SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Olmesartan medoxomil/Amlodipine/HCT Innovis, 20mg/5mg/12,5mg filmomhulde tabletten
Olmesartan medoxomil/Amlodipine/HCT Innovis, 40mg/5mg/12,5mg filmomhulde tabletten
Olmesartan medoxomil/Amlodipine/HCT Innovis, 40mg/10mg/12,5mg filmomhulde tabletten
Olmesartan medoxomil/Amlodipine/HCT Innovis, 40mg/5mg/25mg filmomhulde tabletten
Olmesartan medoxomil/Amlodipine/HCT Innovis, 40mg/10mg/25mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Olmesartan medoxomil/Amlodipine/HCT Innovis 20 mg/5 mg/12.5 mg film-coated tablets
Each tablet contains 20 mg olmesartan medoxomil, 5 mg amlodipine (as amlodipine besilate) and 12.5 mg hydrochlorothiazide.

Excipient with known effect
Each tablet contains 19 mg of lactose (as monohydrate).

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/5 mg/12.5 mg film-coated tablets
Each tablet contains 40 mg olmesartan medoxomil, 5 mg amlodipine (as amlodipine besilate) and 12.5 mg hydrochlorothiazide.

Excipient with known effect
Each tablet contains 38 mg of lactose (as monohydrate).

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/10 mg/12.5 mg film-coated tablets
Each tablet contains 40 mg olmesartan medoxomil, 10 mg amlodipine (as amlodipine besilate) and 12.5 mg hydrochlorothiazide.

Excipient with known effect
Each tablet contains 38 mg of lactose (as monohydrate).

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/5 mg/25 mg film-coated tablets
Each tablet contains 40 mg olmesartan medoxomil, 5 mg amlodipine (as amlodipine besilate) and 25 mg hydrochlorothiazide.

Excipient with known effect
Each tablet contains 38 mg of lactose (as monohydrate).

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/10 mg/25 mg film-coated tablets
Each tablet contains 40 mg olmesartan medoxomil, 10 mg amlodipine (as amlodipine besilate) and 25 mg hydrochlorothiazide.

Excipient with known effect
Each tablet contains 38 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Olmesartan medoxomil/Amlodipine/HCT Innovis 20 mg/5 mg/12.5 mg film-coated tablets
White, round (of diameter 7.5 mm) tablet, with bevelled edges, debossed with “OA” one side and “05” on the other side.

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/5 mg/12.5 mg film-coated tablets
Yellow, round (of diameter 9.5 mm) tablet, with bevelled edges, debossed with "OA" one side and "06" on the other side.

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/10 mg/12.5 mg film-coated tablets
Pink, round (of diameter 9.5 mm) tablet, with bevelled edges, debossed with "OA" one side and "03" on the other side.

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/5 mg/25 mg film-coated tablets
Yellow, capsule shaped (length: 12.8 mm, width 6.0 mm) tablet, with bevelled edges, debossed with "OA" one side and "04" on the other side.

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/10 mg/25 mg film-coated tablets
Pink, capsule shaped (length: 12.8 mm, width 6.0 mm) tablet, with bevelled edges, debossed with "OA" one side and "02" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Add-on therapy
Olmesartan medoxomil/Amlodipine/HCT Innovis is indicated in adult patients whose blood pressure is not adequately controlled on the combination of olmesartan medoxomil and amlodipine taken as dual-component formulation.

Substitution therapy
Olmesartan medoxomil/Amlodipine/HCT Innovis is indicated as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component (olmesartan medoxomil and amlodipine or olmesartan medoxomil and hydrochlorothiazide) and a single-component formulation (hydrochlorothiazide or amlodipine).

4.2 Posology and method of administration

Posology

Adults
The recommended dose of Olmesartan medoxomil/Amlodipine/HCT Innovis is 1 tablet per day.

Add-on therapy
Olmesartan medoxomil/Amlodipine/HCT Innovis 20 mg/5 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled on olmesartan medoxomil 20 mg and amlodipine 5 mg taken as dual-component combination.

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/5 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled on olmesartan medoxomil 40 mg and amlodipine 5 mg taken as dual-component combination or in patients whose blood pressure is not adequately controlled on Olmesartan medoxomil/Amlodipine/HCT Innovis 20 mg/5 mg/12.5 mg.

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/5 mg/25 mg may be administered in patients whose blood pressure is not adequately controlled on Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/5 mg/12.5 mg.
Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/10 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled on olmesartan medoxomil 40 mg and

amlodipine 10 mg taken as dual-component combination or by Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/5 mg/12.5 mg.

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/10 mg/25 mg may be administered in patients whose blood pressure is not adequately controlled on Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/10 mg/12.5 mg or by Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/5 mg/25 mg.

A step-wise titration of the dosage of the individual components is recommended before changing to the triple-component combination. When clinically appropriate, direct change from dual-component combination to the triple-component combination may be considered.

Substitution therapy
Patients controlled on stable doses of olmesartan medoxomil, amlodipine and hydrochlorothiazide taken at the same time as a dual-component (olmesartan medoxomil and amlodipine or olmesartan medoxomil and hydrochlorothiazide) and a single-component formulation (hydrochlorothiazide or amlodipine) may be switched to Olmesartan medoxomil/Amlodipine/HCT Innovis containing the same component doses.

The maximum recommended dose of Olmesartan medoxomil/Amlodipine/HCT Innovis is 40 mg/10 mg/25 mg per day.

Elderly population (age 65 years or over)
Caution, including more frequent monitoring of blood pressure, is recommended in elderly people, particularly at the maximum dose of Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/10 mg/25 mg per day.

An increase of the dosage should take place with care in elderly people (see sections 4.4 and 5.2).

Very limited data are available on the use of fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide in patients aged 75 years or older. Extreme caution, including more frequent monitoring of blood pressure, is recommended.

Renal impairment
The maximum dose in patients with mild to moderate renal impairment (creatinine clearance of 30 – 60 mL/min) is Olmesartan medoxomil/Amlodipine/HCT Innovis 20 mg/5 mg/12.5 mg, owing to limited experience of the 40 mg olmesartan medoxomil dosage in this patient group.

Monitoring of serum concentrations of potassium and creatinine is advised in patients with moderate renal impairment.

The use of Olmesartan medoxomil/Amlodipine/HCT Innovis in patients with severe renal impairment (creatinine clearance < 30 mL/min) is contraindicated (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
Olmesartan medoxomil/Amlodipine/HCT Innovis should be used with caution in patients with mild hepatic impairment (see sections 4.4 and 5.2).

