Summary of product characteristics (SmPC)

1.Name of the medicinal product

Senergy® Plus (10/160/12.5) F.C Tablets

2.Qualitative and quantitative composition

Each Film Coated tablet contains:
Amlodipine Besylate Ph. Eur 14.28mg
Eq. to Amlodipine.....10mg
Valsartan USP.....160mg
Hydrochlorothiazide Ph. Eur.....12.5mg

3.Pharmaceutical form

Film Coated Tablets.
Beige oblong convex shaped tablet embossed with N45 from one side and plain from the other side.

4.Clinical particulars

4.1 Therapeutic indications

Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation.

4.2 Posology and method of administration

Route of administration: Oral**.**

Posology

The recommended dose of **Senergy® Plus** is one tablet per day, to be taken preferably in the morning.

Before switching to **Senergy® Plus** patients should be controlled on stable doses of the monocomponents taken at the same time. The dose of **Senergy® Plus** should be based on the doses of the individual components of the combination at the time of switching.
The maximum recommended dose of **Senergy® Plus** is 10 mg/320 mg/25 mg.
Special
populations
Renal
impairment
Due to the hydrochlorothiazide component, **Senergy® Plus** is contraindicated for use in patients with anuria and in patients with severe renal impairment (glomerular filtration rate (GFR)
<30 ml/min/1.73 m2).
No adjustment of the initial dose is required for patients with mild to moderate renal impairment.
Hepatic impairment
Due to the valsartan component, **Senergy® Plus** is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan and therefore **Senergy® Plus** is not suitable in this group of patients. Amlodipine dose recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients with hepatic impairment to **Senergy® Plus**, the lowest available dose of the amlodipine component should be used.
Heart failure and coronary artery disease
There is limited experience with the use of **Senergy® Plus**, particularly at the maximum dose, in patients with heart failure and coronary artery disease. Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of **Senergy® Plus**, 10 mg/320 mg/25 mg.
Elderly (age 65 years or over)
Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of **Senergy® Plus**, 10 mg/320 mg/25 mg, since available data in this patient population are limited. When switching eligible elderly hypertensive patients to **Senergy® Plus**, the lowest available dose of the amlodipine component should be used.
Paediatric population
There is no relevant use of **Senergy® Plus** in the paediatric population (patients below age 18 years) for the indication of essential hypertension.
Method of administration
Oral use.
Senergy® Plus can be taken with or without food.
The tablets should be swallowed whole with some water, at the same time of the day and preferably in the morning.

4.3 Contraindications

- Hypersensitivity to the active substances, to other sulphonamide derivatives, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1.
- Second and third trimesters of pregnancy.

- Hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (GFR <30 ml/min/1.73 m2), anuria and patients undergoing dialysis.
- Concomitant use of **Senergy® Plus** with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m2).
- Refractory hypokalemia, hyponatremia, hypercalcaemia, and symptomatic hyperuricemia.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Hemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Sodium- and/or volume-depleted patients

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

In sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur after initiation of treatment with **Senergy® Plus**. **Senergy® Plus** should be used only after correction of any pre-existing sodium and/or volume depletion.

If excessive hypotension occurs with **Senergy® Plus**, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Serum electrolyte changes

Amlodipine/valsartan/hydrochlorothiazide

In the controlled trial of **Senergy® Plus**, the counteracting 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.

Periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals to detect possible electrolyte imbalance, especially in patients with other risk factors such as impaired renal function, treatment with other medicinal products or history of prior electrolyte imbalances.

