

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Eprosartan Mylan 400mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 490.53 mg of eprosartan mesilate equivalent to 400 mg of eprosartan.

Excipient with known effect:

28.518 mg of lactose monohydrate per 400 mg tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet

400 mg: A pink, film coated, capsule shaped, biconvex, bevelled edge tablet imprinted with 'M EN2' in black ink on one side of the tablet and blank on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Eprosartan is indicated for the treatment of essential hypertension.

Eprosartan is indicated in adults.

4.2 Posology and method of administration

Posology

The recommended dose is 600 mg eprosartan once daily.

Achievement of maximal blood pressure reduction in most patients may take 2 to 3 weeks of treatment.

Eprosartan may be used alone or in combination with other anti-hypertensives (see sections 4.3, 4.4, 4.5 and 5.1). In particular, addition of a thiazide-type diuretic such as hydrochlorothiazide or a calcium channel blocker such as sustained release nifedipine has been shown to have an additive effect with eprosartan.

Duration of treatment is not limited.

Geriatric patients

No dose adjustment is required in the elderly.

Dosage in hepatically impaired patients

There is limited experience in patients with hepatic impairment (see section 4.3).

Dosage in renally impaired patients

In patients with moderate or severe renal impairment (creatinine clearance <60 ml/min), the daily dose should not exceed 600 mg.

Paediatric population

Eprosartan is not recommended for use in children or adolescents due to lack of data on safety and efficacy.

Method of administration

For oral use.

Eprosartan may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Severe hepatic impairment.

Haemodynamically significant bilateral renovascular disease or severe stenosis of a single functioning kidney.

The concomitant use of Eprosartan Mylan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m²) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Hepatic impairment

When eprosartan is used in patients with mild to moderate hepatic impairment, special care should be exercised due to the fact that there is limited experience in this patient population.

Risk of renal impairment

No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance \geq 30 ml/min). Caution is recommended for use in patients with creatinine clearance $<$ 30 ml/min or in patients undergoing dialysis.

Renin-angiotensin-aldosterone system dependent patients

Some patients, whose renal function is dependent on the continued inherent activity of the renin-angiotensin-aldosterone system (e.g. patients with severe cardiac insufficiency (NYHA class IV), bilateral renal artery stenosis, or renal artery stenosis of a solitary kidney) have risks of developing oliguria and/or progressive azotaemia and in rare cases acute renal failure during treatment with an angiotensin converting enzyme inhibitor (ACE-inhibitors). These events are more likely to occur in patients treated concomitantly with a diuretic. Angiotensin II receptor blockers, such as eprosartan, have not had adequate therapeutic experience to determine if there is a similar risk of developing renal function compromise in these susceptible patients. When eprosartan is to be used in patients with renal impairment, renal function should be assessed before starting treatment with eprosartan and regularly during treatment. If worsening of renal function is observed during therapy, treatment with eprosartan should be reassessed.

The following precautions are based on experience from other drugs belonging to the same class and ACE-inhibitors.

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.

Hypotension

Symptomatic hypotension may occur in patients with severe volume depletion and/or salt depletion (e.g. high dose diuretic therapy). These conditions should be corrected before commencing therapy.

Hyperkalaemia

During treatment with other drugs affecting the renin-angiotensin-aldosterone system, hyperkalaemia may occur, especially in patients with impaired renal function and/or cardiac failure. Regular monitoring for serum potassium levels is recommended in risk patients.

Based on experience with the use of other medicinal products which affect the renin-angiotensin-aldosterone system concomitant administration with potassium-sparing

diuretics, potassium-supplements, salt replacing preparations containing potassium or other drug which may elevate potassium levels (e.g. heparin, trimethoprim containing medicines) may lead to increased serum potassium levels and should therefore be administered cautiously with eprosartan.

Primary hyperaldosteronism

Treatment with eprosartan is not recommended for these patients.

Coronary heart disease

There is limited experience of treatment of patients with coronary heart disease.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with all vasodilators caution should be exercised in patients with aortic and mitral valve stenosis or hypertrophic cardiomyopathy.