In patients with moderate hepatic impairment the maximum dose should not exceed Olmesartan medoxomil/Amlodipine/HCT Innovis 20 mg/5 mg/12.5 mg once daily. Close monitoring of blood pressure and renal function is advised in patients with hepatic impairment.

As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. Olmesartan medoxomil/Amlodipine/HCT Innovis should therefore be administered with caution in these patients. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment.

Amlodipine should be initiated at the lowest dose and titrated slowly in patients with impaired liver function.

Use of Olmesartan medoxomil/Amlodipine/HCT Innovis is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2), cholestasis or biliary obstruction (see section 4.3).

Paediatric population
Fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Method of administration

The tablet should be swallowed with a sufficient amount of fluid (e. g. one glass of water). The tablet should not be chewed and should be taken at the same time each day.
Olmesartan medoxomil/Amlodipine/HCT Innovis can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substances, to dihydropyridine derivates or to sulfonamide-derived substances (since hydrochlorothiazide is a sulfonamide-derived drug) or to any of the excipients listed in section 6.1.

Severe renal impairment (see sections 4.4 and 5.2).

Refractory hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia.

Severe hepatic insufficiency, cholestasis and biliary obstructive disorders (see section 5.2).

2nd and 3rd trimester of pregnancy (see sections 4.4 and 4.6).

The concomitant use of Olmesartan medoxomil/Amlodipine/HCT Innovis with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2) (see sections 4.5 and 5.1).

Due to the amlodipine component, Olmesartan medoxomil/Amlodipine/HCT Innovis is contraindicated in patients with:
- Shock (including cardiogenic shock).
- Severe hypotension
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

Patients with hypovolaemia or sodium depletion:
Symptomatic hypotension may occur in patients who are volume and/or sodium depleted as a result of vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting, especially after the first dose. Correction of this condition prior to administration of Olmesartan medoxomil/Amlodipine/HCT Innovis or close medical supervision at the start of the treatment is recommended.

Other conditions with stimulation of the renin-angiotensin-aldosterone system:
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e. g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure.

Renovascular hypertension:

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation:
When Olmesartan medoxomil/Amlodipine/HCT Innovis is used in patients with impaired renal function, periodic monitoring of serum concentrations of potassium and creatinine is recommended.

Use of Olmesartan medoxomil/Amlodipine/HCT Innovis is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see sections 4.2, 4.3 and 5.2).

Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function.

If progressive renal impairment becomes evident, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy.

There is no experience of the administration of fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide in patients with a recent kidney transplant or in patients with end-stage renal impairment (i. e. creatinine clearance < 12 mL/min).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Intestinal angioedema
Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, [including olmesartan] (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, olmesartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Hepatic impairment:
Exposure to amlodipine and olmesartan medoxomil is increased in patients with hepatic impairment (see section 5.2).

Furthermore, minor alterations of fluid and electrolyte balance during thiazide therapy may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

Care should be taken when Olmesartan medoxomil/Amlodipine/HCT Innovis is administered in patients with mild to moderate hepatic impairment.

In patients with moderate hepatic impairment, the dose of olmesartan medoxomil should not exceed 20 mg (see section 4.2).

In patients with impaired hepatic function, amlodipine should be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose.

Use of Olmesartan medoxomil/Amlodipine/HCT Innovis is contraindicated in patients with severe hepatic impairment, cholestasis or biliary obstruction (see section 4.3).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:
Due to the amlodipine component of Olmesartan medoxomil/Amlodipine/HCT Innovis, as with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism:
Patients with primary aldosteronism generally will not respond to anti-hypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Olmesartan medoxomil/Amlodipine/HCT Innovis is not recommended in such patients.

Metabolic and endocrine effects:
Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels are undesirable effects known to be associated with thiazide diuretic therapy.

Hyperuricaemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy.

Electrolyte imbalance:
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscle fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting (see section 4.8).

The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).

Conversely, due to antagonism at the angiotensin-II receptors (AT_1) through the olmesartan medoxomil component of Olmesartan medoxomil/Amlodipine/HCT Innovis hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Close monitoring of serum potassium in patients at risk is recommended. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes and other medicinal products that may increase serum potassium levels (e. g. heparin) should be co-administered cautiously with Olmesartan medoxomil/Amlodipine/HCT Innovis (see section 4.5) and with frequent monitoring of potassium levels.

There is no evidence that olmesartan medoxomil would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism.

Hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Lithium:
As with other angiotensin II receptor antagonists, the co-administration of Olmesartan medoxomil/Amlodipine/HCT Innovis and lithium is not recommended (see section 4.5).

Heart failure:
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 angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death.

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study of amlodipine in patients with severe heart failure (NYHA III and IV), the reported incidence of pulmonary oedema was higher in the amlodipine group than in the placebo group (see section 5.1). 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.

Sprue-like enteropathy:
In very rare cases severe, chronic diarrhoea with substantial weight loss has been reported in patients taking olmesartan few months to years after drug initiation, possibly caused by a localized delayed hypersensitivity reaction. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan, and in the absence of other apparent etiologies, olmesartan treatment should be immediately discontinued and should not be restarted. If diarrhoea does not improve during the week after the discontinuation, further specialist (e.g. a gastro-enterologist) advice should be considered.

Choroidal effusion, acute Myopia and Secondary Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy (see section 4.8).

Acute Respiratory Toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Olmesartan medoxomil/Amlodipine/HCT Innovis should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Pregnancy:
Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonists therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Paediatric population:
Olmesartan medoxomil/Amlodipine/HCT Innovis is not indicated in children and adolescents under the age of 18 years.

Elderly:
In the elderly, increase of the dosage should take place with care (see section 5.2).

Photosensitivity:
Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with Olmesartan medoxomil/Amlodipine/HCT Innovis, it is recommended to stop the treatment. If re-administration of the diuretic is deemed necessary, it is recommended to protect the areas exposed to the sun or to artificial UVA.

Non-melanoma skin cancer:
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Other:
As with any antihypertensive agent, excessive blood pressure reduction in patients with ischaemic heart disease or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

As with all other angiotensin II receptor antagonists, the blood pressure lowering effect of olmesartan is somewhat less in black patients than in non-black patients, however, this effect was not seen in one of the three clinical trials with a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide that included black patients (30 %), see also section 5.1.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Potential interactions related to a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide:

Concomitant use not recommended

Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and, rarely, with angiotensin II receptor antagonists. In addition, renal clearance of lithium is reduced by thiazides and consequently the risk of lithium toxicity may be increased. Therefore use of Olmesartan medoxomil/Amlodipine/HCT Innovis and lithium in combination is not recommended (see section 4.4). If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution

Baclofen:
Potentiation of antihypertensive effect may occur.