Valsartan

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Hydrochlorothiazide

Treatment with **Senergy® Plus** should only start after correction of hypokalemia and any coexisting hypomagnesaemia. Thiazide diuretics can precipitate new onset hypokalemia or exacerbate preexisting 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 develops during hydrochlorothiazide therapy, **Senergy® Plus** should be discontinued until stable correction of the potassium balance.
Thiazide diuretics can precipitate new onset hyponatremia and Hypochloraemic alkalosis or exacerbate pre-existing hyponatremia. Hyponatremia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed. Treatment with hydrochlorothiazide should only be started after correction of pre-existing hyponatremia. In case severe or rapid hyponatremia develops during **Senergy® Plus** therapy, the treatment should be discontinued until normalisation of natraemia.
All patients receiving thiazide diuretics should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium.
Renal impairment
Thiazide diuretics may precipitate azotemia in patients with chronic kidney disease. When **Senergy® Plus** is used in patients with renal impairment periodic monitoring of serum electrolytes (including potassium), creatinine and uric acid serum levels is recommended. **Senergy® Plus** is contraindicated in patients with severe renal impairment, anuria or undergoing dialysis.
No dose adjustment of **Senergy® Plus** is required for patients with mild to moderate renal impairment (GFR ≥30 ml/min/1.73 m2).
Renal artery stenosis
Senergy® Plus should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.
Kidney transplantation
To date there is no experience of the safe use of **Senergy® Plus** in patients who have had a recent kidney transplantation.
Hepatic impairment
Valsartan is mostly eliminated unchanged via the bile. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dose recommendations have not been established. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan, and therefore, **Senergy® Plus** is not suitable in this group of patients.
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 medicinal products including ACE inhibitors. **Senergy® Plus** should be discontinued immediately in patients who develop angioedema and should not be re-administered.
Heart failure and coronary artery disease/post-myocardial infarction
As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with
ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or

death. Similar outcomes have been reported with valsartan. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.
In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic etiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality. Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of **Senergy® Plus**, 10 mg/320 mg/25 mg, since available data in these patient populations is limited.
Aortic and mitral valve stenosis
As with all other vasodilators, special caution is indicated in patients with mitral stenosis or significant aortic stenosis that is not high grade.
Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).
Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is not activated. Therefore, **Senergy® Plus** is not recommended in this population.
Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.
Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required.
Due to the hydrochlorothiazide component, **Senergy® Plus** is contraindicated in symptomatic hyperuricemia. 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 reduce urinary calcium excretion and may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. **Senergy® Plus** is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. **Senergy® Plus** should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Photosensitivity

Cases of photosensitivity reactions have been reported with thiazide diuretics. If photosensitivity reaction occurs during treatment with **Senergy® Plus**, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma

Hydrochlorothiazide, a sulphonamide, 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 a week of treatment 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 sulphonamide or penicillin allergy.

General

Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Elderly (age 65 years or over)

Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of **Senergy® Plus**, 10 mg/320 mg/25 mg, since available data in this patient population are limited.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined 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 frequent close monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with other medicinal products have been performed with Senergy® Plus. Thus, only information on interactions with other medicinal products that are known for the individual active substances is provided in this section.

However, it is important to take into account that **Senergy® Plus** may increase the hypotensive effect of other antihypertensive agents.

Concomitant use not recommended

Senergy® Plus individual component	**Known interactions with the following agents**	**Effect of the interaction with other medicinal products**
Valsartan and 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 including valsartan or thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with **Senergy® Plus**. Therefore careful monitoring of serum lithium concentrations is recommended during concomitant use.
Valsartan	Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels	If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, frequent monitoring of potassium plasma levels is advised.
Amlodipine	Grapefruit or grapefruit juice	Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

Caution required with concomitant use

Senergy® Plus individual component	**Known interactions with the following agents**	**Effect of the interaction with other medicinal products**
Amlodipine	*CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir)*	Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to

		significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.
	CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone] , rifampicin, Hypericum perforatum [St. John's wort])	There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, *Hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.
	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. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.
	Dantrolene (infusion)	In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Valsartan and HCT	*Non-steroidal anti-inflammatory Drugs (NSAIDs), including Selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid (>3 g/day), and nonselective NSAIDs*	NSAIDS can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of **Senergy® Plus** and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.
Valsartan	*Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)*	The results of an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.
HCT	*Alcohol, barbiturates or narcotics*	Concomitant administration of thiazide diuretics with substances that also have a blood pressure lowering effect (E.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.
	Amantadine	Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.
	Anticholinergic agents	The bioavailability of thiazide-

	and other medicinal products affecting gastric motility	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, it is anticipated that prokinetic substances such as cisapride may decrease the bioavailability of thiazide-type diuretics.
	Antidiabetic agents (e.g. insulin and oral antidiabetic agents)	Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary.
	- Metformin	Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.
	Beta blockers and diazoxide	Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycemic effect of diazoxide.
	Ciclosporin	Concomitant treatment with ciclosporin may increase the risk of hyperuricemia and gout-type complications.
	Cytotoxic agents	Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.
	Digitalis glycosides	Thiazide-induced hypokalemia or hypomagnesaemia may occur as

		undesirable effects, favouring the onset of digitalis-induced cardiac arrhythmias.

