Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benetor Plus 20 mg/25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Benetor Plus 20 mg/25 mg film coated tablets: Each film-coated tablet contains 20 mg olmesartan medoxomil and 25 mg hydrochlorothiazide.

Excipients:
Benetor Plus 20 mg/25 mg film coated tablets: Each film-coated tablet contains lactose monohydrate (98.2mg),
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablets

Product imported from France:
Pinkish round film-coated tablet with ‘C24’ debossed on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension.

Benetor Plus fixed dose combination is indicated in patients whose blood pressure is not adequately controlled on olmesartan medoxomil alone.

4.2 Posology and method of administration

Adults

Benetor Plus is not for use as initial therapy, but in patients whose blood pressure is not adequately controlled by 20 mg olmesartan medoxomil alone. Benetor Plus is administered once daily, with or without food.

When clinically appropriate, direct change from monotherapy with 20 mg olmesartan medoxomil to the fixed combination may be considered, taking into account that the antihypertensive effect of olmesartan medoxomil is maximal by about 8 weeks after initiating therapy (see section 5.1). Dose titration of the individual components is recommended:

20 mg olmesartan medoxomil/12.5 mg hydrochlorothiazide may be administered in patients whose blood pressure is not adequately controlled by the optimal monotherapy olmesartan medoxomil 20 mg alone.

20 mg olmesartan medoxomil/25 mg hydrochlorothiazide may be administered in patients whose blood pressure is not adequately controlled by 20 mg olmesartan medoxomil/ 12.5 mg hydrochlorothiazide.

A maximum daily dose of 20 mg olmesartan medoxomil and 25 mg hydrochlorothiazide in combination should not be exceeded.

Elderly

In elderly patients the same dosage of the combination is recommended as for adults.

Renal impairment

When Benetor Plus is used in patients with mild to moderate renal impairment (creatinine clearance of 30 – 60 ml/min) periodic monitoring of renal function is advised (see section 4.4). Benetor Plus is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see section 4.3).

Hepatic impairment

Benetor Plus should be used with caution in patients with mild to moderate hepatic impairment (see sections 4.4, 5.2). In patients with moderate hepatic impairment, an initial dose of 10 mg olmesartan medoxomil once daily is recommended and the maximum dose should not exceed 20 mg once daily. Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are receiving diuretics and/or other antihypertensive agents. There is no experience of olmesartan medoxomil in patients with severe hepatic impairment.

Benetor Plus should not be used in patients with severe hepatic impairment (see sections 4.3, 5.2), cholestasis and biliary obstruction (see section 4.3).

Children and adolescents

Benetor Plus is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients (see section 6.1) or to other sulfonamide-derived substances (since hydrochlorothiazide is a sulfonamide-derived medicinal product).

Severe renal impairment (creatinine clearance < 30 mL/min).

Refractory hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia.

Severe hepatic impairment, cholestasis and biliary obstructive disorders.

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

4.4 Special warnings and precautions for use

Intravascular volume depletion:

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Benetor Plus.

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:

Benetor Plus should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3). No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance is ≥ 30 ml/min, < 60 mL/min). However, in such patients Benetor Plus should be administered with caution and periodic monitoring of serum potassium, creatinine and uric acid levels is recommended. 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 Benetor Plus in patients with a recent kidney transplantation.

Hepatic impairment:

There is currently no experience of olmesartan medoxomil in patients with severe hepatic impairment. 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. Therefore care should be taken in patients with mild to moderate hepatic impairment (see section 4.2). Use of Benetor Plus in patients with severe hepatic impairment, cholestasis and biliary obstruction is contraindicated (see sections 4.3, 5.2).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:

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 Benetor Plus 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, muscular 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 (AT1) through the olmesartan medoxomil component of Benetor Plus hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure, and diabetes mellitus. Adequate 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 Benetor Plus (see section 4.5).