Non-steroidal anti-inflammatory medicinal products:
NSAIDs (i.e. acetylsalicylic acid (> 3 g/day), COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of thiazide diuretics and angiotensin II receptor antagonists.

In some patients with compromised renal function (e. g. dehydrated patients or elderly people with compromised renal function) the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

Concomitant use to be taken into account

Amifostine:
Potentiation of antihypertensive effect may occur.

Other antihypertensive agents:
The blood pressure lowering effect of Olmesartan medoxomil/Amlodipine/HCT Innovis can be increased by concomitant use of other antihypertensive medicinal products.

Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Potential interactions related to olmesartan medoxomil:

Concomitant use not recommended

ACE-inhibitors, angiotensin II receptor blockers or aliskiren:
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Medicinal products affecting potassium levels:
Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e. g. heparin, ACE inhibitors) may lead to increases in serum potassium (see section 4.4). If medicinal products that affect potassium are to be prescribed in combination with Olmesartan medoxomil/Amlodipine/HCT Innovis, monitoring of serum potassium is advised.

Additional information

Bile acid sequestering agent colesevelam:
Concurrent administration of the bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan and reduces t1/2. Administration of olmesartan medoxomil at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect. Administering olmesartan medoxomil at least 4 hours before the colesevelam hydrochloride dose should be considered (see section 5.2).

After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of olmesartan was observed.

Olmesartan medoxomil had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin.

Coadministration of olmesartan medoxomil with pravastatin had no clinically relevant effects on the pharmacokinetics of either component in healthy subjects.

Olmesartan had no clinically relevant inhibitory effects on human cytochrome P450 enzymes 1A1/2, 2A6, 2C8/9, 2C19, 2D6, 2E1 and 3A4 in vitro, and had no or minimal inducing effects on rat cytochrome P450 activities. No clinically relevant interactions between olmesartan and medicinal products metabolised by the above cytochrome P450 enzymes are expected.

Potential interactions related to amlodipine

Concomitant use requiring caution

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors:
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. There is an increased risk of hypotension. Close observation of patients is recommended and dose adjustment may thus be required.

CYP3A4 inducers:
Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

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.

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, 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.

Effects of amlodipine on other medicinal products
The blood pressure-lowering effect of amlodipine adds to the blood pressure-lowering effects of other antihypertensive agents.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

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

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors: mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Cyclosporine: In a prospective study in renal transplant patients, an average 40% increase in trough cyclosporine levels was observed when used concomitantly with amlodipine. The co-administration of Olmesartan medoxomil/Amlodipine/HCT Innovis with cyclosporine may increase exposure to cyclosporine. Monitor trough cyclosporine levels during concomitant use and cyclosporine dose reductions should be made as necessary.

Potential interactions related to hydrochlorothiazide:

Concomitant use not recommended

Medicinal products affecting potassium levels:
The potassium-depleting effect of hydrochlorothiazide (see section 4.4) may be potentiated by the co-administration of other medicinal products associated with potassium loss and hypokalaemia (e. g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium or salicylic acid derivatives). Such concomitant use is therefore not recommended.

Concomitant use requiring caution

Calcium salts:
Thiazide diuretics may increase serum calcium owing to decreased excretion. If calcium supplements must be prescribed, serum calcium should be monitored and calcium dosage adjusted accordingly.

Cholestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

Digitalis glycosides:
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances:
Periodic monitoring of serum potassium and ECG is recommended when Olmesartan medoxomil/Amlodipine/HCT Innovis is administered with medicinal products affected by serum potassium disturbances (e. g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrhythmics (e. g. quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (e. g. amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (e. g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e. g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloxacin, terfenadine, vincamine IV).

Non-depolarizing skeletal muscle relaxants (e. g. tubocurarine):

The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Anticholinergic agents (e. g. atropine, biperiden):
Increase of the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Antidiabetic medicinal products (oral agents and insulin):
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic medicinal product may be required (see section 4.4).

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:
The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Pressor amines (e. g. noradrenaline):
The effect of pressor amines may be decreased.

Medicinal products used in the treatment of gout (e. g. probenecid, sulfinpyrazone and allopurinol):
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine:
Thiazides may increase the risk of adverse effects caused by amantadine.

Cytotoxic agents (e. g. cyclophosphamide, methotrexate):
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Salicylates:
In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa:
There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Cyclosporine:
Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Tetracyclines:
Concomitant administration of tetracyclines and thiazides increases the risk of tetracycline-induced increase in urea. This interaction is probably not applicable to doxycycline.

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of Olmesartan medoxomil/Amlodipine/HCT Innovis is contra-indicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4). Given the effects of the individual components in this combination product on pregnancy, the use of Olmesartan medoxomil/Amlodipine/HCT Innovis is not recommended during the first trimester of pregnancy (see section 4.4).

Olmesartan medoxomil
The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II receptor antagonists is contra-indicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

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, similar risks may exist for this class of drugs. Unless continued angiotensin receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments, which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonists therapy during the 2nd and 3rd trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3).

Should exposure to angiotensin II receptor antagonists have occurred from the 2nd trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants, whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension (see also sections 4.3 and 4.4).

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 2nd and 3rd trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Amlodipine
Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery.

Breast-feeding
During breast-feeding, Olmesartan medoxomil/Amlodipine/HCT Innovis is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Olmesartan is excreted into the milk of lactating rats. However, it is not known whether olmesartan passes into human milk.

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 - 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production.

The use of Olmesartan medoxomil/Amlodipine/HCT Innovis during breast-feeding is not recommended. If Olmesartan medoxomil/Amlodipine/HCT Innovis is used during breast-feeding, doses should be kept as low as possible.

Fertility
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. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, it should be borne in mind that dizziness, headache, nausea or fatigue may occasionally occur in patients taking antihypertensive therapy and that these symptoms may impair the ability to react. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

The safety of a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide was investigated in clinical trials in 7826 patients receiving olmesartan medoxomil in combination with amlodipine and hydrochlorothiazide.

Adverse reactions from clinical trials, post-authorization safety studies and spontaneous reporting are summarized in table 1 for a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide as well as for the individual components olmesartan medoxomil, amlodipine and hydrochlorothiazide based on the known safety profile of the single components.

The most commonly reported adverse reactions during treatment with a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide are peripheral oedema, headache and dizziness.