	Iodine contrasting agents	In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be re-hydrated before the administration.
	Ion exchange resins	Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. This could result in sub-therapeutic effects of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimize the interaction.
	Medicinal products affecting serum potassium level	The hypokalemic effect of hydrochlorothiazide may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G and salicylic acid derivatives or antiarrhythmics. If these medicinal products are to be prescribed with the amlodipine /valsartan /hydrochlorothiazide combination, monitoring of potassium plasma levels is advised.
	Medicinal products affecting serum sodium level	The hyponatremia effect of diuretics may be intensified by concomitant administration of medicinal products such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these medicinal products.

	Medicinal products that could induce torsades de pointes	Due to the risk of hypokalemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce *torsades de pointes,* in particular Class Ia and Class III antiarrhythmics and some antipsychotics.
	Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)	Dose adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dose of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.
	Methyldopa	There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.
	Non-depolarizing skeletal muscle relaxants (e.g. tubocurarine)	Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.
	Other anti-hypertensive medicinal products	Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, ARBs and Direct Renin Inhibitors [DRIs]).
	Pressor amines (e.g. noradrenaline, adrenaline)	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.
	Vitamin D and calcium salts	Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin

		D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren
Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent

4.6 Fertility, pregnancy and lactation

Pregnancy

Amlodipine
The safety of amlodipine in human pregnancy has not been established. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.
Valsartan

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to AIIRA therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, and hyperkalemia).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension.
Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Amlodipine/valsartan/hydrochlorothiazide

There is no experience on the use of **Senergy® Plus** in pregnant women. Based on the existing data with the components, the use of **Senergy® Plus** is not recommended during first trimester and contraindicated during the second and third trimester of pregnancy

Breast-feeding

No information is available regarding the use of valsartan and/or amlodipine during breast-feeding. Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production. The use of **Senergy® Plus** during breast-feeding is not recommended. If **Senergy® Plus** is used during breast-feeding, doses should be kept as low as possible. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

There are no clinical studies on fertility.

Valsartan

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 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).

Amlodipine

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility.

4.7 Effects on ability to drive and use machines

Patients taking **Senergy® Plus** and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.

Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

Summary of the safety profile

The safety of **Senergy® Plus** has been evaluated at its maximum dose of 10 mg/320 mg/25 mg, valsartan in combination with amlodipine and hydrochlorothiazide. Adverse reactions were generally mild and transient in nature and only infrequently required discontinuation of therapy. No significant new or unexpected adverse reactions were observed with triple therapy treatment compared to the known effects of the monotherapy or dual therapy components. Changes in laboratory parameters observed with the combination of **Senergy® Plus** were minor and consistent with the pharmacological

mechanism of action of the monotherapy agents. The presence of valsartan in the triple combination attenuated the hypokalemic effect of hydrochlorothiazide.

Tabulated list of adverse reactions

The following adverse reactions, listed by MedDRA System Organ Class and frequency, concern **Senergy® Plus** (amlodipine/valsartan/HCT) and amlodipine, valsartan and HCT individually. 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); not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Adverse reactions**	**Frequency**			
		Senergy® Plus	**Amlodipine**	**Valsartan**	**HCT**
Blood and lymphatic system disorders	Agranulocytosis, bone marrow failure	- -	--	--	Very rare
	Hemoglobin and hematocrit decreased	- -	--	Not known	--
	Haemolytic anaemia	-	--	--	Very rare
	Leukopenia	-	Very rare	--	Very rare
	Neutropenia	-	--	Not known	--
	Thrombocytopenia, sometimes with purpura	- -	Very rare	Not known	Rare
	Aplastic anaemia	-	--	--	Not known
Immune system disorders	Hypersensitivity	- -	Very rare	Not known	Very rare
Metabolism and nutrition disorders	Anorexia	Uncommon	—	--	--
	Hypercalcaemia	Uncommon	--	--	Rare
	Hyperglycemia	-	Very rare	--	Rare
	Hyperlipidemia	Uncommon	--	--	--
	Hyperuricemia	Uncommon	--	--	Common
	Hypochloraemic alkalosis	-	--	--	Very rare
	Hypokalemia	Common	--	--	Very common
	Hypomagnesaemia	-	--	--	Common
	Hyponatremia	Uncommon	--	--	Common
	Worsening of diabetic metabolic state	- -	--	--	Rare
Psychiatric disorders	Depression	-	Uncommon	--	Rare
	Insomnia/sleep disorders	Uncommon	Uncommon	--	Rare
	Mood swings	-	Uncommon	--	
	Confusion	-	Rare	--	--
Nervous system disorders	Coordination abnormal	Uncommon	--	--	--
	Dizziness	Common	Common	--	Rare
	Dizziness postural, dizziness exertional	Uncommon	--	--	--
	Dysgeusia	Uncommon	Uncommon	--	--

