SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Exforge HCT 10 mg/160 mg/12.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Exforge HCT 10 mg/160 mg/12.5 mg film-coated tablets
Each film-coated tablet contains:
Amlodipine besylate
Equivalent to Amlodipine .....10 mg
Valsartan .....160 mg
Hydrochlorothiazide .....12.5 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)
Exforge HCT 10 mg/160 mg/12.5 mg film-coated tablets
Pale yellow, ovaloid, biconvex tablets with bevelled edge, debossed "NVR" on one side and "VDL" on the other side. Approximate size: 15 mm (length) x 5.9 mm (width).

4. CLINICAL PARTICULARS

4.1 Indications/Uses

Treatment of essential hypertension.
Exforge HCT is indicated in patients whose blood pressure is not adequately controlled by dual therapy. Exforge HCT is indicated as substitution therapy in patients already taking the same dosage strengths of valsartan, amlodipine and hydrochlorothiazide as separate tablets.

4.2 Dosage/Administration

Usual dosage
When switching from dual therapy to Exforge HCT, it is recommended that 1 Exforge HCT film-coated tablet be taken once daily at a dose of 5 mg/160 mg/12.5 mg.
Patients receiving valsartan, amlodipine and hydrochlorothiazide as separate tablets may be switched to the corresponding dose of Exforge HCT.
The maximum recommended dose of Exforge HCT is 10 mg/320 mg/25 mg (2 tablets of Exforge HCT 5 mg/160 mg/12.5 mg).
Exforge HCT should be taken with some water, with or without food.
See "Warnings and precautions" with regard to discontinuation of beta blockers.

Special dosage instructions
Patients with hepatic impairment
Due to the active substance components valsartan, hydrochlorothiazide and amlodipine, Exforge HCT should be used with particular caution in patients with hepatic impairment or biliary tract disorders.

Consideration should be given to starting treatment with the lowest available dose of amlodipine. The lowest strength of Exforge HCT contains 5 mg amlodipine. (See "Warnings and precautions" and "Pharmacokinetics").

Patients with renal impairment
No dosage adjustment is required for patients with mild to moderate renal impairment (creatinine clearance 30 ml/min).
Due to the active substance component hydrochlorothiazide, Exforge HCT is contraindicated in patients with anuria (see "Contraindications") and should be used with caution in patients with severe renal impairment (GFR <30 ml/min) (see "Warnings and precautions" and "Pharmacokinetics").
Thiazide diuretics are ineffective as monotherapy in severe renal impairment (GFR <30 ml/min), but may be useful even in patients with a GFR <30 ml/min when used with due caution in combination with a loop diuretic.

Elderly patients
Due to the amlodipine contained in Exforge HCT, consideration should be given to starting treatment with the lowest available dose of amlodipine. The lowest strength of Exforge HCT contains 5 mg amlodipine (see "Properties/Effects" and "Pharmacokinetics").

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

4.3 Contraindications
Hypersensitivity to any of the active substances, other sulphonamide derivatives or to any of the excipients.
Pregnancy, lactation (see "Pregnancy, lactation"). Biliary cirrhosis or cholestasis.
Anuria.
Hereditary angioedema or angioedema during previous treatment with an ACE inhibitor or angiotensin II receptor antagonist.
Combination of Exforge HCT with aliskiren in patients with diabetes mellitus (type 1 and type 2) and patients with renal impairment (eGFR <60 ml/min/1.73m^2).
Severe hypotension.
Shock (including cardiogenic shock).
Obstruction of the left ventricular outflow tract (e.g. high-grade aortic stenosis).
Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Warnings and precautions
Dual blockade of the renin-angiotensin-aldosterone (RAA) system: see "Interactions".
Sodium and/or volume-depleted patients
Excessive hypotension, including orthostatic hypotension, was seen in 1.7% of patients treated with 10 mg/320 mg/25 mg amlodipine/valsartan/HCT, 1.8% of patients treated with 320 mg/25 mg valsartan/HCT, 0.4% of patients treated with 10 mg/320 mg amlodipine/valsartan and 0.2% of patients treated with 25 mg/10 mg HCT/amlodipine in a controlled study in patients with moderate to severe uncomplicated hypertension.
If excessive hypotension occurs with Exforge HCT, the patient should be placed in the supine position and, if necessary, given an IV infusion of saline solution. Treatment can be continued once blood pressure has stabilised.

Serum electrolytes
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g. heparin) should be undertaken with caution.

Electrolytes
Potassium
Thiazide diuretics may cause hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazides should be administered with caution and subject to regular monitoring of serum potassium in patients with conditions involving enhanced potassium loss.
Hypokalaemia should be corrected prior to the initiation of thiazide therapy. Coexisting hypomagnesaemia may make hypokalaemia more difficult to correct. As Exforge HCT contains an angiotensin II receptor blocker, supplementation of potassium should be undertaken with great caution. Potassium and magnesium concentrations should be monitored regularly. All patients receiving thiazide diuretics should be monitored for electrolyte imbalances.
Sodium
Thiazide diuretics can precipitate new-onset hyponatraemia or exacerbate pre-existing hyponatraemia. This may be associated with neurological symptoms (vomiting, confusion, apathy). Thiazide diuretics should only be administered after correction of any pre-existing hyponatraemia. Serum sodium concentrations should be monitored regularly.
Calcium
Thiazide diuretics decrease urinary calcium excretion and may cause elevation of serum calcium. Thiazide diuretics should only be initiated after correcting any pre-existing hypercalcaemia or treating the condition responsible for it. Serum calcium concentrations should be monitored regularly.
Volume depletion
In severely volume-depleted patients, symptomatic hypotension may occur after initiation of therapy with Exforge HCT. Existing volume depletion should be corrected before the start of treatment.
Amlodipine – valsartan – hydrochlorothiazide
In the controlled study in moderately to severely hypertensive patients, the incidence of hypokalaemia (serum potassium <3.5 mmol/l) at any time was 9.9% with 10 mg/320 mg/25 mg amlodipine/valsartan/HCT, 24.5% with 25 mg/10 mg HCT/amlodipine, 6.6% with 320 mg/25 mg valsartan/HCT and 2.7% with 10 mg/320 mg amlodipine/valsartan. One patient (0.2%) discontinued therapy due to hypokalaemia in each of the amlodipine/valsartan/HCT and HCT/amlodipine groups. The incidence of hyperkalaemia (serum potassium >5.7 mmol/l) was 0.4% with amlodipine/valsartan/HCT compared to 0.2-0.7% with the dual therapies.
In the controlled study, the opposing effects of 320 mg valsartan and 25 mg hydrochlorothiazide on serum potassium approximately balanced each other out in many patients. In other patients, one or the other effect was dominant.