The following terminologies have been used in order to classify the occurrence of undesirable effects:

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)

Table 1: Overview of adverse reactions with a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide and the single components

MedDRA System Organ Class	**Adverse reactions**	**Frequency**			
		the fixed-dose combination of olmesartan medoxomil/ amlodipine/ hydrochlorothiazid	**Olmesartan**	**Amlodipine**	**HCTZ**

		e			
Infections and infestations	Upper respiratory tract infection	Common	-	-	-
	Nasopharyngitis	Common	-	-	-
	Urinary tract infection	Common	Common	-	-
	Sialadenitis	-	-	-	Rare
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)	-	-		Not known
Blood and lymphatic system disorders	Leucopenia	-	-	Very rare	Rare
	Thrombocytopenia	-	Uncommon	Very rare	Rare
	Bone marrow depression	-	-	-	Rare
	Neutropenia/ Agranulocytosis	-	-	-	Rare
	Haemolytic anaemia	-	-	-	Rare
	Aplastic anaemia		-	-	Rare
Immune system disorders	Anaphylactic reaction	-	Uncommon	-	-
	Drug hypersensitivity	-	-	Very rare	-
Metabolism and nutrition disorders	Hyperkalaemia	Uncommon	Rare	-	-
	Hypokalaemia	Uncommon	-	-	Common
	Anorexia	-	-	-	Uncommon
	Glycosuria	-	-	-	Common
	Hypercalcaemia	-	-	-	Common
	Hyperglycaemia	-	-	Very rare	Common
	Hypomagnesaemia	-	-	-	Common
	Hyponatriaemia	-	-	-	Common
	Hypochloraemia	-	-	-	Common
	Hypertriglyceridaemia	-	Common	-	Very common
	Hypercolesterolaemia	-	-	-	Very common
	Hyperuricaemia	-	Common	-	Very common
	Hypochloraemic alkalosis	-	-	-	Very rare
	Hyperamylasaemia	-	-	-	Common
Psychiatric disorders	Confusional state	-	-	Rare	Common
	Depression	-	-	Uncommon	Rare
	Apathy	-	-	-	Rare
	Irritability	-	-	Uncommon	-
	Restlessness	-	-		Rare
	Mood changes (including anxiety)	-	-	Uncommon	
	Sleep disorders (including insomnia)	-	-	Uncommon	Rare

Nervous system disorders	Dizziness	Common	Common	Common	Common
	Headache	Common	Common	Common	Rare
	Postural dizziness	Uncommon	-	-	-
	Presyncope	Uncommon	-	-	-
	Dysgeusia	-	-	Uncommon	-
	Hypertonia	-	-	Very rare	-
	Hypoaesthesia	-	-	Uncommon	-
	Paraesthesia	-	-	Uncommon	Rare
	Peripheral neuropathy	-	-	Very rare	-
	Somnolence	-	-	Common	-
	Syncope	-	-	Uncommon	-
	Convulsions	-	-	-	Rare
	Loss of appetite	-	-	-	Uncommon
	Tremor	-	-	Uncommon	-
	Extrapyramidal disorder	-	-	Not known	
Eye disorders	Visual disturbance (including diplopia, blurred vision)	-	-	Common	Rare
	Lacrimation decreased	-	-	-	Rare
	Worsening of myopia	-	-	-	Uncommon
	Xanthopsia	-	-	-	Rare
	Choroidal effusion				Not known
	Acute myopia, acute angle-closure glaucoma (see section 4.4.)	-	-	-	Not known
Ear and labyrinth disorders	Vertigo	Uncommon	Uncommon	-	Rare
	Tinnitus	-	-	Uncommon	-
Cardiac disorders	Palpitations	Common	-	Common	-
	Tachycardia	Uncommon	-	-	-
	Myocardial infarction	-	-	Very rare	-
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	-	-	Uncommon	Rare
	Angina pectoris	-	Uncommon	Uncommon (incl. aggravation of angina pectoris)	-
Vascular disorders	Hypotension	Common	Rare	Uncommon	-
	Flushing	Uncommon	-	Common	-
	Orthostatic hypotension	-	-	-	Uncommon
	Vasculitis (including	-	-	Very rare	Rare

	necrotising angiitis)				
	Thrombosis	-	-	-	Rare
	Embolism	-	-	-	Rare
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Common	Uncommon	-
	Bronchitis		Common		
	Dyspnoea	-	-	Common	Rare
	Pharyngitis	-	Common	-	-
	Rhinitis	-	Common	Uncommon	-
	Acute interstitial pneumonia	-	-	-	Rare
	Respiratory distress	-	-	-	Uncommon
	Pulmonary oedema	-	-	-	Rare
	Acute respiratory distress syndrome (ARDS) (see section 4.4)				Very rare
Gastrointestinal disorders	Diarrhoea	Common	Common	-	Common
	Nausea	Common	Common	Common	Common
	Constipation	Common	-	-	Common
	Dry mouth	Uncommon	-	Uncommon	-
	Abdominal pain	-	Common	Common	Common
	Altered bowel habits (including diarrhoea and constipation)	-	-	Common	-
	Meteorism	-			Common
	Dyspepsia	-	Common	Common	-
	Gastritis	-		Very rare	-
	Gastric irritation	-	-	-	Common
	Gastroenteritis	-	Common	-	-
	Gingival hyperplasia	-	-	Very rare	-
	Paralytic ileus	-	-	-	Very rare
	Pancreatitis	-	-	Very rare	Rare
	Vomiting	-	Uncommon	Uncommon	Common
	Sprue-like enteropathy (see section 4.4)	-	Very rare	-	-
	Intestinal angioedema	-	Rare	-	-
Hepatobiliary disorders	Hepatitis	-	-	Very rare	-
	Jaundice (intrahepatic cholestatic icterus)	-	-	Very rare	Rare
	Acute cholecystitis	-	-	-	Rare
	Autoimmune hepatitis*	-	Not known	-	-
Skin and subcutaneous tissue disorders	Alopecia	-	-	Uncommon	-
	Angioedema	-	Rare	Very rare	-
	Allergic dermatitis		Uncommon		
	Erythema multiforme	-	-	Very rare	-
	Erythema	-	-	-	Uncommon