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 medicinal products containing angiotensin II receptor antagonists and thiazide in combination, the coadministration of Benetor Plus and lithium is not recommended (see section 4.5).

Ethnic differences:

As with all other angiotensin II antagonists, the blood pressure lowering effect of olmesartan medoxomil is somewhat less in black patients than in non-black patients, possibly because of a higher prevalence of low-renin status in the black hypertensive population.

Anti-doping test:

Hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.

Pregnancy:

Angiotensin II antagonists should not be initiated during pregnancy. Unless continued angiotensin II 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 antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Other:

In general arteriosclerosis, in patients with ischaemic heart disease or ischaemic cerebrovascular disease, there is always a risk that excessive blood pressure decrease 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.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Potential interactions related to both olmesartan medoxomil and hydrochloro-thiazide:

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 antagonists. In addition, renal clearance of lithium is reduced by thiazides and consequently the risk of lithium toxicity may be increased. Therefore use of Benetor Plus 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 antagonists.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of angiotensin II antagonists and agents that inhibit cyclo-oxygenase 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 Benetor Plus 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

Medicinal products affecting potassium levels:

Based on experience with the use of other medicinal products that affect the rennin angiotensin system, 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 product which affect potassium levels are to be prescribed in combination with Benetor Plus, monitoring of potassium plasma levels is advised.

Additional information

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 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 coadministration 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 levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels 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 Benetor Plus 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 antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide).
- Class III antiarrythmics (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 (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.

Cyclosporin:

Concomitant treatment with cyclosporin 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 (see section 4.3):

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

The use of antiotensin II antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II 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 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 antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Angiotensin II antagonists therapy exposure 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 5.3 “Preclinical safety data”.)

Should exposure to angiotensin II 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 antagonists should be closely observed for hypotension (see also sections 4.3 and 4.4).

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 the electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia 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

Lactation:

Olmesartan is excreted into the milk of lactating rats. However, it is not known whether olmesartan passes into human milk. Thiazides pass into human milk and may inhibit lactation. Because no information is available regarding the use of Benetor Plus during breast-feeding, Benetor Plus is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

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 or fatigue may occasionally occur in patients taking antihypertensive therapy.

4.8 Undesirable effects

Fixed dose combination:

In clinical trials involving 1155 patients treated with olmesartan medoxomil/hydrochlorothiazide combinations at dosages of 20/12.5 mg or 20/25 mg and 466 patients treated with placebo for periods of up to 21 months, the overall frequency of adverse events on olmesartan medoxomil/hydrochlorothiazide combination therapy was similar to that on placebo. Discontinuations due to adverse events were also similar for olmesartan medoxomil/hydrochlorothiazide 20/12.5 mg - 20/25 mg (2%) and placebo (3%). The frequency of adverse events on olmesartan medoxomil/hydrochlorothiazide overall relative to placebo appeared to be unrelated to age (<65 years versus ≥ 65 years), gender or race although the frequency of dizziness was somewhat increased in patients aged > 75 years.

The most frequent adverse event on olmesartan medoxomil/hydrochlorothiazide 20/12.5 mg – 20/25 mg, and the only adverse event for which the frequency exceeded that on placebo by at least 1%, was dizziness (2.6% on olmesartan medoxomil/hydrochlorothiazide 20/12.5 mg - 20/25 mg and 1.3% on placebo).

Adverse events of potential clinical relevance are listed below by System Organ Class. Frequencies are defined as: common (≥1/100 <1/10); uncommon (≥1/1,000 <1/100); rare (≥1/10,000 <1/1,000); very rare (<1/10000).

Adverse drug reactions additionally reported from post marketing experience are also listed. For all the adverse drug reactions reported from post marketing experience only, it is not possible to assign frequency and therefore they are mentioned with a “not known” frequency (cannot be estimated from the available data).

