Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Eprosartan Mylan 600mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 735.80 mg of eprosartan mesylate equivalent to 600 mg of eprosartan.

Excipient(s): 42.788 mg of lactose monohydrate per 600 mg tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet

A white to off-white, film coated, capsule shaped, biconvex, bevelled edge tablet imprinted with ‘M EN3’ in black ink on one side of the tablet and blank on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Eprosartan Mylan is indicated for the treatment of essential hypertension.

Eprosartan Mylan is indicated in adults.

4.2 Posology and method of administration

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.

Eprosartan could be taken with or without food.

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: As clinical experience is limited in patients with creatinine clearance <60 ml/min a daily dose of 600 mg should not be exceeded.
Paediatric population

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

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients.

2nd and 3rd trimester of pregnancy. (see section 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/1.73m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

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

Risk of renal impairment
No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min). Caution in patients with creatinine clearance < 30 ml/min and in patients undergoing dialysis.

Patients dependent on the renin-angiotensin-aldosterone system (see section 4.3)

Patients, whose renal function is dependent on the activity of the renin-angiotensin-aldosterone system (e.g. patient with severe cardiac insufficiency (HYHA class IV), bilateral renal stenosis or unilateral renal stenosis having only one kidney left) have developed oliguria and/or progressive azotaemia and in rare cases acute renal failure during treatment with ACE-inhibitors. Since there currently is limited experience from treatment of patients with severe cardiac insufficiency or renal stenosis, deterioration of the kidney function cannot be excluded in these patients if administered eprosartan due to inhibition of the renin-angiotensin-aldosterone system. In renally impaired patients the kidney function should be controlled before treatment initiation and regularly during treatment with eprosartan. If the kidney function gets worse, treatment with eprosartan should be reconsidered.

The below 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.

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 K-sparing diuretics, K-supplements, salt replacing preparations containing potassium or other drug elevating potassium levels (e.g heparin) may lead to increased potassium levels and should therefore be administered cautiously with eprosartan.

Primary hyperaldosteronism
Treatment with eprosartan is not recommended for these patients.

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

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

Aortic and mitral valvular stenosis, hypertrophic cardiomyopathy
As with all vasodilators caution should be exercised in patients with aortic and mitral valvular 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 Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs 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 AIIRAs 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 antagonists 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

No effect on the pharmacokinetics of digoxin and the pharmacodynamics of warfarin or glyburide (glibenclamide) has been shown with eprosartan. Similarly no effect on eprosartan pharmacokinetics has been shown with ranitidine, ketoconazole or fluconazole.

Eprosartan has been safely used concomitantly with thiazide diuretics (e.g. hydrochlorothiazide) and calcium channel blockers (e.g. sustained-release nifedipine) without evidence of clinically significant adverse interactions. It has been safely co-administered with hypolipidaemic agents (eg lovastatin, simvastatin, pravastatin, fenofibrate, gemfibrozil, niacin).

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 saving diuretics, potassium supplements, salt replacing agents containing potassium or other drugs elevating serum potassium levels (e.g. heparin) 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 can not 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*.

When Angiotensin II antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (ie selective COX-2 inhibitors, acetyl salicylic acid (>3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of Angiotensin II antagonists and NSAIDs may lead to an increase 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 an decrease in efficacy of the angiotensin II antagonist; a class effect can not 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 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued ARB 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 AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started. Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

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

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

Breastfeeding: Because no information is available regarding the use of eprosartan during breastfeeding, 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

In placebo-controlled clinical trials, the overall incidence of adverse events reported with eprosartan was comparable to placebo. Adverse events have usually been mild and transient in nature and have only required discontinuation of therapy in 4.1% of patients treated with eprosartan in placebo-controlled studies (6.5% for placebo).

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

ADVERSE EVENTS FROM CLINICAL TRIALS

MedDRA classification of organ system	Very common (≥1/10)	Common (>1/100, >1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10,000, <1/1000)	Not known
Infections and infestations		Virus infection			
Metabolism and nutrition disorders		Hypertriglycerideaemia	Hyperkalaemia		
Immune system disorders			Hypersensitivity*		
Nervous system disorders	Headache*	Dizziness* Fatigue, depression			Hypotonia
Cardiac disorders		Chest pain, palpitations			
Vascular disorders			Hypotension		Postural hypotension
Respiratory thoracic and mediastinal disorders		Rhinitis, pharyngitis, dyspnoea, upper airway infections, cough			
Gastrointestinal disorders		Abdominal pain, Unspecific gastrointestinal complaints (e.g. nausea, vomiting, diarrhoea), dyspepsia			
Skin and subcutaneous tissue disorders		Allergic skin reactions (e.g. rash, pruritus, urticaria)	Angioedema*		Facial oedema
Musculoskeletal and connective tissue disorders		Back pain, arthralgia			
Renal and urinary disorders		Urinary tract infection			
General disorders and administration site disorders		Asthenia, body damage, pain			
Investigations				Decrease haemoglobin and elevated urea readings	