Beta blocker discontinuation
Exforge HCT does not contain a beta blocker and therefore provides no protection against the risks of abrupt beta blocker discontinuation. Any such discontinuation should always be by gradual reduction of the beta blocker dose.

Patients with renal artery stenosis

No data are available on the use of Exforge HCT; therefore, Exforge HCT should be used with particular caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis of a solitary kidney. As other medicinal products that affect the renin-angiotensin-aldosterone system may increase blood urea and serum creatinine in patients with unilateral or bilateral renal artery stenosis, monitoring of such patients is recommended as a precautionary measure.

Patients with kidney transplantation
There is no experience with the safe use of Exforge HCT in patients who have recently undergone kidney transplantation.

Patients with renal impairment
There is no experience in patients with severe renal impairment (creatinine clearance <10 ml/min).

Patients with hepatic impairment
Particular caution is required when administering Exforge HCT to patients with mild to moderate hepatic impairment (see "Dosage/Administration") or biliary obstructive disorders. Due to the active substance components valsartan, hydrochlorothiazide and amlodipine, Exforge HCT should be used with particular caution in patients with severe hepatic impairment (see "Dosage/Administration" and "Pharmacokinetics").
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 had previously experienced angioedema with other medicinal products, including ACE inhibitors. Exforge HCT must be immediately discontinued in patients who develop angioedema and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms. Adrenaline should be administered if there is involvement of the tongue, glottis or larynx. In addition, measures should be taken to ensure the patient's airways remain open and Exforge HCT must not be re-administered to such patients.
Intestinal angioedema
Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including valsartan (see "Undesirable effects"). These patients experienced abdominal pain, nausea, vomiting and diarrhoea. The symptoms subsided after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, Exforge HCT should be discontinued and appropriate monitoring initiated until symptoms have completely resolved.
Patients with heart failure and prior myocardial infarction
In general, calcium channel blockers, including amlodipine, should be used with particular caution in patients with severe heart failure (NYHA class III-IV).
In patients whose renal function depends on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe heart failure), treatment with ACE inhibitors or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and, in rare cases, with acute renal failure and/or death. Evaluation of patients with heart failure or patients who have previously had a myocardial infarction should always include assessment of renal function.
Risk of myocardial infarction or exacerbation of angina pectoris
Exacerbation of angina pectoris or acute myocardial infarction may occur after starting or increasing the dose of amlodipine, particularly in patients with severe

obstructive coronary artery disease.
Aortic or mitral valve stenosis or obstructive hypertrophic cardiomyopathy
Special caution is required when using amlodipine in patients with aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy.

Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.
Metabolism disorders
Thiazide diuretics, including hydrochlorothiazide, may impair glucose tolerance and raise serum levels of cholesterol and triglycerides.
Metabolic effects
Exforge HCT may raise serum uric acid concentrations due to reduced uric acid clearance and may cause or exacerbate hyperuricaemia and precipitate gout in susceptible patients. Exforge HCT is therefore not recommended for use in patients with hyperuricaemia and/or gout.
Pathological changes have been observed in the parathyroid gland of a few patients with hypercalcaemia and hypophosphataemia on prolonged thiazide therapy. If hypercalcaemia occurs, further diagnostic clarification is necessary.
Other
Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergies and asthma.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Sulphonamides and sulphonamide derivatives can cause an idiosyncratic reaction that may lead to choroidal effusion with scotoma, transient myopia and acute angle-closure glaucoma. Symptoms include acute-onset vision loss or eye pain and typically occur within a few hours to weeks of treatment initiation. Untreated angle-closure glaucoma may lead to permanent vision loss.
The primary treatment consists of immediate discontinuation of the medicinal product. If intraocular pressure remains elevated, immediate medical treatment or surgery must be considered. Risk factors for angle-closure glaucoma include a history of sulphonamide or penicillin allergy.

Non-melanoma skin cancer (NMSC)
An increased risk of non-melanoma skin cancer (NMSC) (basal cell carcinoma and squamous cell carcinoma) with increasing cumulative hydrochlorothiazide exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. The risk of NMSC appears to increase with long-term use (see “Properties/Effects”). The photosensitising action of hydrochlorothiazide could be involved as a potential mechanism in the development of NMSC.
Patients using hydrochlorothiazide are to be informed of the NMSC risk and must be instructed to regularly check their skin for any new lesions and promptly report any suspicious skin changes. Patients should be advised to take preventive measures such as limiting sunlight/UV exposure and use of adequate sun protection when exposed to sunlight in order to minimise the risk of skin cancer. Suspicious skin changes are to be promptly examined, potentially using histological analysis of biopsies. In addition, the use of hydrochlorothiazide may need to be reconsidered in patients with a
history of NMSC (see also “Undesirable effects”).

Acute respiratory toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS), have been reported after hydrochlorothiazide intake. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset symptoms include dyspnoea, fever, deterioration of pulmonary function and hypotension. If ARDS is suspected, Exforge HCT should be discontinued and appropriate treatment initiated.
Hydrochlorothiazide must not be administered to patients who have previously experienced ARDS following hydrochlorothiazide intake.