	Cutaneous lupus erythematodes-like reactions	-	-	-	Rare
	Exanthema	-	Uncommon	Uncommon	-
	Exfoliative dermatitis	-	-	Very rare	-
	Hyperhydrosis	-	-	Uncommon	-
	Photosensitivity reaction	-	-	Very rare	Uncommon
	Pruritus	-	Uncommon	Uncommon	Uncommon
	Purpura	-	-	Uncommon	Uncommon
	Quincke oedema	-	-	Very rare	-
	Rash	-	Uncommon	Uncommon	Uncommon
	Reactivation of cutaneous lupus erythematodes	-	-	-	Rare
	Toxic epidermal necrolysis	-	-	Not known	Rare
	Skin discolouration	-	-	Uncommon	-
	Stevens-Johnson syndrome	-	-	Very rare	-
	Urticaria	-	Uncommon	Uncommon	Uncommon
Musculoskeletal and connective tissue disorders	Muscle spasm	Common	Rare	Common	-
	Joint swelling	Common	-	-	
	Muscular weakness	Uncommon	-	-	Rare
	Ankle swelling	-	-	Common	-
	Arthralgia	-	-	Uncommon	-
	Arthritis	-	Common	-	
	Back pain	-	Common	Uncommon	-
	Paresis	-	-	-	Rare
	Myalgia	-	Uncommon	Uncommon	-
	Skeletal pain	-	Common	-	-
Renal and urinary disorders	Pollakiuria	Common	-	-	-
	Increased urinary frequency	-	-	Uncommon	
	Acute renal failure	-	Rare	-	-
	Haematuria	-	Common		
	Micturition disorder		-	Uncommon	-
	Nocturia	-	-	Uncommon	-
	Interstitial nephritis	-	-	-	Rare
	Renal insufficiency	-	Rare	-	Rare
Reproductive system and breast disorders	Erectile dysfunction	Uncommon	-	Uncommon	Uncommon
	Gynaecomastia	-	-	Uncommon	-
General disorders and administration site conditions	Asthenia	Common	Uncommon	Common	-
	Peripheral oedema	Common	Common	-	
	Fatigue	Common	Common	Common	-
	Chest pain	-	Common	Uncommon	-
	Fever	-	-	-	Rare
	Influenza-like symptoms	-	Common	-	-
	Lethargy	-	Rare	-	-
	Malaise	-	Uncommon	Uncommon	-

	Oedema	-	-	Very common	-
	Pain	-	Common	Uncommon	-
	Face oedema	-	Uncommon	-	-
Investigations	Blood creatinine increased	Common	Rare	-	Common
	Blood urea increased	Common	Common	-	Common
	Blood uric acid increased	Common	-	-	-
	Blood potassium decreased	Uncommon	-	-	-
	Gamma glytamyl transferase increased	Uncommon	-	-	-
	Alanine aminotransferase increased	Uncommon	-	-	-
	Aspartate aminotransferase increased	Uncommon	-	-	
	Hepatic enzymes increased	-	Common	Very rare (mostly consistent with cholestatis)	-
	Blood creatine phosphokinase increased	-	Common	-	-
	Weight decrease	-	-	Uncommon	-
	Weight increase	-	-	Uncommon	-

*Cases of autoimmune hepatitis with a latency of few months to years have been reported post-marketing, that were reversible after the withdrawal of olmesartan.

Single cases of rhabdomyolysis have been reported in temporal association with the intake of angiotensin II receptor blockers. Single cases of extrapyramidal syndrome have been reported in patients treated with amlodipine.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1). Further adverse reactions reported in clinical trials or from post marketing experience with a fixed-dose combination of olmesartan medoxomil and amlodipine and not already reported for a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide, olmesartan medoxomil monotherapy or amlodipine monotherapy or reported in a higher frequency for the dual combination (Table 2):

Table 2: Combination of olmesartan medoxomil and amlodipine

System Organ Class	**Frequency**	**Adverse reactions**
Immune system disorders	Rare	Drug hypersensitivity
Gastrointestinal disorders	Uncommon	Upper abdominal pain
Reproductive system and breast disorders	Uncommon	Libido decreased
General disorders and administration site conditions	Common	Pitting oedema
	Uncommon	Lethargy
Musculoskeletal and connective tissue disorders	Uncommon	Pain in extremity

Further adverse reactions reported in clinical trials or from post marketing experience with a fixed-dose combination of olmesartan medoxomil and hydrochlorothiazide and not already reported for a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide, olmesartan medoxomil monotherapy or hydrochlorothiazide monotherapy or reported in a higher frequency for the dual combination (Table 3):

Table 3: Combination of olmesartan medoxomil and hydrochlorothiazide		
System Organ Class	**Frequency**	**Adverse reactions**
Nervous system disorders	Rare	Disturbances in consciousness (such as loss of consciousness)
Skin and subcutaneous tissue disorders	Uncommon	Eczema
Musculosceletal and connective tissue disorders	Uncommon	Pain in extremity
Investigations	Rare	Minor decreases in mean haemoglobin and haematocrit values

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Nederlands Bijwerkingen Centrum Lareb
Website: www.lareb.nl

4.9 Overdose

Symptoms:
The maximum dose of Olmesartan medoxomil/Amlodipine/HCT Innovis is 40 mg/10 mg/25 mg once daily. There is no information on overdosage with fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide in humans. The most likely effect of a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide overdosage is hypotension.

The most likely effects of olmesartan medoxomil overdosage are hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurred.

Amlodipine overdosage can be expected to lead to excessive peripheral vasodilatation with marked hypotension and possibly a reflex tachycardia. Marked and potentially prolonged systemic hypotension, up to and including shock with fatal outcome, has been reported.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Overdosage with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and dehydration resulting from excessive diuresis.

The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Treatment:

In the event of overdosage with Olmesartan medoxomil/Amlodipine/HCT Innovis, treatment should be symptomatic and supportive. Management depends upon the time since ingestion and the severity of the symptoms.

If intake is recent, gastric lavage may be considered. In healthy subjects, the administration of activated charcoal immediately or up to 2 hours after ingestion of amlodipine has been shown to reduce substantially the absorption of amlodipine.

Clinically significant hypotension due to an overdose of a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide requires active support of the cardiovascular system, including close monitoring of heart and lung function, elevation of the 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.

Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit. The dialysability of olmesartan or hydrochlorothiazide is unknown.

The degree to which olmesartan and hydrochlorothiazide are removed by haemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, calcium channel blockers and diuretics.

ATC code: C09DX03.

Mechanism of action
Olmesartan medoxomil/Amlodipine/HCT Innovis is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, a calcium channel blocker, amlodipine besilate and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than each component alone.

Pharmacodynamic effects

Olmesartan medoxomil
Olmesartan medoxomil is an orally active, selective angiotensin II receptor (type AT_1) antagonist. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension. The effects of angiotensin II include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by blocking its binding to the AT_1 receptor in tissues including vascular smooth muscle and the adrenal gland. The action of olmesartan is independent of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT_1) receptors by olmesartan results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.

