Very rare	Hepatic enzyme increased *(mostly consistent with cholestasis)*

Valsartan

Adverse Drug Reactions (ADRs) reported in the hypertension indication from clinical studies, post-marketing experience and laboratory findings are listed below according to system organ class.

For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a "not known" frequency.

Table 2 Adverse drug reactions with valsartan

Blood and lymphatic system disorders

Not known	Hemoglobin decreased, hematocrit decreased, neutropenia, thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Blood potassium increased
Ear and labyrinth system disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepato-biliary disorders	
Not known	Liver function test abnormal including blood bilirubin increase
Skin and subcutaneous tissue disorders	
Not known	Angioedema, dermatitis bullous, rash, pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, blood creatinine increased
General disorders and administration site conditions	
Uncommon	Fatigue

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Insomnia, libido decrease, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Hydrochlorothiazide

Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those contained in Exforge HCT. The following additional adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide:

Table 3 Adverse drug reactions with hydrochlorothiazide

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Not Known:	Non-Melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma) (see sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY)
Blood and lymphatic system disorders	
Rare:	Thrombocytopenia sometimes with purpura.
Very rare:	Leucopenia, agranulocytosis, bone marrow failure and hemolytic anaemia.
Not known:	Aplastic anemia
Immune system disorders	
Very rare:	Vasculitis necrotizing, hypersensitivity reactions - respiratory distress including pneumonitis and pulmonary edema.
Metabolism and nutrition disorders	
Very common:	(mainly at higher doses) Hypokalaemia, blood lipids increased.
Common:	Hyponatraemia, hypomagnesaemia, hyperuricaemia, decreased appetite.
Rare:	Hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state.
Very rare:	Alkalosis hypochloremic.
Psychiatric disorder	
Rare:	Sleep disorders
Nervous system disorders	
Rare:	Headache, dizziness, depression and paresthesia.

Eye disorders	
Rare:	Visual impairment particularly in the first few weeks of treatment.
Not known:	angle-closure glaucoma
Cardiac disorders	
Rare:	Arrhythmias.
Vascular disorders	
Common:	Orthostatic hypotension, which may be aggravated by alcohol, anesthetics or sedatives.
Gastrointestinal disorders	
Common:	Mild nausea and vomiting.
Rare:	Abdominal discomfort, constipation and diarrhoea
Very rare:	Pancreatitis.
Hepatobiliary disorders	
Rare:	Cholestasis or jaundice.
Skin and subcutaneous tissue disorders	
Common:	Urticaria and other forms of rash.
Rare:	Photosensitivity reaction.
Very rare:	Toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus.
Not known	Erythema multiforme
Musculoskeletal and connective tissue disorders	
Not known	Muscle spasms
Renal and urinary disorders	
Not known:	Acute renal failure, renal disorder
Reproductive system and breast disorders	
Common:	Erectile dysfunction.
General disorders and administration site conditions	
Not known	Pyrexia, asthenia

INTERACTIONS

Valsartan-hydrochlorothiazide

The following drug interactions may occur due to both components (valsartan and/or hydrochlorothiazide) of Exforge HCT:

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, angiotensin II receptor antagonists or thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with Exforge HCT. Therefore, careful monitoring of serum lithium concentrations is recommended during concomitant use.

Amlodipine

The following potential drug interactions may occur due to the amlodipine component of Exforge HCT:

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

CYP3A4 Inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 1.6 fold increase in amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Caution should therefore be exercised when co-administering amlodipine with CYP3A4 inhibitors.

Grapefruit Juice:

The exposure of amlodipine may be increased when co-administered with grapefruit juice due to CYP3A4 inhibition. However, co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

CYP3A4 Inducers: No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, Maalox® (aluminium hydroxide gel, magnesium hydroxide and simeticone), cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Valsartan

The following potential drug interactions may occur due to the valsartan component of Exforge HCT:

Dual blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren: The concomitant use of ARBs, including valsartan, with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on Exforge HCT and other agents that affect the RAS (see section WARNINGS AND PRECAUTIONS).

The concomitant use of ARBs - including valsartan - or ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section WARNINGS AND PRECAUTIONS).

The concomitant use of ARBs - including valsartan - or ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes (see section CONTRAINDICATIONS).

Potassium: Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, in patients who are elderly, volume-depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

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

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

Hydrochlorothiazide

The following potential drug interactions may occur due to the hydrochlorothiazide component of Exforge HCT:

Other anti-hypertensive drugs: Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, Angiotensin Receptor Blocker (ARBs) and Direct Renin Inhibitors (DRIs)).