4.5 Interactions
Valsartan – hydrochlorothiazide: Interactions related to both components Lithium
The following interactions may occur when using both components of Exforge HCT (valsartan and/or hydrochlorothiazide):
Reversible increases in serum lithium concentrations and lithium toxicity have been reported during co- administration of lithium with ACE inhibitors, angiotensin II receptor antagonists or thiazides. Since thiazides reduce renal clearance of lithium, lithium toxicity may be increased after administration of Exforge HCT. Therefore, careful monitoring of serum lithium concentrations is recommended during concomitant use.

Amlodipine
Amlodipine may be co-administered with thiazide diuretics, alpha blockers, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, non-steroidal anti-inflammatory drugs, antibiotics and oral antidiabetics.
Calcium antagonists can interfere with the cytochrome P450-dependent metabolism of theophylline and ergotamine. As neither in vitro nor in vivo interaction studies with theophylline or ergotamine and amlodipine are available, regular monitoring of theophylline or ergotamine blood levels is recommended at the start of co-administration.

Valsartan
As valsartan is only metabolised to a slight extent, no clinically relevant drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are to be expected.

Although valsartan is extensively bound to plasma proteins, in vitro studies have not shown any interactions based on this mechanism with a range of other substances that are also extensively bound to plasma proteins such as diclofenac, furosemide and warfarin.
There is no experience with concomitant use of valsartan and lithium. Regular monitoring of serum lithium levels is therefore recommended during concomitant use of lithium and valsartan.

Potassium: Concomitant use of angiotensin II receptor antagonists with other medicinal products capable of increasing serum potassium (e.g. potassium-sparing diuretics, medicinal products containing potassium, heparin) may increase the risk of hyperkalaemia. In such cases, valsartan, which is contained in Exforge HCT, should be used with caution and subject to monitoring of potassium levels.

Hydrochlorothiazide
Other antihypertensives: Thiazides potentiate the antihypertensive action of other antihypertensive medicinal products (e.g. guanethidine, methyldopa, beta blockers, vasodilators, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers (ARBs) and direct renin inhibitors (DRIs).
Skeletal muscle relaxants: Thiazides, including hydrochlorothiazide, potentiate the effect of skeletal muscle relaxants such as curare derivatives.
Non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 selective inhibitors: Co-administration of non-steroidal anti-inflammatory drugs (e.g. salicylic acid derivatives or indometacin) may weaken the diuretic and antihypertensive activity of thiazides. Concurrent hypovolaemia may induce acute renal failure.
Medicinal products affecting serum potassium levels: The hypokalaemic effect of hydrochlorothiazide may be increased by co-administration of other kaliuretic diuretics, corticosteroids, ACTH, amphotericin B, penicillin G, salicylic acid derivatives or antiarrhythmics (see “Warnings and precautions”).
Medicinal products affecting serum sodium levels: The hyponatraemic effect of diuretics may be potentiated by co-administration of medicinal products such as antidepressants, antipsychotics or antiepileptics. Caution is advised in long-term administration of these medicinal products. (See also “Warnings and precautions”).
Cardiac glycosides (digitalis): Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias (see “Warnings and precautions”).
Antidiabetic medicinal products: Thiazides may alter glucose tolerance. It may be necessary to adjust the dosage of insulin and oral antidiabetics in view of the hyperglycaemic effect of hydrochlorothiazide.
Anticholinergics: The bioavailability of thiazide diuretics may be increased by anticholinergics (e.g. atropine, biperiden), probably due to a decrease in gastrointestinal peristalsis and delayed gastric

emptying. Conversely, prokinetic medicinal products such as cisapride may decrease the bioavailability of thiazide diuretics.
Methyldopa: There have been reports in the literature of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.
Ion exchange resins: Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. Administration of hydrochlorothiazide and an ion-exchange resin should thus be staggered, leaving as long an interval as possible to minimise interactions.
Vitamin D: Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or calcium salts may potentiate the rise in serum calcium.
Ciclosporin: Concomitant treatment with ciclosporin and hydrochlorothiazide may increase the risk of hyperuricaemia and gout-type complications.
Calcium salts: Concomitant use of thiazide-type diuretics may lead to hypercalcaemia by increasing tubular calcium reabsorption.
Allopurinol: Concomitant treatment with thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.
Amantadine: Concomitant treatment with thiazide diuretics, including hydrochlorothiazide, may increase the risk of undesirable effects caused by amantadine.
Diazoxide: Concomitant treatment with thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.
Antineoplastics (e.g. cyclophosphamide, methotrexate): Concomitant treatment with thiazide diuretics, including hydrochlorothiazide, may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.
Alcohol, barbiturates or narcotics: Co-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. However, the clinical significance of this effect is not sufficient to preclude their use.
Dantrolene (infusion): In animal models, lethal ventricular fibrillation and cardiovascular collapse were observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended to avoid the co-administration of calcium channel blockers such as amlodipine in patients known to be at increased risk of malignant hyperthermia or who are being treated for malignant hyperthermia.
In vitro studies
Transporters: In vitro studies 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 transporters OATP1B1 (rifampicin, ciclosporin) or MRP2 (ritonavir) may therefore increase systemic exposure to valsartan.

No clinically relevant interactions have been found with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine and glibenclamide.

