

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benetor 10 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 40 mg tablet contains 40 mg of olmesartan medoxomil

Excipients: Also contains lactose monohydrate (see section 4.4)

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

Product imported from France:

White, circular, film-coated tablets with C15 embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension.

4.2 Posology and method of administration

Adults

The recommended starting dose of olmesartan medoxomil is 10 mg once daily. In patients whose blood pressure is not adequately controlled at this dose, the dose of olmesartan medoxomil may be increased to 20 mg once daily as the optimal dose. If additional blood pressure reduction is required, olmesartan medoxomil dose may be increased to a maximum of 40 mg daily or hydrochlorothiazide therapy may be added.

The antihypertensive effect of olmesartan medoxomil is substantially present within 2 weeks of initiating therapy and is maximal by about 8 weeks after initiating therapy. This should be borne in mind when considering changing the dose regimen for any patient.

In order to assist compliance, it is recommended that Benetor tablets be taken at about the same time each day, with or without food, for example at breakfast time.

Elderly

No adjustment of dosage is generally required in elderly patients (see below for dose recommendations in patients with renal impairment). If up-titration to the maximum dose of 40mg daily is required, blood pressure should be closely monitored.

Renal impairment

The maximum dose in patients with mild to moderate renal impairment (creatinine clearance of 20 – 60 mL/min) is 20 mg olmesartan medoxomil once daily, owing to limited experience of higher dosages in this patient group. The use of olmesartan medoxomil in patients with severe renal impairment (creatinine clearance < 20 mL/min) is not recommended, since there is only limited experience in this patient group (*see sections 4.4, 5.2*).

Hepatic impairment

No adjustment of dosage recommendations is required for patients with mild hepatic impairment. 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 already receiving diuretics and/or other antihypertensive agents. There is no experience of olmesartan medoxomil in patients with severe hepatic impairment, therefore use is not recommended in this patient group (*see sections 4.4 and 5.2*). Olmesartan medoxomil should not be used in patients with biliary obstruction (*see section 4.3*).

Children and adolescents

Benetor 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 substance or to any of the excipients (*see section 6.1*).

Second and third trimesters of pregnancy (*see sections 4.4 and 4.6*).

Biliary obstruction (*see section 5.2*).

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 olmesartan medoxomil.

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 other drugs that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with angiotensin II receptor antagonists.

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 is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of olmesartan medoxomil is not recommended in patients with severe renal impairment (creatinine clearance < 20 mL/min) (*see sections 4.2, 5.2*). There is no experience of the administration of olmesartan medoxomil in patients with a recent kidney transplant or in patients with end-stage renal impairment (ie creatinine clearance <12 mL/min).

Hepatic impairment:

There is no experience in patients with severe hepatic impairment and therefore use of olmesartan medoxomil in this patient group is not recommended (*see section 4.2 for dosage recommendations in patients with mild or moderate hepatic impairment*).

Hyperkalaemia:

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.

The risk, that may be fatal, is increased in elderly, in patients with renal insufficiency and in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events.

Before considering the concomitant use of medicinal products that affect the renin-angiotensin- aldosterone system, the benefit risk ratio should be evaluated and other alternatives considered.

The main risk factors for hyperkalaemia to be considered are:

- o Diabetes, renal impairment, age (> 70 years)
- o Combination with one or more other medicinal products that affect the renin-angiotensin- aldosterone system and/or potassium supplements. Some medicinal products or therapeutic class of medicinal products may provoke a hyperkalaemia: salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptors antagonists, non steroidal anti-inflammatory drugs (including selective COX-2 inhibitors), heparin, immunosuppressor as ciclosporin or tacrolimus, trimethoprim.
- o Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extended trauma).
- o Close-monitoring of serum potassium in at risk patients is recommended (*see section 4.5*).

Lithium:

As with other angiotensin-II receptor antagonists, the combination of lithium and olmesartan medoxomil is not recommended (*see section 4.5*).

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy:

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism:

Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of olmesartan medoxomil is not recommended in such patients.

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.

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:

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

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

Interaction studies have only been performed in adults.

Effects of other medicinal products on olmesartan medoxomil:

Potassium supplements and potassium sparing diuretics:

Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (eg heparin) may lead to increases in serum potassium (*see section 4.4*). Such concomitant use is therefore not recommended.