Kidney transplantation

There is no experience from treatment with eprosartan in patients that have had a recent kidney transplantation.

Pregnancy

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

Other warnings and precautions

As observed for ACE inhibitors, eprosartan and other Angiotensin II Receptor Blockers are apparently less effective in lowering the blood pressure in black people than in non-blacks, possibly because of higher prevalence of low renin status in the black hypertensive population.

Excipient

This medicinal product contains lactose monohydrate. 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

Elevated serum potassium levels have been observed in placebo controlled clinical trials. Experience from other drugs affecting the renin-angiotensin-aldosterone system indicate that concomitant use of potassium sparing diuretics, potassium supplements, salt replacing agents containing potassium or other drugs which may elevate serum potassium levels (e.g. heparin, trimethoprim containing medicines) may cause an increase in serum potassium.

The blood pressure lowering effect may be enhanced during concomitant treatment with other blood pressure lowering drugs.

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).

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. While this is not documented with eprosartan, the possibility of a similar effect cannot be excluded and careful monitoring of serum lithium levels is recommended during concomitant use.

Eprosartan has been shown not to inhibit human cytochrome P450 enzymes CYP1A, 2A6, 2C9/8, 2C19, 2D6, 2E and 3A *in vitro*.

As with ACE inhibitors, concomitant use of Angiotensin II Receptor Blockers and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Concomitant use of losartan with the NSAID indometacin led to a decrease in efficacy of the angiotensin II receptor blocker; a class effect cannot be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated 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 Receptor Blockers, similar risks may exist for this class of drugs. Unless continued Angiotensin II 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 Blockers should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to Angiotensin II Receptor Blocker therapy 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 section 5.3).

Should exposure to Angiotensin II Receptor Blockers have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken Angiotensin II Receptor Blockers should be closely observed for hypotension (see also sections 4.3 and 4.4).

Breast-feeding

Because no information is available regarding the use of eprosartan during breast-feeding, eprosartan 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 has been performed. Based on its pharmacodynamic properties, eprosartan is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account, that occasionally dizziness or weariness may occur during treatment of hypertension.

4.8 Undesirable effects

The most commonly reported adverse drug reactions of patients treated with eprosartan are headache and unspecific gastrointestinal complaints, occurring in approximately 11% and 8%, respectively, of patients.

Adverse reactions have been ranked under headings of frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

ADVERSE EXPERIENCES BY EPROSARTAN-TREATED PATIENTS PARTICIPATING IN CLINICAL TRIALS (n = 2316)

MedDRA classification of organ system	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $> 1/10$)	Uncommon ($> 1/1000$ to $< 1/100$)	Not known (frequency cannot be estimated from the available data)
Immune system disorders			Hypersensitivity*	
Nervous system disorders	Headache*	Dizziness*		
Vascular disorders			Hypotension	
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Gastrointestinal disorders		Unspecific gastrointestinal complaints (e.g. nausea, vomiting, diarrhoea)		
Skin and subcutaneous		Allergic skin	Angioedema*	

tissue disorders		reactions (e.g. rash, pruritus)		
Musculoskeletal and connective tissue disorders				Arthralgia
General disorders and administration site disorders		Asthenia		

*Did not occur in a higher frequency than in placebo.

In addition to those adverse events reported during clinical trials the following side effects have been reported spontaneously during postmarketing use of eprosartan. A frequency cannot be estimated from available data (not known).

Renal and urinary disorders

Impaired renal function including renal failure in patients at risk (e.g. renal artery stenosis).

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Limited data are available with regard to overdose in humans. There have been individual reports from postmarketing experience where doses up to 12,000 mg had been ingested. Most patients reported no symptoms. In one subject circulatory collapse occurred after ingestion of 12,000 mg eprosartan. The subject recovered completely. The most likely manifestation of overdose would be hypotension. If symptomatic hypotension should occur, supportive treatment should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA02

Mechanism of action

Eprosartan is a potent, synthetic, orally active non-biphenyl non-tetrazole angiotensin II receptor antagonist, which binds selectively to the AT₁ receptor.