Skeletal muscle relaxants: Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

Medicinal products affecting serum potassium level: The hypokalemic effect of diuretics may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhythmics (see section WARNINGS AND PRECAUTIONS).

Medicinal products affecting serum sodium level: The hyponatremic effect of diuretics may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these drugs (see section WARNINGS AND PRECAUTIONS).

Antidiabetic agents: Thiazides may alter glucose tolerance. It may be necessary to adjust the dosage of insulin and of oral antidiabetic agents.

Digitalis glycosides: Thiazide-induced hypokalemia or hypomagnesemia may occur as unwanted effects, favoring the onset of digitalis-induced cardiac arrhythmias (see section WARNINGS AND PRECAUTIONS).

NSAIDs and Cox-2 selective inhibitors: Concomitant administration of NSAIDs (e.g. salicylic acid derivative, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of Exforge HCT. Concurrent hypovolemia may induce acute renal failure.

Allopurinol: Co-administration of thiazide diuretics (including hydrochlorothiazide) may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine: Co-administration of thiazide diuretics (including hydrochlorothiazide) may increase the risk of adverse effects caused by amantadine.

Antineoplastic agents (e.g. cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.

Anticholinergic agents: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely prokinetic drugs such as cisapride may decrease the bioavailability of thiazide-type diuretics.

Ion exchange resins: Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 h before or 4-6 h after the administration of resins would potentially minimize the interaction.

Vitamin D: Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Ciclosporin: Concomitant treatment with ciclosporin may increase the risk of hyperuricemia and gout-type complications.

Calcium salts: Concomitant use of thiazide type diuretics may lead to hypercalcemia by increasing tubular calcium reabsorption.

Diazoxide: Thiazide diuretics may enhance the hyperglycemic effect of diazoxide.

Methyldopa: There have been reports in the literature of hemolytic anemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Alcohol, barbiturates or narcotics: Concomitant administration of thiazide diuretics with alcohol, barbiturates, or narcotics may potentiate orthostatic hypotension.

Pressor amines: Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

As for any drug that acts directly on the RAAS, Exforge HCT must not be used during pregnancy (see section CONTRAINDICATIONS).

Due to the mechanism of action of angiotensin II antagonists, a risk to the fetus cannot be excluded. Administration of angiotensin converting enzyme (ACE) inhibitors (a specific class of drugs acting on the renin-angiotensin-aldosterone system, RAAS) to pregnant women during the second and third trimesters has been reported to cause injury and death to the developing foetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. Hydrochlorothiazide crosses the placenta. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have inadvertently taken valsartan.

There are no adequate clinical data with amlodipine in pregnant women. Animal studies with amlodipine have shown reproductive toxicity at dose 8 times the maximum recommended human dose of 10 mg (see section Animal data). The potential risk to humans is unknown.

Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with fetal or neonatal jaundice or thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.

If pregnancy is detected during therapy, Exforge HCT should be discontinued as soon as possible (See section Animal data).

Clinical considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death.

Fetal/Neonatal Risk

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death.

In case of accidental exposure to ARB therapy, appropriate fetal monitoring should be considered.

Infants whose mothers have taken ARB therapy should be closely observed for hypotension.

Animal data

Valsartan: In embryofetal development studies in mice, rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats at valsartan doses of 600 mg/kg/day approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient) and in rabbits at doses of 10 mg/kg/day approximately 0.6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). There was no evidence of maternal toxicity or fetotoxicity in mice up to a dose level of 600 mg/kg/day approximately 9 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Hydrochlorothiazide: Hydrochlorothiazide was not teratogenic and had no effects on fertility and conception. No teratogenic potential was revealed in 3 animal species tested. There was no dose-related fetotoxicity at oral dose levels of 0, 100, 300 and 1000 mg/kg in rats. A decrease in weight gain in suckling rat pups was attributed to the high dose and diuretic effects of hydrochlorothiazide, with subsequent effects on milk production.

Amlodipine: No evidence of teratogenicity or embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold). Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

Valsartan and amlodipine: In an oral embryo-fetal development study in rats with dose levels of 5:80 mg/kg/day, amlodipine:valsartan, 10:160 mg/kg/day amlodipine:valsartan, and 20:320 mg/kg/day amlodipine:valsartan, treatment-related maternal and fetal effects (developmental delays and alterations noted in the presence of significant maternal toxicity) were noted with the high dose combination. The no-observed-adverse-effect level (NOAEL) for embryo-fetal effects was 10:160 mg/kg/day amlodipine:valsartan. These doses are, respectively, 4.3 and 2.7 times the systemic exposure in humans receiving the MRHD (10/320 mg/60 kg).