	Extrapyramidal syndrome	-	Not known	--	--
	Headache	Common	Common	--	Rare
	Hypertonia	--	Very rare	--	--
	Lethargy	Uncommon	--	--	--
	Paresthesia	Uncommon	Uncommon	--	Rare
	Peripheral neuropathy, neuropathy	Uncommon	Very rare	--	--
	Somnolence	Uncommon	Common	--	--
	Syncope	Uncommon	Uncommon	--	--
	Tremor	-	Uncommon	--	--
	Hypoesthesia	-	Uncommon	--	--
Eye disorders	Acute angle-closure glaucoma	- -	--	--	Not known
	Visual disturbance	-	Uncommon	--	--
	Visual impairment	Uncommon	Uncommon	--	Rare
Ear and labyrinth disorders	Tinnitus	-	Uncommon	--	--
	Vertigo	Uncommon	--	Uncommon	--
Cardiac disorders	Palpitations	-	Common	--	--
	Tachycardia	Uncommon	--	--	--
	Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	- -	Very rare	--	Rare
	Myocardial infarction	-	Very rare	--	--
Vascular disorders	Flushing	-	Common	--	--
	Hypotension	Common	Uncommon	--	--
	Orthostatic hypotension	Uncommon	--	--	Common
	Phlebitis, thrombophlebitis	Uncommon	--	--	--
	Vasculitis	-	Very rare	Not known	--
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Very rare	Uncommon	--
	Dyspnoea	Uncommon	Uncommon	--	--
	Respiratory distress, pulmonary oedema, pneumonitis	- -	--	--	Very rare
	Rhinitis	-	Uncommon	--	--
	Throat irritation	Uncommon	--	--	--
Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Uncommon	Common	Uncommon	Rare
	Breath odour	Uncommon	--	--	--
	Change of bowel habit	-	Uncommon	--	--
	Constipation	-	--	--	Rare
	Decreased appetite	-	--	--	Common
	Diarrhoea	Uncommon	Uncommon	--	Rare
	Dry mouth	Uncommon	Uncommon	--	--

	Dyspepsia	Common	Uncommon	--	--
	Gastritis	-	Very rare	--	--
	Gingival hyperplasia	-	Very rare	--	--
	Nausea	Uncommon	Common	--	Common
	Pancreatitis	-	Very rare	--	Very rare
	Vomiting	Uncommon	Uncommon	--	Common
Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	- -	Very rare**	Not known	--
	Hepatitis	-	Very rare	--	--
	Intrahepatic cholestasis, jaundice	- -	Very rare	--	Rare
Skin and subcutaneous tissue disorders	Alopecia	-	Uncommon	--	
	Angioedema	-	Very rare	Not known	--
	Dermatitis bullous	-	--	Not known	--
	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus	- -	--	--	Very rare
	Erythema multiforme	-	Very rare	--	Not known
	Exanthema	-	Uncommon	--	--
	Hyperhidrosis	Uncommon	Uncommon	--	--
	Photosensitivity reaction*	-	Very rare	--	Rare
	Pruritus	Uncommon	Uncommon	Not known	--
	Purpura	-	Uncommon	--	Rare
	Rash	-	Uncommon	Not known	Common
	Skin discoloration	-	Uncommon	--	--
	Urticaria and other forms of rash	- -	Very rare	--	Common
	Vasculitis necrotizing and toxic epidermal necrolysis	- -	--	--	Very rare
	Exfoliative dermatitis	-	Very rare	--	--
	Stevens-Johnson syndrome	-	Very rare	--	--
	Quincke oedema	-	Very rare	--	--
Musculoskeletal and connective tissue disorders	Arthralgia	-	Uncommon	--	--
	Back pain	Uncommon	Uncommon	--	--
	Joint swelling	Uncommon	--	--	--
	Muscle spasm	Uncommon	Uncommon	--	Not known
	Muscular weakness	Uncommon	--	--	--
	Myalgia	Uncommon	Uncommon	Not known	--
	Pain in extremity	Uncommon	--	--	--
	Ankle swelling	-	Common	--	--
Renal and urinary disorders	Blood creatinine increased	Uncommon	--	Not known	--
	Micturition disorder		Uncommon		
	Nocturia	-	Uncommon	--	--
	Pollakiuria	Common	Uncommon		