Angiotensin II is a potent vasoconstrictor and the primary active hormone of the renin-angiotensin-aldosterone system, playing a major part in the pathophysiology of hypertension.

Clinical efficacy and safety

Eprosartan antagonised the effect of angiotensin II on blood pressure, renal blood flow and aldosterone secretion in normal volunteers. Blood pressure control is maintained over a 24 hour period with no first dose postural hypotension or reflex tachycardia. Discontinuation of treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.

Eprosartan was evaluated in mild to moderate hypertensive patients (sitting DBP \geq 95 mmHg and $<$ 115 mmHg) and severe hypertensive patients (sitting DBP \geq 115 mmHg and \leq 125 mmHg).

Doses up to 1200 mg per day, for 8 weeks, have been shown in clinical trials to be effective with no apparent dose relationship in the incidence of adverse events reported.

In patients with hypertension, blood pressure reduction did not produce a change in heart rate.

Beneficial effects of eprosartan on mortality and cardiovascular morbidity are currently unknown.

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.

Eprosartan does not compromise renal autoregulatory mechanisms. In normal adult males eprosartan has been shown to increase mean effective renal plasma flow. Eprosartan has no deleterious effects on renal function in patients with essential hypertension and patients with renal insufficiency. Eprosartan does not reduce glomerular filtration rate in normal males, in patients with hypertension or in patients with varying degrees of renal insufficiency. Eprosartan has a natriuretic effect in normal subjects on a salt restricted diet. Eprosartan may be safely administered to

patients with essential hypertension and to patients with varying degrees of renal insufficiency without causing sodium retention or a deterioration of renal function.

Eprosartan does not significantly affect the excretion of urinary uric acid.

Eprosartan does not potentiate effects relating to bradykinin (ACE-mediated), e.g. cough. In a study specifically designed to compare the incidence of cough in patients treated with eprosartan and an angiotensin converting enzyme inhibitor, the incidence of dry persistent cough in patients treated with eprosartan (1.5%) was significantly lower ($p < 0.05$) than that observed in patients treated with an angiotensin converting enzyme inhibitor (5.4%). In a further study investigating the incidence of cough in patients who had previously coughed while taking an angiotensin converting enzyme inhibitor, the incidence of dry, persistent cough was 2.6% on eprosartan, 2.7% on placebo, and 25.0% on an angiotensin converting enzyme inhibitor ($p < 0.01$, eprosartan versus angiotensin converting enzyme inhibitor).

In three clinical studies ($n = 791$) the blood pressure lowering effect of eprosartan has been shown to be at least as great as the ACE inhibitor enalapril, with one study in severe hypertensives showing a statistically significantly greater decrease in sitting and standing systolic blood pressure for eprosartan over enalapril.

Angiotensin II binds to the AT_1 receptor in many tissues (e.g. smooth vascular musculature, suprarenals, kidney, heart) and produces important biological effects such as vasoconstriction, sodium retention and release of aldosterone. More recently, angiotensin II has been implicated in the genesis of cardiac and vascular hypertrophy through its effect on cardiac and smooth muscle cell growth.

In hypertensive patients eprosartan does not affect fasting triglycerides, total cholesterol, or LDL (low density lipoprotein) cholesterol levels. In addition, eprosartan has no effect on fasting blood sugar levels.

5.2 Pharmacokinetic properties

Absorption

Absolute bioavailability following a single 300 mg oral dose of eprosartan is about 13%, due to limited oral absorption. Eprosartan plasma concentrations peak at one to two hours after an oral dose in the fasted state. Plasma concentrations are dose proportional from 100 to 200 mg, but less than proportional for 400 and 800 mg doses. A slight accumulation (14%) is seen with chronic use of eprosartan. Administration of eprosartan with food delays absorption with minor increases ($< 25\%$) observed in C_{max} and AUC.

Distribution

The volume of distribution of eprosartan is about 13 litres. Plasma protein binding of eprosartan is high (approximately 98%) and constant over the concentration range achieved with therapeutic doses. The extent of plasma protein binding is not influenced by gender, age, hepatic dysfunction or mild-moderate renal impairment but has shown to be decreased in a small number of patients with severe renal impairment.