Enzyme inhibitors
Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors:
Administration of NSAIDs or COX-2 inhibitors may attenuate the antihypertensive effect of angiotensin II receptor antagonists (AIIRAs). In elderly patients, patients with

renal impairment and patients with volume depletion (including those on diuretic therapy), co-administration of NSAIDs (or COX-2 inhibitors) with an AIIRA may increase the risk of deterioration of renal function (including acute renal failure). These medicinal products should therefore only be combined in such patients with caution and subject to monitoring of renal function.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with ACE inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) or aliskiren
Hypotension, syncope, hyperkalaemia and renal impairment (including acute renal failure) have been observed more frequently with dual blockade of the RAA system with ARBs, ACEIs or aliskiren compared to monotherapy with these substances, particularly in normotensive to hypotensive patients at the start of therapy.
Dual blockade of the RAAS through the concomitant use of ACE inhibitors, ARBs or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to close monitoring of renal function, electrolytes and blood pressure.
ACE inhibitors and angiotensin receptor blockers (ARBs) –including valsartan– should not be used concomitantly in patients with diabetic nephropathy.
In certain patients, this combination is contraindicated (see “Contraindications”).

mTOR (mechanistic target of rapamycin) inhibitors
mTOR inhibitors such as sirolimus, temsirolimus and everolimus are CYP3A substrates and amlodipine is a weak CYP3A inhibitor. Amlodipine may increase mTOR inhibitor exposure if co- administered with mTOR inhibitors.

Other interactions
Effect of Exforge HCT on other medicinal products Effects of amlodipine on other active substances

In vitro studies with human plasma show that amlodipine does not affect the protein binding of digoxin, phenytoin, coumarin, warfarin or indometacin.

Atorvastatin: Co-administration of several doses of amlodipine (10 mg) with atorvastatin (80 mg) did not result in any significant changes in the steady-state pharmacokinetic parameters of atorvastatin.

Simvastatin: Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. The daily dose of simvastatin should be limited to 20 mg per day in patients taking amlodipine.

Digoxin: Studies in healthy subjects have shown that co-administration of amlodipine and digoxin does not result in any changes in digoxin plasma levels or renal digoxin clearance.

Ethanol (alcohol): Single and multiple doses of amlodipine (10 mg) had no significant effect on the pharmacokinetics of ethanol.
Warfarin: Co-administration of amlodipine did not significantly alter the effect of warfarin on prothrombin time in healthy male subjects.

Ciclosporin: Pharmacokinetic studies with ciclosporin have shown that amlodipine does not significantly alter the pharmacokinetics of ciclosporin.
Tacrolimus: There is an increased risk of increased tacrolimus blood levels with co-administration with amlodipine. To avoid tacrolimus toxicity, tacrolimus blood levels must be monitored if amlodipine is administered to patients being treated with tacrolimus and the dose of tacrolimus must be adjusted as necessary.

Effect of other medicinal products on Exforge HCT Effects of other active substances 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. Strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may result in higher plasma concentrations of amlodipine than with diltiazem. Caution should therefore be exercised when co- administering amlodipine with CYP3A4 inhibitors.

CYP3A4 inducers: No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Patients must be monitored to ensure the desired clinical effect when amlodipine is co- administered with CYP3A4 inducers.

Cimetidine: Co-administration of amlodipine and cimetidine does not alter the pharmacokinetics of amlodipine.

Grapefruit juice:
Administration of amlodipine (contained in Exforge HCT) with grapefruit or grapefruit juice is generally not recommended as this may increase the bioavailability of amlodipine in some patients, thereby enhancing the blood pressure-lowering effect. A cause could be genetic polymorphism of CYP3A4, the main enzyme responsible for the metabolism of amlodipine. In a study in 20 healthy subjects, grapefruit juice was found to have no significant effect on the pharmacokinetics of amlodipine.

Aluminium/magnesium (antacids): Co-administration of aluminium/magnesium antacids and a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single dose of sildenafil (100 mg) in patients with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine.

4.6 Pregnancy, lactation

Pregnancy
Exforge HCT must not be administered during pregnancy (see “Contraindications”).
Due to the mechanism of action of angiotensin II receptor antagonists, fetal risk cannot be excluded. Administration of ACE inhibitors (a specific class of medicinal products acting on the renin-angiotensin- aldosterone system (RAAS)) to pregnant women during the second and third trimesters has been reported to cause fetal injury and death. In addition, based on retrospective data, the use of ACE inhibitors in the first trimester has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and neonatal renal impairment when pregnant women have inadvertently taken valsartan.
Animal studies with amlodipine have shown reproductive toxicity (see “Preclinical

data").
Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, can cause fetal or neonatal jaundice or thrombocytopenia and may be associated with other adverse effects that have occurred in adults. Hydrochlorothiazide, like other diuretics, can decrease placental perfusion. Since these medicinal products do not prevent or alter the course of EPH (oedema, proteinuria, hypertension) gestosis (pre-eclampsia), they must not be used to treat hypertension in pregnant women.
As with any active substance that acts directly on the RAAS, Exforge HCT must not be taken by women planning to become pregnant (see "Contraindications"). Healthcare professionals prescribing medicinal products that act on the RAAS should inform women of childbearing potential about the potential risk of these products during pregnancy.
If pregnancy is detected during therapy, Exforge HCT must be discontinued immediately.
All neonates exposed to the medicinal product in utero should be carefully checked for adequate urine output, hyperkalaemia and blood pressure. If necessary, medical measures such as rehydration must be taken to remove the medicinal product from the circulation.

Lactation
It is not known whether valsartan and/or amlodipine are excreted in breast milk. Valsartan was excreted in the milk of rats. Hydrochlorothiazide is excreted in breast milk. Therefore, the use of Exforge HCT is contraindicated during breast-feeding.

4.7 Effects on ability to drive and use machines
There have been no studies on the effects of this product on the ability to drive or use machines. However, when driving or using machines, it must be borne in mind that dizziness or fatigue may occasionally occur during the course of any antihypertensive therapy.