	Renal dysfunction	-	--	--	Not known
	Acute renal failure	Uncommon	--	--	Not known
	Renal failure and impairment	- -	--	Not known	Rare
Reproductive system and breast disorders	Impotence	Uncommon	Uncommon	--	Common
	Gynaecomastia		Uncommon	--	--
General disorders and administration site conditions	Abasia, gait disturbance	Uncommon	--	--	--
	Asthenia	Uncommon	Uncommon	--	Not known
	Discomfort, malaise	Uncommon	Uncommon	--	--
	Fatigue	Common	Common	Uncommon	--
	Non cardiac chest pain	Uncommon	Uncommon	--	--
	Oedema	Common	Common	--	--
	Pain	-	Uncommon	--	--
	Pyrexia	-	--	--	Not known
Investigations	Lipids increased		--		Very common
	Blood urea nitrogen increased	Uncommon	--	--	--
	Blood uric acid increased	Uncommon	--	--	
	Glycosuria				Rare
	Blood potassium decreased	Uncommon	--	--	--
	Blood potassium increased	-	--	Not known	--
	Weight increase	Uncommon	Uncommon	--	--
	Weight decrease	-	Uncommon	--	--

* See section 4.4 Photosensitivity
** Mostly consistent with cholestasis

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose

Symptoms

There is no experience of overdose with **Senergy® Plus**. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension, including shock with fatal outcome, have been reported with amlodipine.

Treatment

Amlodipine/Valsartan/Hydrochlorothiazide

Clinically significant hypotension due to **Senergy® Plus** overdose 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.

Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
Amlodipine
If 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. Amlodipine is unlikely to be removed by hemodialysis.
Valsartan
Valsartan is unlikely to be removed by hemodialysis.
Hydrochlorothiazide
Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalemia, Hypochloraemic) and hypovolemia resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalemia may result in muscle spasms and or accentuate arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.
The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

5.Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists, other combinations, **ATC code**: C09DX01.
Mechanism of action
Senergy® Plus combines three antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these substances has an additive antihypertensive effect.
Amlodipine/Valsartan/Hydrochlorothiazide
Clinical efficacy and safety
Senergy® Plus was studied in a double-blind, active controlled study in hypertensive patients. A total of 2,271 patients with moderate to severe hypertension (mean baseline systolic/diastolic blood pressure was 170/107 mmHg) received treatments of amlodipine/valsartan/hydrochlorothiazide 10 mg/320 mg/25 mg, valsartan/hydrochlorothiazide 320 mg/25 mg, amlodipine/valsartan
10 mg/320 mg, or hydrochlorothiazide/amlodipine 25 mg/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.
At week 8, the mean reductions in systolic/diastolic blood pressure were 39.7/24.7 mmHg with **Senergy® Plus**, 32.0/19.7 mmHg with valsartan/hydrochlorothiazide, 33.5/21.5 mmHg with amlodipine/valsartan, and 31.5/19.5 mmHg with amlodipine/hydrochlorothiazide. 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 **Senergy® Plus** were 7.6/5.0 mmHg greater than with valsartan/hydrochlorothiazide,

6.2/3.3 mmHg greater than with amlodipine/valsartan, and 8.2/5.3 mmHg greater than with amlodipine/hydrochlorothiazide. The full blood pressure lowering effect was achieved 2 weeks after being on their maximal dose of **Senergy® Plus**.
Statistically greater proportions of patients achieved blood pressure control (<140/90 mmHg) with **Senergy® Plus** (71%) compared to each of the three dual combination therapies (45-54%) (p<0.0001).
In a subgroup of 283 patients focusing on ambulatory blood pressure monitoring, clinically and statistically superior reductions in 24-hour systolic and diastolic blood pressures were observed with the triple combination compared to valsartan/hydrochlorothiazide, valsartan/amlodipine, and hydrochlorothiazide/amlodipine.