Common (≥1/100 <1/10)	**Uncommon** (≥1/1,000 <1/100)	**Rare** (≥1/10,000 <1/1,000)	**Very rare** (<1/10,000)	**Not known** (cannot be estimated from the available data)
System Organ Class: Metabolism and nutrition disorders				
	Hyperuricaemia Hypertriglyceridaemia			
System Organ Class: Nervous system disorders				
Dizziness	Syncope			Headache Disturbances in consciousness (such as loss of consciousness)

System Organ Class: Cardiac disorders				
	Palpitations			
System Organ Class: Vascular disorders				
	Hypotension Orthostatic hypotension			
System Organ Class: Respiratory, thoracic and mediastinal disorders				
				Cough
System Organ Class: Gastrointestinal disorders				
				Abdominal pain Nausea Vomiting Diarrhoea
System Organ Class: Skin and subcutaneous tissue disorders				
	Rash Eczema			Allergic conditions (such as angioneurotic oedema, and urticaria)
System Organ Class: Musculoskeletal and connective tissue disorders				
				Myalgia Muscle spasm
System Organ Class: Renal and urinary disorders				
				Acute renal failure
System Organ Class: General disorders and administration site conditions				
Fatigue	Weakness			Asthenic conditions (such as asthenia, malaise)
System Organ Class: Investigations				
	Blood potassium decreased Blood potassium increased Blood calcium increased Blood urea increased Blood lipids increased			Abnormal renal function tests
System Organ Class: Laboratory Findings				
		Minor increases in mean uric acid Minor increases in nitrogen and creatinine values Minor decreases in mean haemoglobin and haematocrit values		

Additional information on the individual components:

Adverse reactions previously reported with either of the individual components may be potential adverse reactions with Benetor Plus, even if not observed in post marketing experience and clinical trials with this product.

Olmesartan medoxomil:

Further adverse events reported in clinical trials with olmesartan medoxomil monotherapy in hypertension are listed by body system and ranked under headings of frequency.

Adverse drug reactions additionally reported from post marketing experience are also listed. For all the adverse drug reactions reported from post marketing experience only, it is not possible to assign frequency and therefore they are mentioned with a “not known” frequency (cannot be estimated from the available data).

Common (≥1/100 <1/10)	**Uncommon** (≥1/1,000 <1/100)	**Rare** (≥1/10,000 <1/1,000)	**Very rare** (<1/10,000)	**Not known** (cannot be estimated from the available data)
System Organ Class: Blood and lymphatic system disorders:				
				Thrombocytopenia
System Organ Class: Metabolism and nutrition disorders				
Increased creatine phosphokinase				
System Organ Class: Nervous system disorders				
	Vertigo			
System Organ Class: Cardiac disorders				
	Angina pectoris			
System Organ Class: Respiratory, thoracic and mediastinal disorders				
Bronchitis Pharyngitis Rhinitis				
System Organ Class: Gastrointestinal disorders				
Dyspepsia Gastroenteritis				
System Organ Class: Skin and subcutaneous tissue disorders				
				Pruritus Exanthem Allergic conditions such as dermatitis allergic and face oedema
System Organ Class: Musculoskeletal and connective tissue disorders				
Arthritis Back pain Skeletal pain				
System Organ Class: Renal and urinary disorders				
Haematuria Urinary tract infection				Renal insufficiency
System Organ Class: General disorders and administration site conditions				
Chest pain Influenza-like symptoms Peripheral oedema Pain				Lethargy

Single cases of rhabdomyolysis have been reported in temporal association with the intake of angiotensin II receptor blockers. A causal relationship, however, has not been established.

Hydrochlorothiazide:

Hydrochlorothiazide may cause or exacerbate volume depletion which may lead to electrolyte imbalance (see section 4.4).