4.8 Undesirable effects
The safety of Exforge HCT was evaluated at the maximum dose of 10 mg/320 mg/25 mg in a controlled clinical study in 2,271 patients, 582 of whom received valsartan in combination with amlodipine and hydrochlorothiazide. No new or unexpected undesirable events were reported with the triple combination compared to the known effects of the individual active substances. No risks other than those previously known were observed with long-term treatment. Exforge HCT was well tolerated regardless of age, gender or race.
Frequencies
Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to
<1/1,000), very rare (<1/10,000).
Metabolism and nutrition disorders Common:
Hypokalaemia
Uncommon: Anorexia, hypercalcaemia, hyperlipidaemia, hyperuricaemia, hyponatraemia, weight gain
Psychiatric diseases
Uncommon: Insomnia, sleep disorders
Nervous system disorders
Common: Dizziness, headache

Uncommon: Abnormal coordination, postural dizziness, exertional dizziness, dysgeusia, lethargy, paraesthesia, peripheral neuropathy, neuropathy, somnolence, syncope
Eye disorders
Uncommon: Visual disturbances Ear and labyrinth disorders
Uncommon: Vertigo
Cardiac disorders
Uncommon: Tachycardia Vascular disorders Common: Hypotension
Uncommon: Orthostatic hypotension, phlebitis, thrombophlebitis
Respiratory, thoracic and mediastinal disorders Uncommon: Cough, dyspnoea, throat irritation
Very rare: Acute respiratory distress syndrome (ARDS) (see "Warnings and precautions")
Gastrointestinal disorders
Common: Dyspepsia
Uncommon: Abdominal discomfort, upper abdominal pain, breath odour, diarrhoea, dry mouth, nausea, vomiting
Very rare: Intestinal angioedema
Skin and subcutaneous tissue disorders
Uncommon: Rash, erythema
Rare: Hyperhidrosis, exanthema, pruritus
Musculoskeletal and connective tissue disorders
Uncommon: Back pain, joint swelling, muscle spasm, muscle weakness, myalgia, pain in the extremities
Renal and urinary disorders
Common: Pollakiuria
Uncommon: Increased serum creatinine, acute renal failure
Reproductive system and breast disorders
Uncommon: Erectile dysfunction
General disorders and administration site conditions Common: Fatigue, oedema
Uncommon: Abasia, gait disturbance, asthenia, discomfort, malaise, non-cardiac chest pain
Investigations
Uncommon: Increased blood urea nitrogen (BUN), increased blood uric acid
In an 8-week controlled clinical study, changes in laboratory values observed with Exforge HCT were minor and consistent with the pharmacological mechanism of action of the individual active substances. The presence of valsartan in the triple combination attenuates the hypokalaemic effect of hydrochlorothiazide.
Additional information on the individual active substances
The following undesirable effects, which were not observed in the study with Exforge HCT, have occurred during treatment with the individual active substances:
Amlodipine
Blood and lymphatic system disorders Very rare: Leukopenia, thrombocytopenia Immune system

disorders
Very rare: Hypersensitivity
Metabolism and nutrition disorders Very rare: Hyperglycaemia Psychiatric diseases
Uncommon: Depression, insomnia, mood swings (including anxiety)
Rare: Confusion
Nervous system disorders
Common: Somnolence, dizziness, headache
Uncommon: Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia
Very rare: Peripheral neuropathy, hypertension
Eye disorders
Common: Visual impairment (including diplopia)
Ear and labyrinth disorders Uncommon: Tinnitus Cardiac disorders Common: Palpitations
Uncommon: Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Very rare: Myocardial infarction
Vascular disorders
Common: Flushing
Uncommon: Hypotension
Very rare: Vasculitis
Respiratory, thoracic and mediastinal disorders Common: Dyspnoea
Uncommon: Rhinitis, cough
Gastrointestinal disorders
Common: Abdominal pain, nausea, dyspepsia, change in bowel habits (including diarrhoea and constipation)
Uncommon: Vomiting, dry mouth
Very rare: Gastritis, gingival hyperplasia, pancreatitis
Hepatobiliary disorders
Very rare: Increased liver enzymes, including increased serum bilirubin, hepatitis, intrahepatic cholestasis, jaundice
Skin and subcutaneous tissue disorders
Uncommon: Alopecia, exanthema, purpura, skin discolouration, hyperhidrosis, pruritus, rash, urticaria Very rare: Angioedema, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, photosensitivity
Not known: Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders Common: Ankle swelling, muscle spasms Uncommon: Arthralgia, myalgia, back pain Renal and urinary disorders
Uncommon: Micturition disorder, nocturia, increased micturition frequency
Reproductive system and breast disorders
Uncommon: Gynaecomastia, impotence
General disorders and administration site conditions Very common: Oedema

Common: Fatigue, asthenia
Uncommon: Pain, malaise, chest pain
Investigations
Uncommon: Weight gain, weight loss

Valsartan
Infections and infestations
Common: Viral infections
Uncommon: Upper respiratory tract infection, pharyngitis, sinusitis
Very rare: Rhinitis
Blood and lymphatic system disorders Uncommon: Neutropenia
Very rare: Thrombocytopenia, decreased haemoglobin and haematocrit
Immune system disorders Very rare: Hypersensitivity
Metabolism and nutrition disorders Uncommon: Hyperkalaemia Psychiatric diseases
Uncommon: Decreased libido Nervous system disorders Common: Postural dizziness Rare: Light-headedness
Cardiac disorders
Uncommon: Heart failure Very rare: Arrhythmias.
Vascular disorders
Very rare: Vasculitis
Hepatobiliary disorders
Very rare: Abnormal liver function values, including increased blood bilirubin
Skin and subcutaneous tissue disorders Very rare: Angioedema, rash, exanthema Not known: Bullous dermatitis
Musculoskeletal and connective tissue disorders Very rare: Arthralgia
Renal and urinary disorders
Very rare: Renal dysfunction, acute renal failure, renal impairment, increased blood creatinine
Pregnancy, puerperium and perinatal conditions Very rare: Fetal complications
Hydrochlorothiazide
Hydrochlorothiazide has been used extensively for many years, sometimes at higher doses than those used in Exforge HCT. The following additional undesirable effects have been observed on monotherapy with thiazide diuretics, including hydrochlorothiazide:

Benign, malignant and unspecified neoplasms (incl. cysts and polyps)
Frequency not known: Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma).