Lactation

It is not known whether valsartan is transferred into human milk. It is reported that amlodipine is transferred into human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. Valsartan was transferred into the milk of lactating rats. Hydrochlorothiazide is transferred into human milk. It is therefore not advisable for women who are breast-feeding to use Exforge HCT.

Females and males of reproductive potential

Female and males of reproductive potential

As for any drug that acts directly on the RAAS, Exforge HCT should not be used in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy.

Infertility

There is no information on effects of amlodipine, valsartan or hydrochlorothiazide on human fertility. Studies in rats did not show any effects of amlodipine, valsartan or hydrochlorothiazide on fertility (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

There is no experience of overdosage with Exforge HCT. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness.

Overdosage with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. If the ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by hemodialysis whereas clearance of HCTZ will be achieved by dialysis.

CLINICAL PHARMACOLOGY

Pharmacodynamics (PD)

Exforge HCT combines three antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class, valsartan to the angiotensin II (Ang II) antagonist class and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine

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

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

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

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

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

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta-blockers

to patients with either hypertension or angina, no adverse experiences on electrocardiographic parameters were observed.

Amlodipine has demonstrated beneficial clinical effects in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Valsartan

Valsartan is an orally active, potent, and specific angiotensin 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 angiotensin II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor.

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

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

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

Valsartan has been demonstrated to significantly reduce hospitalizations in patients with chronic heart failure (NYHA class II-IV). The benefits were greatest in patients not receiving either an ACE inhibitor or a beta blocker. Valsartan has also been shown to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

Hydrochlorothiazide

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter perhaps by competing for the Cl- site, thereby affecting electrolyte reabsorption mechanisms: - directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship

was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A clear cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg). For example: A 100,000 mg cumulative dose corresponds to more than 10 years' daily use with a defined daily dose of 25 mg (see section WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS).

Pharmacokinetics (PK)

Linearity

Amlodipine, valsartan and HCTZ exhibit linear pharmacokinetics.

Amlodipine

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

Distribution: Volume of distribution is approximately 21 L/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins. Amlodipine crosses the placenta and is excreted into breast milk.

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

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

Valsartan

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

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

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

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

Hydrochlorothiazide

Absorption: The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h).The increase in mean AUC is linear and dose proportional in the therapeutic range. Concomitant

administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has little clinical importance. Absolute bioavailability of hydrochlorothiazide is 70 % after oral administration.

Distribution: The distribution and elimination kinetics have generally been described as a bi-exponential decay function. The apparent volume of distribution is 4-8 L/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Biotransformation/Metabolism: Hydrochlorothiazide is eliminated predominantly as unchanged drug.

Elimination: Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. More than 95 % of the absorbed dose is excreted as unchanged compound in the urine.

Amlodipine/ Valsartan/ Hydrochlorothiazide

Following oral administration of Exforge HCT in normal healthy adults, peak plasma concentrations of amlodipine, valsartan and HCTZ are reached in 6-8 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan and HCTZ from Exforge HCT are the same as when administered as individual dosage forms.

Special populations

Geriatric patients

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

Systemic exposure to valsartan is slightly elevated in the elderly as compared to the young, but this has not been shown to have any clinical significance.

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Renal impairment

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. There is no apparent correlation between renal function (measured by GFR) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Patients with mild to moderate renal impairment may therefore receive the usual initial dose (see section DOSAGE REGIMEN AND ADMINISTRATION and also section WARNINGS AND PRECAUTIONS).

In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, the mean elimination half-life is almost doubled. The renal clearance of hydrochlorothiazide is also reduced to a great extent compared with the renal clearance of around 300 mL/min in patients with normal renal function. Therefore, Exforge HCT should be used with caution in patients with severe renal impairment (GFR <30 mL/min) (see section WARNINGS AND PRECAUTIONS).

Hepatic impairment

Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%. On average, in patients with mild to moderate chronic liver disease

exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide, and no dose reduction is considered necessary. However, Exforge HCT should be used with particular caution in patients with biliary obstructive disorders and severe hepatic impairment (see section WARNINGS AND PRECAUTIONS).