Further adverse reactions reported with the hydrochlorothiazide monotherapy include:

Common (≥1/100 <1/10)	**Uncommon** (≥1/1,000 <1/100)	**Rare** (≥1/10,000 <1/1,000)	**Very rare** (<1/10,000)	**Not known** (cannot be estimated from the available data)
System Organ Class: Infections and infestations				
		Sialadenitis		
System Organ Class: Blood and lymphatic system disorders				
		Leukopenia Neutropenia/Agranulocytosis		

		Thrombocytopenia Aplastic anaemia Haemolytic anaemia Bone marrow depression		
System Organ Class: Metabolism and nutrition disorders				
Hyperglycaemia Glykosuria Electrolyte imbalance (including hyponatraemia, hypomagnesaemia, hypochloraemia)	Anorexia			
System Organ Class: Psychiatric disorders				
		Restlessness Depression Sleep disturbances Apathy		
System Organ Class: Nervous system disorders				
Light-headedness Confusional state	Loss of appetite	Paraesthesia Convulsions		
System Organ Class: Eye disorders				
		Xanthopsia Transient blurred vision Lacrimation decreased		
System Organ Class: Ear and labyrinth disorders				
Vertigo				
System Organ Class: Cardiac disorders				
		Cardiac arrhythmias		
System Organ Class: Vascular disorders				
		Necrotising angiitis (vasculitis, cutaneous vasculitis) Thrombosis Embolism		
System Organ Class: Respiratory, thoracic and mediastinal disorders				
		Dispnoea (including interstitial pneumonia and pulmonary oedema)		
System Organ Class: Gastrointestinal disorders				
Gastric irritation Constipation and meteorism		Pancreatitis	Paralytic ileus	
System Organ Class: Hepatobiliary disorders				
		Jaundice (intrahepatic cholestatic icterus) Acute cholecystitis		
System Organ Class: Skin and subcutaneous tissue disorders				
	Photosensitivity reactions	Cutaneous lupus erythematosus-like reactions, Reactivation of cutaneous lupus erythematosus, Anaphylactic reactions, Toxic epidermal necrolysis		
System Organ Class: Musculoskeletal and connective tissue disorders				
		Muscle weakness Paresis		

System Organ Class: Renal and urinary disorders				
		Renal dysfunction Interstitial nephritis		
System Organ Class: Reproductive Symptoms and Breast disorders				
		Erectile dysfunction		
System Organ Class: General disorders and administration site conditions				
		Fever		

4.9 Overdose

No specific information is available on the effects or treatment of Benetor Plus overdose. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends upon the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. 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.

The most likely manifestations of olmesartan overdose are expected to be hypotension and tachycardia; bradycardia might also occur. Overdose 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.

No information is available regarding the dialysability of olmesartan or hydrochlorothiazide.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Angiotensin II antagonists and diuretics, ATC code: C09D A 08.

Benetor Plus is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Once daily dosing with Benetor Plus provides an effective and smooth reduction in blood pressure over the 24 hour dose interval.

Olmesartan medoxomil is an orally active, selective angiotensin II receptor (type AT1) 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 AT1 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 (AT1) 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.

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.

The combination of olmesartan medoxomil and hydrochlorothiazide produces additive reductions in blood pressure which generally increase with the dose of each component. In pooled placebo-controlled studies, administration of the 20/12.5 mg and 20/25 mg combinations of olmesartan medoxomil/hydrochlorothiazide resulted in mean placebo-subtracted systolic/diastolic blood pressure reductions at trough of 12/7 mm Hg and 16/9 mm Hg, respectively. Age and gender had no clinically relevant effect on response to treatment with olmesartan medoxomil /hydrochlorothiazide combination therapy.

Administration of 12.5 mg and 25 mg hydrochlorothiazide in patients insufficiently controlled by olmesartan medoxomil 20 mg monotherapy gave additional reductions in 24-hour systolic/diastolic blood pressures measured by ambulatory blood pressure monitoring of 7/5 mm Hg and 12/7 mm Hg, respectively, compared with olmesartan medoxomil monotherapy baseline. The additional mean systolic/diastolic blood pressure reductions at trough compared with baseline, measured conventionally, were 11/10 mm Hg and 16/11 mm Hg, respectively.