Blood and lymphatic system disorders
Rare: Thrombocytopenia, sometimes with purpura
Very rare: Leukopenia, agranulocytosis, bone marrow failure, haemolytic anaemia
Immune system disorders
Very rare: Necrotising vasculitis, hypersensitivity reactions
Metabolism and nutrition disorders
Very common: (mainly at higher doses) Hypokalaemia, increased blood lipids
Common: Hyponatraemia, decreased appetite and hypomagnesaemia
Rare: Hypercalcaemia, hyperglycaemia, glycosuria, worsening of diabetic metabolic state
Very rare: Hypochloraemic alkalosis
Psychiatric diseases
Rare: Sleep disorders
Nervous system disorders
Rare: Headache, dizziness and depression
Eye disorders
Rare: Visual impairment, particularly in the first few weeks of treatment
Frequency not known: Choroidal effusion
Cardiac disorders Rare: Arrhythmias
Vascular disorders
Common: Orthostatic hypotension, which may be aggravated by alcohol, anaesthetics or sedatives
Respiratory, thoracic and mediastinal disorders
Very rare: Respiratory symptoms, including pneumonitis and pulmonary oedema
Gastrointestinal disorders
Common: Mild nausea and vomiting
Rare: Abdominal discomfort, constipation and diarrhoea
Very rare: Pancreatitis
Hepatobiliary disorders
Rare: Cholestasis or icterus
Skin and subcutaneous tissue disorders Common: Urticaria and other forms of rash Rare: Photosensitivity reactions
Very rare: Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus and toxic epidermal necrolysis
Reproductive system and breast disorders
Common: Impotence

Post-marketing undesirable effects
The following undesirable effects have been identified based on post-marketing experience. As these effects are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequencies.
Frequency not known: Acute renal failure, renal impairment, aplastic anaemia,

erythema multiforme, pyrexia, muscle spasms, asthenia, acute myopia and acute angle-closure glaucoma.

Description of selected adverse effects
Non-melanoma skin cancer (NMSC) (basal cell carcinoma and squamous cell carcinoma): Based on available data from epidemiological studies, a cumulative dose-dependent association between hydrochlorothiazide exposure and the development of NMSC has been observed (see "Warnings and precautions" and "Properties/Effects").

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose
Signs and symptoms
There is no experience of overdose with Exforge HCT. The major symptom of overdose with valsartan is probably hypotension with dizziness.
Non-cardiogenic pulmonary oedema, which may manifest with a delayed onset (24-48 hours post- ingestion) and necessitate ventilatory support, has been reported in rare cases as a consequence of amlodipine overdose. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.
Overdose with amlodipine may result in marked peripheral vasodilation and possibly reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome has been reported.
Hydrochlorothiazide overdose may cause nausea, drowsiness, hypovolaemia and electrolyte disturbances associated with arrhythmias and muscle cramps.

Treatment
Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support, including close monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.
A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may help to reverse calcium channel blockade.
If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy subjects immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

General supportive measures should be initiated in all cases of overdose. This may involve close monitoring of, and measures to stabilise, cardiovascular function.

Valsartan and amlodipine are unlikely to be removed by haemodialysis. Hydrochlorothiazide is dialysable.

5 Pharmacological

properties

5.1 Pharmacodynamic properties

ATC code
C09DX01

Mechanism of action
Exforge HCT combines three antihypertensive active substances with complementary mechanisms of action to control blood pressure in patients with hypertension: the calcium antagonist amlodipine, the angiotensin II receptor antagonist valsartan and the thiazide diuretic hydrochlorothiazide. The combination of these active substances has an additive antihypertensive effect.

Amlodipine
Amlodipine inhibits the transmembrane entry of calcium ions into cardiac muscle cells and vascular smooth muscle cells. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle cells, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine 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 hypertensive patients, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressure. This decrease in blood pressure is 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 a change in filtration fraction or proteinuria.
As with other calcium antagonists, haemodynamic 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 haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered at therapeutic doses to healthy animals and humans, even when co-administered with beta blockers to humans.
Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in healthy animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with hypertension or angina pectoris, no undesirable effects on these electrocardiographic parameters were observed.

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 mechanisms 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 greater affinity (about 20,000-fold) 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 studies comparing valsartan with an ACE inhibitor, the incidence of dry cough was significantly lower ($p < 0.05$) in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9%). In a clinical study of patients with a history of dry cough due to ACE inhibitor therapy, 19.5% of study patients 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 that play a role in cardiovascular regulation.
Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting heart rate.
In most patients, the antihypertensive effect starts within 2 hours of administration of a single oral dose and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect lasts for 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained after 2-4 weeks and is sustained during long-term therapy. Abrupt discontinuation of valsartan has not been associated with rebound hypertension or other undesirable clinical effects.

Hydrochlorothiazide (HCT)
The site of action of thiazide diuretics is primarily the distal convoluted tubule in the renal cortex. It has been shown that there is a high-affinity receptor here that acts as the primary binding site of thiazides. The mode of action of thiazides is through inhibition of the Na^+Cl^- symporter, perhaps by competing for the Cl^- binding site, thus inhibiting Na^+ and Cl^- reabsorption and increasing the excretion of these electrolytes. Indirectly, plasma volume is reduced, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss and a decrease in serum potassium.