In hypertension, olmesartan medoxomil causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after abrupt cessation of therapy.

Once daily dosing with olmesartan medoxomil provides an effective and smooth reduction in blood pressure over the 24 hour dose interval. Once daily dosing produced similar decreases in blood pressure as twice daily dosing at the same total daily dose.

With continuous treatment, maximum reductions in blood pressure are achieved by 8 weeks after the initiation of therapy, although a substantial proportion of the blood pressure lowering effect is already observed after 2 weeks of treatment.

The effect of olmesartan medoxomil on mortality and morbidity is not yet known.

The Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study in 4447 patients with type 2 diabetes, normo-albuminuria and at least one additional cardiovascular risk factor, investigated whether treatment with olmesartan could delay the onset of microalbuminuria. During the median follow-up duration of 3.2 years, patients received either olmesartan or placebo in addition to other antihypertensive agents, except ACE inhibitors or ARBs.

For the primary endpoint, the study demonstrated a significant risk reduction in the time to onset of microalbuminuria, in favour of olmesartan. After adjustment for BP differences this risk reduction was no longer statistically significant. 8.2% (178 of 2160) of the patients in the olmesartan group and 9.8% (210 of 2139) in the placebo group developed microalbuminuria.

For the secondary endpoints, cardiovascular events occurred in 96 patients (4.3%) with olmesartan and in 94 patients (4.2%) with placebo. The incidence of cardiovascular mortality was higher with olmesartan compared to placebo treatment (15 patients (0.7%) vs. 3 patients (0.1%)), despite similar rates for non-fatal stroke (14 patients (0.6%) vs. 8 patients (0.4%)), non-fatal myocardial infarction (17 patients (0.8%) vs. 26 patients (1.2%)) and non-cardiovascular mortality (11 patients (0.5%) vs. 12 patients (0.5%)). Overall mortality with olmesartan was numerically increased (26 patients (1.2%) vs. 15 patients (0.7%)), which was mainly driven by a higher number of fatal cardiovascular events.

The Olmesartan Reducing Incidence of End-stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) investigated the effects of olmesartan on renal and cardiovascular outcomes in 577 randomized Japanese and Chinese type 2 diabetic patients with overt nephropathy. During a median follow-up of 3.1 years, patients received either olmesartan or placebo in addition to other antihypertensive agents including ACE inhibitors.

The primary composite endpoint (time to first event of the doubling of serum creatinine, end-stage renal disease, all-cause death) occurred in 116 patients in the olmesartan group (41.1%) and 129 patients in the placebo group (45.4%) (HR 0.97 (95% CI 0.75 to 1.24); p=0.791). The composite secondary cardiovascular endpoint occurred in 40 olmesartan-treated patients (14.2%) and 53 placebo-treated patients (18.7%). This composite cardiovascular endpoint included cardiovascular death in 10 (3.5%) patients receiving olmesartan versus 3 (1.1%) receiving placebo, overall mortality 19 (6.7%) versus 20 (7.0%), non-fatal stroke 8 (2.8%) versus 11 (3.9%) and non-fatal myocardial infarction 3 (1.1%) versus 7 (2.5%), respectively.

Amlodipine

The amlodipine component of Olmesartan medoxomil/Amlodipine/HCT Innovis is a calcium channel blocker that inhibits the transmembrane influx of calcium ions through the potential-dependent L-type channels into the heart and smooth muscle. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. The antihypertensive effect of amlodipine derives from a direct relaxant effect on arterial smooth muscle, which leads to a lowering of peripheral resistance and hence of blood pressure.

In hypertensive patients, amlodipine causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after abrupt cessation of therapy.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces an effective reduction in blood pressure in the supine, sitting and standing positions. Chronic use of amlodipine is not associated with significant changes in heart rate or plasma catecholamine levels. In hypertensive patients with normal renal function, therapeutic doses of amlodipine reduce renal vascular resistance and increase glomerular filtration rate and effective renal plasma flow, without changing filtration fraction or proteinuria.

In haemodynamic studies in patients with heart failure and in clinical studies based on exercise tests in patients with NYHA class II-IV heart failure, amlodipine was found not to cause any clinical deterioration, as measured by exercise tolerance, left ventricular ejection fraction and clinical signs and symptoms.

A placebo-controlled study (PRAISE) designed to evaluate patients with NYHA class III-IV heart failure receiving digitalis, diuretics and ACE inhibitors, has shown that amlodipine did not lead to an increase in the risk of mortality and morbidity in patients with heart failure.

In a follow-up, long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension."

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (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 CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: 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% vs. 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.

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics. With hydrochlorothiazide, onset of diuresis occurs at about 2 hours and peak effect occurs at about 4 hours post-dose, whilst the action persists for approximately 6-12 hours.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide monotherapy reduces the risk of cardiovascular mortality and morbidity.

Clinical efficacy and safety

In a 12-week, double-blind, randomised, parallel-group study in 2492 patients (67% Caucasian patients), treatment with a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide 40 mg/10 mg/25 mg resulted in significantly greater reductions in diastolic and systolic blood pressures than treatment with either of the corresponding dual combinations, olmesartan medoxomil 40 mg plus amlodipine 10 mg, olmesartan medoxomil 40 mg plus hydrochlorothiazide 25 mg and amlodipine 10 mg plus hydrochlorothiazide 25 mg, respectively.

The additional blood pressure lowering effect from a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide 40 mg/10 mg/25 mg compared to the analogous dual combinations was between -3.8 and -6.7 mmHg for seated diastolic and between -7.1 and -9.6 mmHg for seated systolic blood pressure and occurred within the first 2 weeks.

The proportions of patients reaching blood pressure goal (< 140/90 mmHg for non-diabetic patients and < 130/80 mmHg for diabetic patients) at week 12 ranged from 34.9% to 46.6% for the dual combination treatment groups compared to 64.3% for a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide 40 mg/10 mg/25 mg.

In a second double-blind, randomised, parallel-group study in 2690 patients (99.9% Caucasian patients), treatment with a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide (20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg, 40 mg/10 mg/25 mg) resulted in significantly greater reductions in diastolic and systolic blood pressure compared to the corresponding dual combinations, olmesartan medoxomil 20 mg plus amlodipine 5 mg, olmesartan medoxomil 40 mg plus 5 mg amlodipine and olmesartan medoxomil 40 mg plus 10 mg amlodipine, respectively, after 10 weeks of treatment.