CLINICAL STUDIES

Exforge HCT was studied in a double-blind, active controlled study in hypertensive patients. A total of 2271 patients with moderate to severe hypertension (mean baseline systolic/diastolic blood pressure was 170/107 mmHg) received treatments of amlodipine/valsartan/HCTZ 10/320/25 mg, valsartan/HCTZ 320/25 mg, amlodipine/valsartan 10/320 mg, or HCTZ/amlodipine 25/10 mg. At study initiation patients were assigned lower doses of their treatment combination and were titrated to their full treatment dose by week 2. A total of 55% of patients were male, 14% were 65 years or older, 72% were Caucasian and 17% were Black.

At week 8, the mean reductions in systolic/diastolic blood pressure were 39.7/24.7 mmHg with Exforge HCT (n=571), 32.0/19.7 mmHg with valsartan/HCTZ (n=553), 33.5/21.5 mmHg with amlodipine/valsartan (n=558) and 31.5/19.5 with amlodipine/HCTZ (n=554). The triple combination therapy was statistically superior to each of the three dual combination treatments in reduction of diastolic and systolic blood pressures. The reductions in systolic/diastolic blood pressure with Exforge HCT were 7.6/5.0 mmHg greater than with valsartan/HCTZ, 6.2/3.3 mmHg greater than with amlodipine/valsartan, and 8.2/5.3 mmHg greater than with amlodipine/HCTZ. The full blood pressure lowering effect was achieved 2 weeks after being on their maximal dose of Exforge HCT. Statistically significant greater proportions of patients achieved BP control (<140/90 mmHg) with Exforge HCT (71%) compared to each of the three dual combination therapies (45-54%).

A subgroup of 268 patients was studied with ambulatory blood pressure monitoring. Clinically and statistically superior reductions in 24-hour systolic and diastolic blood pressures with the triple combination compared to valsartan/HCTZ, valsartan/amlodipine, and HCTZ/amlodipine were observed.

In controlled double-blind studies, age, gender, and race did not significantly influence the response to Exforge HCT.

EXCITE (EXperienCe of amlodIpine and valsarTan in hypErtension) Study

In an open, uncontrolled study, 9,794 hypertensive patients across 13 countries in the Middle East and Asia were treated according to routine clinical practice and prospectively observed for 26 weeks. A total of 8,603 were prescribed amlodipine/valsartan and 1,191 prescribed amlodipine/valsartan/hydrochlorothiazide. Among these, 15.5% were elderly, 32.5% were obese, 31.3% had diabetes, and 9.8% had isolated systolic hypertension. Both amlodipine/ valsartan and amlodipine/valsartan/hydrochlorothiazide single-pill combinations, respectively, were associated with clinically relevant and significant mean sitting systolic/diastolic BP reductions in the overall population (-31.0/-16.6 mmHg and -36.6/-17.8 mmHg, respectively. These results were consistent regardless of age, body mass index, and diabetic status. Similarly, clinically relevant and significant systolic BP reductions were observed in patients with isolated systolic hypertension (−25.5 mmHg and −30.2 mmHg, respectively).

NON-CLINICAL SAFETY DATA

Amlodipine:Valsartan:Hydrochlorothiazide

In a variety of preclinical safety studies conducted in several animal species with amlodipine/valsartan/hydrochlorothiazide (Exforge HCT), there were no findings that would exclude the use of therapeutic doses of Exforge HCT in humans. Preclinical safety studies with

amlodipine/valsartan/ hydrochlorothiazide were conducted in rats up to 13-weeks duration and a no observable adverse effect level (NOAEL) was determined to be 0.5/8/1.25 mg/kg/day. Higher doses of this combination (≥2/32/5 mg/kg/day) resulted in expected reduction of red blood cell mass (erythrocytes, hemoglobin, hematocrit, and reticulocytes), increase in serum urea, increase in serum creatinine, increase in serum potassium, juxtaglomerular (JG) hyperplasia in the kidney and focal erosions in the glandular stomach in rats. All these changes were reversible after a 4-week recovery period and were considered to be exaggerated pharmacological effects.

The amlodipine/valsartan/hydrochlorothiazide combination was not tested for mutagenicity, clastogenicity, reproductive performance or carcinogenicity as there was no evidence of any interaction between these drugs, which have been on the market for a long time.

Amlodipine

Safety data for amlodipine are well established both clinically and non-clinically. No relevant findings were observed in carcinogenicity studies, mutagenicity studies.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times the maximum recommended human dose of 10 mg on a mg/m^2 basis, based on patient weight of 50 kg).

Amlodipine has been tested individually for mutagenicity, clastogenicity, reproductive performance and carcinogenicity with negative results.