Pharmacodynamics No data available. Clinical efficacy
Amlodipine/valsartan/hydrochlorothiazide
Exforge HCT was studied in a double-blind, active-controlled study in hypertensive patients. A total of 2,271 patients with moderate to severe hypertension (mean systolic/diastolic blood pressure of 170/107 mmHg) were treated with 10 mg/320 mg/25 mg amlodipine/valsartan/HCT, 320 mg/25 mg valsartan/HCT, 10 mg/320 mg amlodipine/valsartan or 25 mg/10 mg HCT/amlodipine. At study initiation, the active substance combination was given at lower doses; in the second week, patients were titrated to the full dose. A total of 55% of patients were male, 14% were 65 years of age 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/HCT (n = 553), 33.5/21.5 mmHg with amlodipine/valsartan (n = 558) and 31.5/19.5 with HCT/amlodipine (n = 554). The triple combination therapy was statistically superior to each of the three dual combination treatments in reduction of diastolic and systolic

blood pressure. The full blood pressure lowering effect was achieved after 2 weeks on the maximum dose of Exforge HCT. A significantly greater proportion of patients (71%) achieved blood pressure control (<140/90 mmHg) with Exforge HCT compared to each of the three dual combination therapies (45-54%).
Ambulatory blood pressure measurements in 283 patients showed clinically and statistically superior reductions in 24-hour systolic and diastolic blood pressure with Exforge HCT compared to valsartan/HCT, valsartan/amlodipine and HCT/amlodipine.
Age, gender and race did not significantly influence the response to Exforge HCT.

Long-term data
Non-melanoma skin cancer
Available data from epidemiological studies indicate a cumulative dose-dependent association between hydrochlorothiazide exposure and the development of NMSC. One study included a population with 71,533 cases of basal cell carcinoma and 8,629 cases of squamous cell carcinoma matched to 1,430,833 and 172,462 population controls, respectively. High hydrochlorothiazide exposure (cumulative dose ≥50,000 mg) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for basal cell carcinoma and 3.98 (95% CI: 3.68-4.31) for squamous cell carcinoma. A clear cumulative dose-response relationship was observed for both basal cell carcinoma and squamous cell carcinoma. Another study showed a potential association between lip cancer (squamous cell carcinoma) and exposure to hydrochlorothiazide: 633 cases of lip cancer were compared with 63,067 population controls using a risk-set sampling strategy. A clear cumulative dose-response relationship was demonstrated, with the adjusted OR increasing from 2.1 (95% CI: 1.7-2.6) to 3.9 (95% CI: 3.0-4.9) at a high cumulative dose (≥25,000 mg) and to 7.7 (5.7-10.5) at the highest cumulative dose (≥100,000 mg). As an example, a cumulative dose of 100,000 mg corresponds to the daily use of a defined daily dose of 25 mg over a period of >10 years (see “Warnings and precautions” and “Undesirable effects”).

5.2 Pharmacokinetics
Absorption
Amlodipine
Following oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached after 6-12 hours. Absolute bioavailability is between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Valsartan
Absorption of valsartan after oral administration is rapid (t_{max} = 3 h), although the amount absorbed varies widely. The mean absolute bioavailability of valsartan is 23% (range 23% ± 7%). When taken once daily, valsartan shows little accumulation. Plasma concentrations were similar in men and women. When taken with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48% and C_{max} by 59%. However, starting from 8 h following ingestion of valsartan in the fasted state or with food, plasma concentrations are similar. The reductions in AUC and C_{max} do not result in a clinically significant reduction in therapeutic effect, meaning valsartan can be taken with or without food.

Hydrochlorothiazide
Hydrochlorothiazide is rapidly absorbed following oral administration (T_{max} about 2

h). Taking with food may both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. However, the effect of food intake is slight and of little clinical importance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration.
Distribution
Amlodipine
The volume of distribution is approximately 21 l/kg. In vitro studies with amlodipine have shown that approximately 97.5% of the circulating dose is bound to plasma proteins in hypertensive patients.

Valsartan
Valsartan is highly bound to serum proteins (94-97%), mainly albumin. Steady state is reached within 1 week. The steady-state volume of distribution is about 17 l.

Hydrochlorothiazide
The apparent volume of distribution is 4-8 l/kg. Hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide accumulates in erythrocytes at approximately 3 times the concentration in plasma.

Metabolism
Amlodipine
Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites. CYP3A4 is involved in this metabolism.

Valsartan
Valsartan is only metabolised to a very slight extent.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolised.
Elimination
Amlodipine
Amlodipine elimination from the 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 about 7-8 days. Excretion is mainly renal. 10% of the dose is recovered in the urine as unchanged amlodipine and 60% as amlodipine metabolites.

Valsartan
Valsartan shows multiexponential decay kinetics (primary (alpha) half-life <1 hour and terminal (beta) half-life about 9 h). Plasma clearance is about 2 l/h.
Approximately 70% of absorbed valsartan is excreted in the faeces and 30% in the urine, mainly in unchanged form.

Hydrochlorothiazide
There is no change in the pharmacokinetics of hydrochlorothiazide on repeated dosing and accumulation is minimal when dosed once daily. More than 95% of the absorbed dose is excreted as unchanged active substance in the urine. Elimination is biphasic, with a terminal half-life of 6-15 hours. Renal clearance of hydrochlorothiazide occurs both by passive filtration and active secretion into the tubule.

Amlodipine/valsartan/hydrochlorothiazide
The rate and extent of absorption of amlodipine, valsartan and HCTZ from Exforge HCT are the same as when they are administered as individual substances.

Linearity/non-linearity
Valsartan, amlodipine and hydrochlorothiazide exhibit linear pharmacokinetics.

Pharmacokinetics in special populations Hepatic impairment
Patients with hepatic impairment have decreased clearance of amlodipine, with an increase in AUC of approximately 40-60%. On average, in patients with mild to moderate chronic hepatic impairment, exposure to valsartan (measured by AUC) is twice that in healthy subjects (matched by age, gender and weight).
Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide and no dose reduction is usually necessary. However, Exforge HCT should be used with particular caution in patients with biliary obstructive disorders and severe hepatic impairment (see “Warnings and precautions”).

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 to valsartan (measured by AUC) in patients with different degrees of renal impairment.
In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and urinary excretion is reduced. In patients with mild to moderate renal impairment, the mean elimination half-life is almost doubled due to the significant reduction in renal clearance.
The renal clearance of hydrochlorothiazide is also considerably reduced compared with that in patients with normal renal function (renal clearance of around 300 ml/min). Therefore, Exforge HCT should be used with caution in patients with severe renal impairment (GFR <30 ml/min) (see “Warnings and precautions”).
Hydrochlorothiazide can be cleared by dialysis.