The effectiveness of olmesartan medoxomil/hydrochlorothiazide combination therapy was maintained over long-term (one-year) treatment. Withdrawal of olmesartan medoxomil therapy, with or without concomitant hydrochlorothiazide therapy, did not result in rebound hypertension.

The effects of fixed dose combination of olmesartan medoxomil/hydrochlorothiazide on mortality and cardiovascular morbidity are currently unknown.

5.2 Pharmacokinetic properties

Absorption and distribution

Olmesartan medoxomil:

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.

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 coadministered 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).

Hydrochlorothiazide:

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.

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

Metabolism and elimination

Olmesartan medoxomil:

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 14C-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).

The terminal elimination half life of olmesartan varied between 10 and 15 hours after multiple oral dosing. Steady state was reached after the first few doses 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.

Hydrochlorothiazide:

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

Benetor Plus

The systemic availability of hydrochlorothiazide is reduced by about 20% when co-administered with olmesartan medoxomil, but this modest decrease is not of any clinical relevance. The kinetics of olmesartan are unaffected by the co-administration of hydrochlorothiazide.

Pharmacokinetics in special populations

Elderly:

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

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly patients 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, 4.4).

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

Hepatic impairment:

After single oral administration, olmesartan AUC values were 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 was 0.26%, 0.34% and 0.41%, respectively. Following repeated dosing in patients with moderate hepatic impairment, olmesartan mean AUC was again about 65% higher than in matched healthy controls. Olmesartan mean Cmax values were similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment (see sections 4.2, 4.4).

Hepatic impairment does not significantly influence the pharmacokinetics of hydrochlorothiazide.

5.3 Preclinical safety data

The toxic potential of olmesartan medoxomil/hydrochlorothiazide combinations was evaluated in repeated dose oral toxicity studies for up to six months in rats and dogs.

As for each of the individual substances and other medicinal products in this class, the main toxicological target organ of the combination was the kidney. The combination of olmesartan medoxomil/hydrochlorothiazide induced functional renal changes (increases in serum urea nitrogen and in serum creatinine). High dosages caused tubular degeneration and regeneration in the kidneys of rats and dogs, probably via a change in renal haemodynamics (reduced renal perfusion resulting from hypotension with tubular hypoxia and tubular cell degeneration). In addition the olmesartan medoxomil/ hydrochlorothiazide combination caused a decrease in red blood cell parameters (erythrocytes, haemoglobin and haematocrit) and a reduction in heart weight in rats.

These effects have also been observed for other AT1 receptor antagonists and for ACE inhibitors and they seem to have been induced by the pharmacological action of high dosages of olmesartan medoxomil and seem to be not relevant to humans at the recommended therapeutic doses.

Genotoxicity studies using combined olmesartan medoxomil and hydrochlorothiazide as well as the individual components have not shown any signs of a clinically relevant genotoxic activity.

The carcinogenic potential of a combination of olmesartan medoxomil and hydrochlorothiazide was not investigated as there was no evidence of relevant carcinogenic effects for the two individual components under conditions of clinical use.

There was no evidence of teratogenicity in mice or rats treated with olmesartan medoxomil/hydrochlorothiazide combinations. As expected from this class of medicinal product, fetal toxicity was observed in rats, as evidenced by significantly reduced fetal body weights, when treated with olmesartan medoxomil/ hydrochlorothiazide combinations during gestation (see sections 4.3, 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Lactose monohydrate
Low substituted hydroxypropylcellulose
Hydroxypropylcellulose
Magnesium stearate

Tablet coat
Talc
Hypromellose
Titanium dioxide (E 171)
Iron (III) oxide yellow (E 172)
Iron (III) oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the producton the market in the country of origin.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Over-labelled aluminium blister strips in over-labelled carton. Packs of 30 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

B&S Healthcare
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UK

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1328/152/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th July 2011

10 DATE OF REVISION OF THE TEXT