Valsartan

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential and effects on fertility.

Safety pharmacology and Long term toxicity: In a variety of preclinical safety studies conducted in several animal species, there were no findings that would exclude the use of therapeutic doses of valsartan in humans. In preclinical safety studies, high doses of valsartan (200 to 600 mg/kg/day body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and evidence of changes in renal hemodynamics (slightly raised blood urea nitrogen, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised blood urea nitrogen and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

Reproductive toxicity: In a rat fertility study, valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day, approximately 6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Mutagenicity: Valsartan was devoid of mutagenic potential at either the gene or chromosome level when investigated in various standard *in vitro* and *in vivo* genotoxicity studies.

Carcinogenicity: There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for 2 years at doses up to 160 and 200 mg/kg/day, respectively.

Hydrochlorothiazide

Hydrochlorothiazide has been tested individually for mutagenicity, clastogenicity, reproductive performance and carcinogenicity with negative results.

According to the experimental data available, hydrochlorothiazide did not reveal evidence of carcinogenic activity in rats and mice (hepatocellular tumors in mice were only seen in the high-dosed males; the incidence did not exceed those levels historically found in controls). The mutagenic potential was assessed in a series of *in vitro* and *in vivo* test systems. While some positive results were obtained *in vitro*, all *in vivo* studies provided negative results. Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine dimers *in vitro* and in the skin of mice following oral treatment. It is therefore concluded that there is no relevant mutagenic potential *in vivo*, although hydrochlorothiazide could enhance the genotoxic effects of UVA light.

Valsartan:Hydrochlorothiazide

In a variety of preclinical safety studies conducted in several animal species, there were no findings that would exclude the use of therapeutic doses of valsartan:hydrochlorothiazide in humans. High doses of valsartan:hydrochlorothiazide (100:31.25 to 600:187.5 mg/kg body weight) caused, in rats, a reduction of red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and evidence of changes in renal hemodynamics (moderate to severe raised plasma urea, increases in plasma potassium and magnesium and mild increases in urinary volume and electrolytes, minimal to slight tubular basophilia, and afferent arteriolar hypertrophy at the highest dose level). In marmosets (30:9.375 to 400:125 mg/kg), the changes were fairly similar though more severe, particularly at the higher dose levels and in the kidney, where the changes developed to a nephropathy, which included raised urea and creatinine. Marmoset also had gastrointestinal mucosal changes at 30: 9.373 to 400: 125 mg/kg. Hypertrophy of the renal juxtaglomerular cells was also seen in rats and marmosets. All changes were considered to be caused by the pharmacological action of valsartan:hydrochlorothiazide which is synergistic (potentiation is about tenfold compared to valsartan alone) rather than additive, producing prolonged hypotension particularly in marmosets. For therapeutic doses of valsartan:hydrochlorothiazide in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance. The main preclinical safety findings are attributed to the pharmacological action of the compounds which appear to act synergistically with no evidence of any interaction between the two compounds. In the clinic, the actions of the two compounds are additive, and the preclinical findings have not been demonstrated to have any clinical significance. The combination valsartan:hydrochlorothiazide was not tested for mutagenicity, clastogenicity or carcinogenicity as there was no evidence for any interaction between the two compounds.

Amlodipine:Valsartan

In a variety of preclinical safety studies conducted in several animal species with amlodipine:valsartan, there were no findings that would exclude the use of therapeutic doses of amlodipine: valsartan in humans. Animal studies lasting 13 weeks have been conducted with amlodipine:valsartan combination in rats and marmosets, as well as studies in rats to investigate embryofetal development toxicity.

In a 13-week oral toxicity study in rats, amlodipine/valsartan-related inflammation of the glandular stomach was observed in males at doses ≥3/48 mg/kg/day and in females at doses ≥7.5/120 mg/kg/day. No such effects have been observed in the 13-week marmoset study at any dose, although inflammation of the large intestine was observed in the high-dose marmosets only (no effects at dose ≤5/80 mg/kg/day). The gastrointestinal adverse effects observed in clinical trials with Exforge were no more frequent with the combination than with the respective monotherapies. The combination amlodipine:valsartan was not tested for mutagenicity, clastogenicity, reproductive performance or carcinogenicity as there was no evidence for any interaction between the two compounds.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Exforge HCT should not be used after the date marked “EXP” on the pack.

Exforge HCT must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

No special requirements.

Manufacturer:

See folding box.

International Package Leaflet

Information issued: February 2021

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Novartis Pharma AG, Basel, Switzerland