Amlodipine

Mechanism of action

The amlodipine component of **Senergy® Plus** 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 in blood pressure.

Pharmacodynamic effects

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 patients with hypertension, amlodipine produces vasodilation, 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 increases 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 effects on electrocardiographic parameters were observed.
Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Clinical efficacy and safety

Use in patients with hypertension

A randomised double-blind morbidity-mortality study called the Antihypertensive and

Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or Lisinopril 10-40 mg/day (ACE inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.
A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of
4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%). The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% versus 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Valsartan

Mechanism of action

Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT1, which is responsible for the known actions of angiotensin II.

Clinical efficacy and safety

Administration of valsartan to patients with hypertension results in a drop in 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 drop in 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.

Hydrochlorothiazide

Mechanism of action

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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with **Senergy® Plus** in all subsets of the paediatric population in essential hypertension.

5.2 Pharmacokinetic properties

Linearity

Amlodipine, valsartan and hydrochlorothiazide exhibit linear pharmacokinetics.

Amlodipine/valsartan/hydrochlorothiazide

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

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.

Biotransformation

Amlodipine is extensively (approximately 90%) metabolised 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 percent 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 exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%, although from about
8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, 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 does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94-97%), mainly serum albumin.

Biotransformation

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 ($t_{½\alpha}$ <1 h and $t_{½ß}$ 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 (Tmax about 2 hours). The increase in mean AUC is linear and dose proportional in the therapeutic range.

The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration.

Distribution

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

Hydrochlorothiazide is eliminated predominantly as unchanged compound.

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 being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Special populations

Paediatric patients (age below 18 years)

No pharmacokinetic data are available in the paediatric population.

Elderly (age 65 years or over)

Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young, therefore caution is required when increasing the dosage.

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. Since the three components are equally well tolerated in younger and elderly patients, normal dose regimens are recommended.

Renal impairment

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan.

Patients with mild to moderate renal impairment may therefore receive the usual initial dose.

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, a 3-fold increase in hydrochlorothiazide AUC has been observed. In patients with severe

renal impairment an 8-fold increase in AUC has been observed. **Senergy® Plus** is contraindicated in patients with severe renal impairment, anuria or undergoing dialysis.

Hepatic impairment

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC. 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). Due to the valsartan component, **Senergy® Plus** is contraindicated in patients with hepatic impairment.

5.3 Preclinical safety data

Amlodipine/Valsartan/Hydrochlorothiazide

In a variety of preclinical safety studies conducted in several animal species with amlodipine, valsartan, hydrochlorothiazide, valsartan/hydrochlorothiazide, amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide (**Senergy® Plus**), there was no evidence of systemic or target organ toxicity that would adversely affect the development of **Senergy® Plus** for clinical use in humans. Preclinical safety studies of up to 13 weeks in duration were conducted with amlodipine/valsartan/hydrochlorothiazide in rats. The combination 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 genotoxicity or carcinogenicity as there was no evidence of any interaction between these substances, which have been on the market for a long time. However, amlodipine, valsartan and hydrochlorothiazide have been tested individually for genotoxicity and carcinogenicity with negative results.

Amlodipine

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labor and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

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/m2 basis). In another rat study in which male rats were treated with amlodipine Besylate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed

no evidence of carcinogenicity.
The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.
* Based on patient weight of 50 kg

Valsartan

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.
In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 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 non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats 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 including 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.

6.Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose
Crosspovidone
Colloidal silicon dioxide
Magnesium Stearate
Opadry White OY-L (28900)
Yellow iron oxide
Red iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Don't store above 30°C, protect from moisture

6.5 Nature and contents of container

Senergy® Plus (10/160/12.5) Tablets are packed in Aluminum /Aluminum blister then packed in cardboard cartons with a multi folded leaflet.

Pack size: 30 F/C Tablets

6.6 Special precautions for disposal and other handling

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

7.Marketing Authorization Holder

The United Pharmaceutical Mfg. Co Ltd.
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E-mail: upm_info@mspharma.com

8.Marketing Authorization Number(s)

H2025/CTD8941/15542

9.Date of first authorization/renewal of the authorization

2nd July 2025

10. Date of revision of the text

Dec., 2017