Biotransformation and elimination

Following intravenous [¹⁴C] eprosartan, about 61% of radioactivity is recovered in the faeces and about 37% in the urine. Following an oral dose of [¹⁴C] eprosartan, about 90% of radioactivity is recovered in the faeces and about 7% in the urine.

Following oral and intravenous dosing with [¹⁴C] eprosartan in human subjects, eprosartan was the only drug-related compound found in the plasma and faeces. In the urine, approximately 20% of the radioactivity excreted was an acyl glucuronide of eprosartan with the remaining 80% being unchanged eprosartan.

The terminal elimination half-life of eprosartan following oral administration is typically five to nine hours. Total plasma clearance is about 130 ml/min. Biliary and renal excretion contribute to the elimination of eprosartan.

Special populations

Geriatric patients

Both AUC and C_{max} values of eprosartan are increased in the elderly (on average, approximately two-fold), but this does not necessitate alterations in dosing.

Hepatically impaired patients

Following administration of a single 100 mg dose of eprosartan, AUC values of eprosartan (but not C_{max}) are increased, on average, by approximately 40% in patients with hepatic impairment.

Renally impaired patients

Compared to subjects with normal renal function (n=7), mean AUC and C_{max} values were approximately 30% higher in patients with creatinine clearance 30-59 ml/min (n=11) and approximately 50% higher in patients with creatinine clearance 5-29 ml/min (n=3).

In a separate investigation, mean AUC was approximately 60% higher in patients undergoing dialysis (n=9) compared to subjects with normal renal function (n=10).

Gender

There is no difference in the pharmacokinetics of eprosartan between males and females.

5.3 Preclinical safety data

a) Acute toxicity

There were no mortalities in rats and mice dosed at up to 3000 mg/kg BW and in dogs given up to 1000 mg/kg BW.

b) Chronic toxicity

In chronic toxicity studies eprosartan did not produce any toxic effects in rats (after oral administration of doses of up to 1000 mg/kg/day for up to six months). In dogs, eprosartan caused a reduction in red cell parameters (erythrocytes, haemoglobin, haematocrit) at doses of 30 mg/kg BW/day or more after oral administration for up to six months, but red cell parameters returned to normal values at 1 year despite continuous drug administration.

c) *Reproductive and developmental toxicity*

In pregnant rabbits, eprosartan has been shown to produce maternal and foetal mortality at 10 mg/kg BW per day during late pregnancy only. Maternal toxicity but no foetal effects were observed at 3 mg/kg BW per day.

d) *Genotoxicity*

Genotoxicity was not observed in a battery of in vitro and in vivo tests

e) *Carcinogenicity*

Carcinogenicity was not observed in rats and mice given up to 600 or 2000 mg/kg BW per day respectively for 2 years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose (Avicel PH101)
Pregelatinised maize starch
Silica, colloidal anhydrous
Polysorbate 80
Povidone (K-12)
Microcrystalline cellulose (Avicel PH102)
Crospovidone (Type B)
Magnesium Stearate

Film coating

Hydroxypropyl cellulose (E462)
Hypromellose 6 cP
Titanium dioxide (E171)
Macrogol 400
Iron oxide red (E172)
Iron oxide yellow (E172)

Imprinting ink.

Shellac
Iron oxide black (E172)
Ammonium hydroxide 28%
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White HDPE bottle with a white opaque polypropylene screw cap with induction sealing liner. Pack size of 500 film-coated tablets

Aluminium foil blisters laminated with PVC on one side and coated with a heat seal lacquer (Aclar/PVC/Al). Pack sizes of 14, 28, 30, 56, 98, 100 or 168 film-coated tablets. Calendar pack sizes of 14, 28, 56, 98 and 168 film-coated 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

Generics [UK] Limited t/a Mylan
Station Close
Potters Bar
Hertfordshire
EN6 1TL

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/1228

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

30/07/2021

10 DATE OF REVISION OF THE TEXT

30/07/2021