The additional blood pressure lowering effect from a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide compared to the corresponding dual combinations was between -1.3 and -1.9 mmHg for seated diastolic and between -2.7 and -4.9 mmHg for seated systolic blood pressure.

The proportions of patients reaching blood pressure goal (< 140/90 mmHg for non-diabetic patients and < 130/80 mmHg for diabetic patients) at week 10 ranged from 42.7% to 49.6% for the dual combination treatment groups compared to 52.4% to 58.8% for a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide.

In a randomised, double-blind, add-on study in 808 patients (99.9 % Caucasian patients) not adequately controlled after 8-weeks therapy with olmesartan medoxomil 40 mg plus amlodipine 10 mg dual combination treatment with a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide resulted in numerically additional seated blood pressure reduction of -1.8/-1.0 mmHg when treated with a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide 40 mg/10 mg/12.5 mg and a statistically significant additional seated blood pressure reduction of -3.6/-2.8 mmHg when treated with a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide 40 mg/10 mg/25 mg compared to the olmesartan medoxomil 40 mg plus amlodipine 10 mg dual combination.

Treatment with a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide 40 mg/10 mg/25 mg triple-combination therapy resulted in a statistically significantly greater percentage of subjects reaching their blood pressure goal compared to olmesartan medoxomil 40 mg plus amlodipine 10 mg dual combination therapy (41.3% vs. 24.2%); while the treatment with a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide 40 mg/10 mg/12.5 mg triple-combination therapy resulted in a numerically greater percentage of subjects reaching their blood pressure goal compared to olmesartan medoxomil 40 mg plus amlodipine 10 mg dual-combination therapy (29.5% vs. 24.2%) in subjects not adequately controlled on dual-combination therapy.

The antihypertensive effect of a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide was similar irrespective of age and gender, and was similar in patients with and without diabetes.

Other information:
Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Non-melanoma skin cancer:
Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing olmesartan medoxomil/amlodipine/hydrochlorothiazide in all subsets of the paediatric population in essential hypertension (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Concomitant administration of olmesartan medoxomil, amlodipine and hydrochlorothiazide had no clinically-relevant effects on the pharmacokinetics of either component in healthy subjects.

Following oral administration of a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide in normal healthy adults, peak plasma concentrations of

olmesartan, amlodipine and hydrochlorothiazide are reached in about 1.5 to 3 hours, 6 to 8 hours, and 1.5 to 2 hours, respectively. The rate and extent of absorption of olmesartan medoxomil, amlodipine and hydrochlorothiazide from a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide are the same as when administered as a dual-fixed combination of olmesartan medoxomil and amlodipine together with a hydrochlorothiazide single-component tablet or when administered as a dual-fixed combination of olmesartan medoxomil and hydrochlorothiazide together with an amlodipine single-component tablet with the same dosages. Food does not affect the bioavailability of a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide.

Olmesartan medoxomil

Absorption

Olmesartan medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, olmesartan, by esterases in the gut mucosa and in portal blood during absorption from the gastrointestinal tract. No intact olmesartan medoxomil or intact side chain medoxomil moiety have been detected in plasma or excreta. The mean absolute bioavailability of olmesartan from a tablet formulation was 25.6%.

The mean peak plasma concentration (C_{max}) of olmesartan is reached within about 2 hours after oral dosing with olmesartan medoxomil, and olmesartan plasma concentrations increase approximately linearly with increasing single oral doses up to about 80 mg.

Food had minimal effect on the bioavailability of olmesartan and therefore olmesartan medoxomil may be administered with or without food.

No clinically relevant gender-related differences in the pharmacokinetics of olmesartan have been observed.

Distribution

Olmesartan is highly bound to plasma protein (99.7%), but the potential for clinically significant protein binding displacement interactions between olmesartan and other highly bound co-administered active substances is low (as confirmed by the lack of a clinically significant interaction between olmesartan medoxomil and warfarin). The binding of olmesartan to blood cells is negligible. The mean volume of distribution after intravenous dosing is low (16 – 29 L).

Biotransformation

Total plasma clearance of olmesartan was typically 1.3 L/h (CV 19%) and was relatively slow compared to hepatic blood flow ca 90 L/h). Following a single oral dose of ^{14}C-labelled olmesartan medoxomil, 10 - 16% of the administered radioactivity was excreted in the urine (the vast majority within 24 hours of dose administration) and the remainder of the recovered radioactivity was excreted in the faeces. Based on the systemic availability of 25.6%, it can be calculated that absorbed olmesartan is cleared by both renal excretion (ca 40%) and hepato-biliary excretion (ca 60%). All recovered radioactivity was identified as olmesartan. No other significant metabolite was detected. Enterohepatic recycling of olmesartan is minimal. Since a large proportion of olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated (see section 4.3).

Elimination

The terminal elimination half life of olmesartan varied between 10 and 15 hours after multiple oral dosing. Steady state was reached after 2-5 days of dosing and no further accumulation was evident after 14 days of repeated dosing. Renal clearance was approximately 0.5 – 0.7 L/h and was independent of dose.

Drug interactions:

Bile acid sequestering agent colesevelam:

Concomitant administration of 40 mg olmesartan medoxomil and 3750 mg colesevelam hydrochloride in healthy subjects resulted in 28% reduction in C_{max} and 39% reduction in AUC of olmesartan. Lesser

effects, 4% and 15% reduction in C_{max} and AUC respectively, were observed when olmesartan medoxomil was administered 4 hours prior to colesevelam hydrochloride. Elimination half life of olmesartan was reduced by 50 – 52% irrespectively of whether administered concomitantly or 4 hours prior to colesevelam hydrochloride (see section 4.5).

Amlodipine

Absorption

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The absorption of amlodipine is unaffected by the concomitant intake of food.

Distribution

The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation

Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Elimination

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing.

Hydrochlorothiazide

Absorption

Following oral administration of olmesartan medoxomil and hydrochlorothiazide in combination, the median time to peak concentrations of hydrochlorothiazide was 1.5 to 2 hours after dosing.

Distribution

Hydrochlorothiazide is 68% protein bound in the plasma and its apparent volume of distribution is 0.83 – 1.14 L/kg.

Biotransformation

Hydrochlorothiazide is not metabolised in man and is excreted almost entirely as unchanged active substance in urine.

Elimination

About 60% of the oral dose is eliminated as unchanged active substance within 48 hours. Renal clearance is about 250 – 300 mL/min. The terminal elimination half-life of hydrochlorothiazide is 10 – 15 hours.