Other antihypertensive medications:

The blood pressure lowering effect of olmesartan medoxomil can be increased by concomitant use of other antihypertensive medications.

Non-steroidal anti-inflammatory drugs (NSAIDs):

NSAIDs (including acetylsalicylic acid at doses > 3g/day and also COX-2 inhibitors) and angiotensin-II receptor antagonists may act synergistically by decreasing glomerular filtration. The risk of the concomitant use of NSAIDs and angiotensin II antagonists is the occurrence of acute renal failure. Monitoring of renal function at the beginning of treatment should be recommended as well as regular hydration of the patient.

Additionally, concomitant treatment can reduce the antihypertensive effect of angiotensin II receptor antagonists, leading to their partial loss of efficacy.

Other compounds:

After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of olmesartan was observed. Coadministration of warfarin and digoxin had no effect on the pharmacokinetics of olmesartan.

Effects of olmesartan medoxomil on other medicinal products:

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and angiotensin II antagonists. Therefore use of olmesartan medoxomil 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.

Other compounds:

Compounds which have been investigated in specific clinical studies in healthy volunteers include warfarin, digoxin, an antacid (magnesium aluminium hydroxide), hydrochlorothiazide and pravastatin. No clinically relevant interactions were observed and in particular olmesartan medoxomil had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin.

Olmesartan had no clinically relevant inhibitory effects on *in vitro* human cytochrome P450 enzymes 1A1/2, 2A6, 2C8/9, 2C19, 2D6, 2E1 and 3A4, and had no or minimal inducing effects on rat cytochrome P450 activities. Therefore *in vivo* interaction studies with known cytochrome P450 enzyme inhibitors and inducers were not conducted, and no clinically relevant interactions between olmesartan and drugs metabolised by the above cytochrome P450 enzymes are expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of angiotensin II antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II antagonists is contraindicated during the second and third 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 second and third 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 second 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).

Lactation

Olmesartan is excreted in the milk of lactating rats but it is not known whether olmesartan is excreted in human milk. Because no information is available regarding the use of Benetor during breast-feeding, Benetor 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 effect on the ability to drive and use machines have been performed.

With respect to driving vehicles or operating machines, it should be taken into account that occasionally dizziness or fatigue may occur in patients taking antihypertensive therapy.

4.8 Undesirable effects

Market experience

The following adverse reactions have been reported in post-marketing experience.

They are listed by System Organ Class and ranked under headings of frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$) including isolated reports.

System Organ Class	Very rare
Blood and lymphatic system disorders	Thrombocytopenia
Metabolism and nutrition disorders	Hyperkalaemia
Nervous system disorders	Dizziness, headache
Respiratory, thoracic and mediastinal disorders	Cough
Gastrointestinal disorders	Abdominal pain, nausea, vomiting
Skin and subcutaneous tissue disorders	Pruritus, exanthem, rash Allergic conditions such as angioneurotic oedema, dermatitis allergic, face oedema and urticaria
Musculoskeletal and connective tissue disorders	Muscle cramp, myalgia
Renal and urinary disorders	Acute renal failure and renal insufficiency (See also under Investigations)
General disorders and administration site conditions	Asthenic conditions such as asthenia, fatigue, lethargy, malaise
Investigations	Abnormal renal function tests such as blood creatinine increased and blood urea increased Increased hepatic enzymes

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.

Clinical trials

In double-blind, placebo-controlled monotherapy studies, the overall incidence of treatment-emergent adverse events was 42.4% on olmesartan medoxomil and 40.9% on placebo.
In placebo-controlled monotherapy studies, the only adverse drug reaction that was unequivocally related to treatment was dizziness (2.5% incidence on olmesartan medoxomil and 0.9% on placebo).

In long-term (2-year) treatment, the incidence of withdrawals due to adverse events on olmesartan medoxomil 10 - 20 mg once daily was 3.7%.