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

A relationship with eprosartan treatment could not always be established.
Besides the reactions observed during clinical trials the following adverse experiences have been reported spontaneously after marketing authorisation. The frequency cannot be estimated from available data (not known)

Renal and urinary disorders
Decreased kidney function including kidney failure in patients at risk (e.g. renal artery stenosis)

In rare cases increases in liver function values were also observed but were not considered to be causally related to eprosartan treatment.

4.9 Overdose

Limited data are available with regard to overdose in humans. Eprosartan was well tolerated after oral dosing

(maximum unit dose taken to date in humans 1200 mg). The most likely manifestation of overdose would be hypotension. If symptomatic hypotension occurs, supportive treatment should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Eprosartan is a potent, synthetic, orally active non-biphenyl non-tetrazole angiotensin II receptor antagonist, which binds selectively to the AT_1 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.
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 ≥ 95 mmHg and <115 mmHg) and severe hypertensive patients (sitting DBP ≥ 115 mmHg and ≤ 125 mmHg).
A dose of 1200 mg once daily, for 8 weeks, has 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.

In the MOSES trial (morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention) 1405 hypertensive patients with a history of cerebrovascular events were treated either with eprosartan or with nitrendipin. In the eprosartan group, 78 % of the patients received 600 mg o.d.; 12 % up to to 800 mg per day; in the nitrendipine group, 47 % received 10 mg and 42 % 20 mg per day (11 % up to 40 mg) in an open label observer blinded randomised prospective design. The primary composite endpoint included all cause mortality, cerebrovascular events (TIA, PRIND, Stroke), and cardiovascular events (unstable angina, myocardial infarction, heart failure, pulmonary embolism and fatal cardiac arrhythmia) including recurrent events. Blood pressure targets were well met in both treatment arms and maintained throughout the course of the study. The primary endpoint showed a significantly better result in the eprosartan group (risk reduction by 21%). In the first event analysis the risk reduction was 25 % for the cerebrovascular and 30 % for the first cardiovascular endpoints. These results were mainly driven by a reduction in the incidence of TIA/PRIND, unstable angina, and heart failure. Overall mortality was numerically in favour of nitrendipine; in the eprosartan group, 57 from 681 patients died vs. 52 from 671 patients in the nitrendipine group (hazard ratio 1.07, 95 % CI 0.73 – 1.56, p= 0.725) . Fatal and nonfatal myocardial infarction occurred in 18 vs. 20 and stroke in 36 vs. 42 patients, i.e. numerically in favour of eprosartan. For the primary endpoint, the effect of eprosartan appeared to be more pronounced in patients not receiving beta-blockers.

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 treated with eprosartan. 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 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).

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

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. The terminal elimination half-life of eprosartan following oral administration is typically five to nine hours. A slight accumulation (14%) is seen with chronic use of eprosartan. Administration of eprosartan with food delays absorption with minor increases (<25%) observed in Cmax and AUC.

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.

Following intravenous dosing with [^{14}C] 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 volume of distribution of eprosartan is about 13 litres. Total plasma clearance is about 130 ml/min. Biliary and renal excretion contribute to the elimination of eprosartan. Both AUC and C_{max} values of eprosartan are increased in the elderly (on average, approximately two-fold).

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.
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).

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

5.3 Preclinical safety data

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.

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, hemoglobin, hematocrit) 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.

In pregnant rabbits, eprosartan has been shown to produce maternal and foetal mortality at 10 mg/kg BW per day during late pregnancy only. This is most likely due to effects on the renin-angiotensin-aldosterone system. Maternal toxicity but no foetal effects were observed at 3 mg/kg BW per day.

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

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

Film coating
Opadry white
Hydroxypropyl cellulose (E462)
Hypromellose 6 cP
Titanium dioxide (E171)
Macrogol 400

Imprinting ink.
Opacode black
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 and other handling

Return any unwanted tablets to your pharmacist.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd t/a Gerard Laboratories,
35/36 Baldoyle Industrial Estate,
Grange Road,
Dublin 13,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 577/139/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 24th August 2012

10 DATE OF REVISION OF THE TEXT

December 2014