Elderly patients
Time to peak plasma concentrations of amlodipine is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in AUC and elimination half-life.
Systemic exposure to valsartan is slightly elevated in elderly patients compared to younger patients, but this has not been shown to have any clinical significance.
Steady-state hydrochlorothiazide concentrations are higher –and systemic clearance considerably slower– in elderly patients than in young patients.

Children and adolescents
No pharmacokinetic data are available in children for Exforge HCT.

5.3 Preclinical data
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 for up to 13 weeks and the 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 an expected reduction of red blood cell mass (red blood cells, haemoglobin, haematocrit and reticulocytes), an increase in serum urea, serum creatinine and serum potassium, juxtaglomerular hyperplasia in the kidney and focal erosions in the glandular stomach in rats. All of 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, carcinogenicity or reproductive toxicity as there was no evidence of any interactions between these drugs, which have been on the market for a long time. However, amlodipine, valsartan and hydrochlorothiazide have been tested individually for mutagenicity and carcinogenicity with negative results.

Amlodipine
Studies have produced no relevant evidence of carcinogenicity or mutagenicity. In the carcinogenicity studies, the maximum doses in mice and rats were, respectively, similar to and double the maximum recommended human dose of 10 mg on a mg/m^2 basis, based on a patient weight of 50 kg.
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 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 a patient weight of 50 kg).

No evidence of teratogenicity 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 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 labour in rats at this dose.

Valsartan
Apart from fetotoxicity in rabbits, preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity and fertility.
Chronic toxicity: In a variety of preclinical studies conducted in several animal species, apart from fetotoxicity, there were no findings to suggest that therapeutic doses of valsartan should not be used in humans. In preclinical safety studies, a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and changes in renal haemodynamics (slightly raised blood urea, and renal tubular hyperplasia and basophilia in males) were observed at high doses of valsartan (200-600 mg/kg body weight/day) in rats. These doses in rats (200 and 600 mg/kg/day) are equivalent to 6 and 18 times the recommended human dose on a mg/m^2 basis (calculations are based an oral dose of 320 mg/day and a 60 kg patient). In marmosets and at comparable doses, the changes were similar but more severe. This was particularly true for the kidneys, where the changes resulted in nephropathy with elevated urea and creatinine levels. Hypertrophy of the renal juxtaglomerular cells was also seen in rats and marmosets. All changes were presumed to be caused by the pharmacological action of valsartan, which produces prolonged hypotension,

particularly in marmosets. For therapeutic doses in humans, hypertrophy of the renal juxtaglomerular cells does not seem to be relevant.
Hydrochlorothiazide
Hydrochlorothiazide has been tested individually for mutagenicity, clastogenicity, carcinogenicity and reproductive performance with negative results.

Mutagenicity
Valsartan
In various in vitro and in vivo standard genotoxicity studies no mutagenic potential was found for valsartan at either the gene or chromosome level.
Hydrochlorothiazide
Mutagenic potential was assessed in a series of in vitro and in vivo tests. While some positive results were obtained in vitro, all in vivo studies provided negative results. Hydrochlorothiazide increased the UVA-induced formation of pyrimidine dimers in vitro and in the skin of mice following oral administration. It is therefore concluded that there is no relevant mutagenic potential in vivo, although hydrochlorothiazide could enhance the genotoxic effects of UVA light.

Carcinogenicity
Valsartan
There was no indication of carcinogenicity when administering valsartan with food to mice and rats over 2 years at doses of up to 160 and 200 mg/kg/day, respectively.
Hydrochlorothiazide
The available experimental data did not reveal any indication of a carcinogenic effect of hydrochlorothiazide in rats and mice (hepatocellular tumours in mice were only seen in male mice treated with high doses; the incidence did not exceed that in historical controls).

Reproductive toxicity
Valsartan
Valsartan had no undesirable effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day.
In embryofetal development studies (segment II) in mice, rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats at valsartan doses of 600 mg/kg/day and in rabbits at doses of 10 mg/kg/day. In a peri- and postnatal development toxicity study (segment III), the offspring of rats whose parents were given 600 mg/kg/day during the last trimester and during lactation showed a slightly reduced survival rate and a slight developmental delay.
Hydrochlorothiazide
Hydrochlorothiazide was not teratogenic and had no effects on fertility and conception. No teratogenic potential was revealed in 3 tested animal species that received doses at least 10 times higher than the recommended human dose of ~1 mg/kg. A decrease in weight gain in suckling rat pups was attributed to the high dose (15 times the human dose) and to the diuretic effect of hydrochlorothiazide, with corresponding effects on milk production.

Toxicity profiles of the dual combinations of valsartan/hydrochlorothiazide and valsartan/amlodipine
The toxicity profiles of the dual combinations of valsartan/hydrochlorothiazide and

valsartan/amlodipine have been documented in preclinical safety studies. The results of the toxicity studies were similar to those for each medicinal product when administered alone. There were no new toxicities.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Exforge HCT 5 mg/160 mg/12.5 mg film-coated tablets

Tablet core

Cellulose microcrystalline
Crospovidone (type A)
Silica, colloidal anhydrous
Magnesium stearate

Coating

Hypromellose, substitution type 2910 (3 mPa.s)
Titanium dioxide (E171)
Macrogol 4000
Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package to protect from moisture. Keep out of the reach of children.

6.5 Nature and content of container

Exforge HCT 5 mg/160 mg/12.5 mg: 28 film-coated tablets (PA/AL/PVC blister – Calendar pack).

6.6 Special precautions for disposal and handling

NA

7. Marketing Authorization Holder

NVS Kenya Limited
P.O. Box 46057 00100
Kenya

8. Market Authorization Number

21441

9. Date of First Authorization/renewal of the authorization

Date of Renewal: 26/02/2026

10. Date of revision of the Text

26/02/2026