Special populations

Paediatric Population:

The European Medicines Agency has waived the obligation to submit the results of studies with a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide in all subsets of the paediatric population in essential hypertension.

Elderly (age 65 years or over):

In hypertensive patients, the olmesartan AUC at steady state was increased by ca 35% in elderly people (65 – 75 years old) and by ca 44% in very elderly people (≥ 75 years old) compared with the younger age group (see section 4.2).

This may be at least in part related to a mean decrease in renal function in this group of patients. The recommended dosage regimen for elderly people is, however, the same, although caution should be exercised when increasing the dosage.

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half life in elderly people. Increases in AUC and elimination half life in patients with congestive heart failure were as expected for the patient age group in this study (see section 4.4).

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

Renal impairment:
In renally impaired patients, the olmesartan AUC at steady state increased by 62%, 82% and 179% in patients with mild, moderate and severe renal impairment, respectively, compared to healthy controls (see sections 4.2 and 4.4). The pharmacokinetics of olmesartan medoxomil in patients undergoing haemodialysis has not been studied.

Amlodipine is extensively metabolised to inactive metabolites. Ten percent of the substance is excreted unchanged in the urine. Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment. In these patients, amlodipine may be administered at the normal dosage. Amlodipine is not dialysable.

The half-life of hydrochlorothiazide is prolonged in patients with impaired renal function.

Hepatic impairment:
After single oral administration, olmesartan AUC values are 6% and 65% higher in mildly and moderately hepatically impaired patients, respectively, than in their corresponding matched healthy controls. The unbound fraction of olmesartan at 2 hours post-dose in healthy subjects, in patients with mild hepatic impairment and in patients with moderate hepatic impairment is 0.26%, 0.34% and 0.41%, respectively.

Following repeated dosing in patients with moderate hepatic impairment, olmesartan mean AUC is again about 65% higher than in matched healthy controls. Olmesartan mean C_{max} values are similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment (see sections 4.2 and 4.4).

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. The clearance of amlodipine is decreased and the half-life is prolonged in patients with impaired hepatic function, resulting in an increase in AUC of about 40% – 60% (see sections 4.2 and 4.4).

Hepatic impairment does not significantly influence the pharmacokinetics of hydrochlorothiazide.n

5.3 Preclinical safety data

Olmesartan medoxomil/ Amlodipine /Hydrochlorothiazide combination
Repeated dose toxicity study in rats demonstrated that the combined administration of olmesartan medoxomil, amlodipine and hydrochlorothiazide neither augmented any of the previously reported and existing toxicities of the individual agents, nor induced any new toxicity, and no toxicologically synergistic effects were observed.

No additional mutagenicity, carcinogenicity, and reproductive toxicity studies for a fixed-dose combination of olmesartan medoxomil/amlodipine/hydrochlorothiazide have been conducted based on the well-understood safety profile of the individual active ingredients.

Olmesartan medoxomil
In chronic toxicity studies in rats and dogs, olmesartan medoxomil showed similar effects to other AT_1 receptor antagonists and ACE inhibitors: raised blood urea (BUN) and creatinine; reduction in heart weight; reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit); histological indications of renal damage (regenerative lesions of the renal epithelium, thickening of the basal

membrane, dilatation of the tubules). These adverse effects caused by the pharmacological action of olmesartan medoxomil have also occurred in preclinical trials on other AT_1 receptor antagonists and ACE inhibitors and can be reduced by simultaneous oral administration of sodium chloride.

Like other AT_1 receptor antagonists olmesartan medoxomil was found to increase the incidence of chromosome breaks in cell cultures in vitro, but not in vivo. The overall data of a comprehensive genotoxicity testing programme suggest that olmesartan is very unlikely to exert genotoxic effects under conditions of clinical use.

Olmesartan medoxomil was not carcinogenic in rats or transgenic mice.

In reproductive studies in rats, olmesartan medoxomil did not affect fertility and there was no evidence of a teratogenic effect. In common with other angiotensin II antagonists, survival of offspring was reduced and pelvic dilatation of the kidney was seen after exposure of the dams in late pregnancy and lactation. In rabbits there was no indication of a fetotoxic effect.

Amlodipine

Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour 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 besilate 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 of 10 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

Hydrochlorothiazide
Studies with hydrochlorothiazide have shown equivocal evidence for a genotoxic or carcinogenic effect in some experimental models. However, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasma.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Povidone (K-30)
Crospovidone
Sodium starch glycolate (type A)
Silica colloidal hydrated

Magnesium stearate

Olmesartan medoxomil/Amlodipine/HCT Innovis 20 mg/5 mg/12.5 mg film-coated tablets
Opadry II 85F18378 White Coating:
Polyvinyl alcohol, part hydrolyzed (E1203)
Titanium dioxide (E171)
Macrogol 4000 (E1521)
Talc (E553b)

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/5 mg/12.5 mg and 40 mg/5 mg/25 mg film-coated tablets
Opadry II 85F22055 Yellow Coating:
Polyvinyl alcohol, part hydrolyzed (E1203)
Titanium dioxide (E171)
Macrogol 4000 (E1521)
Talc (E553b)
Iron oxide yellow (E172)

Olmesartan medoxomil/Amlodipine/HCT Innovis 40 mg/10 mg/12.5 and 40 mg/10 mg/25 mg film-coated tablets
Opadry II 85F94526 Pink Coating:
Polyvinyl alcohol, part hydrolyzed (E1203)
Titanium dioxide (E171)
Macrogol 4000 (E1521)
Talc (E553b)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

OPA/Al/PVC – Al blisters
Pack sizes: Blisters of 28 and 56 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

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Pallini-Attica, 15351-Griekenland

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8. MARKETING AUTHORISATION NUMBER(S)

Olmesartan medoxomil/Amlodipine/HCT Innovis, 20mg/5mg/12,5mg filmomhulde tabletten	RVG 127914
Olmesartan medoxomil/Amlodipine/HCT Innovis, 40mg/5mg/12,5mg filmomhulde tabletten	RVG 127915
Olmesartan medoxomil/Amlodipine/HCT Innovis, 40mg/10mg/12,5mg filmomhulde tabletten	RVG 127916
Olmesartan medoxomil/Amlodipine/HCT Innovis, 40mg/5mg/25mg filmomhulde tabletten	RVG 127917
Olmesartan medoxomil/Amlodipine/HCT Innovis, 40mg/10mg/25mg filmomhulde tabletten	RVG 127918

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 15 november 2021
Datum van verlenging: 2 oktober 2026

10. DATE OF REVISION OF THE TEXT

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