The following adverse events have been reported across all clinical trials with olmesartan medoxomil (including trials with active as well as placebo control), irrespective of causality or incidence relative to placebo. They are listed by body system and ranked under headings of frequency using the conventions described above:

Central nervous system disorders:
Common: Dizziness
Uncommon: Vertigo

Cardiovascular disorders:
Rare: Hypotension
Uncommon: Angina pectoris

Respiratory system disorders:

Common: Bronchitis, cough, pharyngitis, rhinitis

Gastro-intestinal disorders:

Common: Abdominal pain, diarrhoea, dyspepsia, gastroenteritis, nausea

Skin and appendages disorders:

Uncommon: Rash

Musculoskeletal disorders:

Common: Arthritis, back pain, skeletal pain

Urinary system disorders:

Common: Haematuria, urinary tract infection

General disorders:

Common: Chest pain, fatigue, influenza-like symptoms, peripheral oedema, pain

Laboratory parameters

In placebo-controlled monotherapy studies the incidence was somewhat higher on olmesartan medoxomil compared with placebo for hypertriglyceridaemia (2.0% versus 1.1%) and for raised creatine phosphokinase (1.3% versus 0.7%).

Laboratory adverse events reported across all clinical trials with olmesartan medoxomil (including trials without a placebo control), irrespective of causality or incidence relative to placebo, included:

Metabolic and nutritional disorders:

Common: Increased creatine phosphokinase, hypertriglyceridaemia, hyperuricaemia.

Rare: Hyperkalaemia

Liver and biliary disorders:

Common: Liver enzyme elevations.

Additional information on special populations

In elderly patients the frequency of hypotension is slightly increased from rare to uncommon.

4.9 Overdose

Only limited information is available regarding overdosage in humans. The most likely effect of overdosage is hypotension. In the event of overdosage, the patient should be carefully monitored and treatment should be symptomatic and supportive.

No information is available regarding the dialysability of olmesartan.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties****Pharmaco-therapeutic group:**

Angiotensin II antagonists, ATC code: C09C A 08.

Olmesartan medoxomil is a potent, orally active, selective angiotensin II receptor (type AT₁) antagonist. It is expected to block all actions of angiotensin II mediated by the AT₁ receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT₁) receptors results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension via the type 1 (AT₁) receptor.

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 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. When used together with hydrochlorothiazide, the reduction in blood pressure is additive and coadministration is well tolerated.

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

5.2 Pharmacokinetic properties

Absorption and distribution

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 drugs 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).

Metabolism and elimination

Total plasma clearance 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.

Pharmacokinetics in special populations

Elderly:

In hypertensive patients, the 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. This may be at least in part related to a mean decrease in renal function in this group of patients.

Renal impairment:

In renally impaired patients, the 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*).

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 $C_{\max}$ 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*).

5.3 Preclinical safety data

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 (through functional changes to the kidneys caused by blocking AT_1 receptors); reduction in heart weight; a 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.

In both species, increased plasma renin activity and hypertrophy/hyperplasia of the juxtaglomerular cells of the kidney were observed. These changes, which are a typical effect of the class of ACE inhibitors and other AT_1 receptor antagonists, would appear to have no clinical relevance.

Like other AT_1 receptor antagonists olmesartan medoxomil was found to increase the incidence of chromosome breaks in cell cultures *in vitro*. No relevant effects were observed in several *in vivo* studies using olmesartan medoxomil at very high oral doses of up to 2000 mg/kg. The overall data of a comprehensive genotoxicity testing suggest that olmesartan is very unlikely to exert genotoxic effects under conditions of clinical use. Olmesartan medoxomil was not carcinogenic, neither in rats in a 2 year study nor in mice when tested in two 6 month carcinogenicity studies using transgenic models.

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 following exposure to olmesartan medoxomil and pelvic dilatation of the kidney was seen after exposure of the dams in late pregnancy and lactation. In common with other antihypertensive agents, olmesartan medoxomil was shown to be more toxic to pregnant rabbits than to pregnant rats, however, there was no indication of a fetotoxic effect.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose, microcrystalline

Lactose monohydrate

Hydroxypropylcellulose

Low substituted hydroxypropylcellulose

Magnesium stearate

Tablet coat:

Titanium dioxide (E 171)

Talc

Hypromellose

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 product on 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

Aluminium blister pack. Packs of 30 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

B&S Healthcare

Unit 4, Bradfield Road

Ruislip

Middlesex

HA4 0NU

United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1328/151/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th July 2011

10 DATE OF REVISION OF THE TEXT