# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Eprosartan Niche 400 mg Film-coated Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 490.56 mg eprosartan mesilate equivalent to 400 mg eprosartan.

Excipient with known effect:
28 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet

Peached coloured, oval shaped, biconvex film-coated tablets. Tablets are approximately 18 x 7 mm.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Eprosartan is indicated in adults for the treatment of essential hypertension.

### 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.

*Older people*
No dose adjustment is required in older people.

*Patients with Hepatic impairment*
There is limited experience in patients with hepatic insufficiency *(see section 4.3, Contraindications)*.

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

*Paediatric population*
Eprosartan Niche 400mg Film-coated Tablets are not recommended for use in children and adolescents. The safety and efficacy of eprosartan in children and adolescents under 18 years have not been established. No data are available.

Method of administration

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.

Severe hepatic impairment.
Second and third trimester of pregnancy (see sections 4.4 and 4.6).
Hemodynamically significant bilateral renovascular disease or severe stenosis of a solitary functioning kidney.

The concomitant use of Eprosartan Niche 400mg Film-coated Tablets 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**
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.

**Renal Impairment**
No dose adjustment is required in patients with mild to moderate renal insufficiency (creatinine clearance ≥ 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-classification: class IV], bilateral renal artery stenosis, or renal artery stenosis of a solitary kidney), have risks of developing oliguria and/or progressive azotaemia and rarely acute renal failure during therapy with an angiotensin converting enzyme (ACE) inhibitor. 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 at intervals during the course of therapy. If worsening of renal function is observed during therapy, treatment with eprosartan should be reassessed.

**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.

The following precautions have been included based on experience with other agents in this class and also ACE inhibitors:

**Hyperkalaemia**
During treatment with other medicinal products which affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Adequate monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of other medicinal products which affect the renin-angiotensin-aldosterone system, concomitant use of with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products which may increase the potassium level (e.g. heparin) may lead to an increase in serum potassium and should therefore be co-administered cautiously with Eprosartan Niche 400mg Film-coated Tablets.

**Primary Hyperaldosteronism**
Patients with primary hyperaldosteronism are not recommended to be treated with eprosartan.

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

**Coronary Heart Disease**
There is limited experience in patients with coronary heart disease at this time.

**Aortic and Mitral Valve Stenosis / Hypertrophic Cardiomyopathy**
As with all vasodilators, eprosartan should be used with caution in patients with aortic and mitral valve stenosis or hypertrophic cardiomyopathy.

**Renal Transplantation**
There is no experience in patients with recent kidney transplantation.

**Pregnancy**
Eprosartan should not be initiated during pregnancy. Unless continued eprosartan 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 eprosartan 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 angiotensin converting enzyme inhibitors, eprosartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

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

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 can be used concomitantly with thiazide diuretics (e.g. hydrochlorothiazide) and calcium channel blockers (e.g. sustained-release nifedipine) without evidence of clinically significant adverse interactions.

Since in placebo-controlled clinical studies significantly elevated serum potassium concentration were observed, and based on experience with the use of other drugs that affect the renin-angiotensin-aldosterone system, concomitant use of K-sparing diuretics, K-supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (e.g. heparin) may lead to increase in serum potassium.

The antihypertensive effect may be potentiated by other antihypertensives.

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).

Toxicity and a reversible increase in serum lithium concentrations have been reported during concurrent therapy with lithium preparations and ACE inhibitors. The possibility of a similar effect after the use of eprosartan 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 antagonists 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 antagonist; a class effect cannot be excluded.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

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

Angiotensin II receptor blockers therapy exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

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

Infants whose mothers have taken eprosartan should be closely observed for hypotension (see 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

Eprosartan has no or negligible influence on the ability to drive and use machines. 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

*Summary of the safety profile*
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.

*Tabulated summary of adverse reactions*
**ADVERSE EXPERIENCES BY EPROSARTAN-TREATED PATIENTS PARTICIPATING IN CLINICAL TRIALS (n = 2316)**

| MedDRA system organ class | Very common ≥1/10 | Common ≥1/100 to <1/10 | Uncommon ≥1/1,000 to <1/100 | Rare ≥1/10,000 to <1/1000 | Not known |
|---|---|---|---|---|---|
| **Infections and infestations** | | Virus infection | | | |
| **Immune system disorders** | | | Hypersensitivity* | | |
| **Metabolism and nutrition disorders** | | Hypertriglycerideaemia | Hyperkalaemia | | |
| **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, diarrhoea, vomiting), 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 reactions** | | Asthenia, body damage, pain | | | |
| **Investigations** | | | | Decrease haemoglobin | |

| | | | | | |
|---|---|---|---|---|---|
| | | | | and elevated urea readings | |

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

*Description of selected adverse reactions*
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 the 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

## 4.9 Overdose

Limited data are available in 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 synthetic, orally active non-biphenyl non-tetrazole angiotensin II receptor antagonist.

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.

Pharmacodynamic effects

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 mm Hg and <115 mm Hg) and severe hypertensive patients (sitting DBP ≥115 mm Hg and ≤125 mm Hg).

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 experiences 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.

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).

Clinical efficacy and safety

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.

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.

## 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 1 to 2 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.

Elimination

The terminal elimination half-life of eprosartan following oral administration is typically 5 to 9 hours. Eprosartan does not significantly accumulate with chronic use. Administration of eprosartan with food delays absorption with minor changes (<25%) observed in $C_{max}$ and AUC which are not of clinical consequence.

Distribution

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

Following oral and 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 2 fold), but this does not necessitate alterations in dosing.

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

Compared to subjects with normal renal function mean AUC and $C_{max}$ values were approximately 30% higher in patients with moderate renal impairment (creatinine clearance 30-59 mL/min), approximately 50% higher in a small number of patients with severe renal impairment (creatinine clearance 5-29 mL/min) and approximately 60% in patients undergoing dialysis.

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 BW/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 one 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. 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.
*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
Pregelatinised maize starch
Silica colloidal anhydrous
Povidone
Polysorbate 80
Crospovidone
Magnesium stearate

*Tablet film-coating*
Hypromellose
Hydroxypropylcellulose (E463)
Titanium dioxide (E171)
Macrogol 400
Iron oxide yellow (E172)
Iron oxide red (E172)

## 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

Aluminium foil blisters. Pack sizes of 4, 7, 14, 28, 50, 56, 98 and 280 film-coated tablets. Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Niche Generics
1 The Cam Centre
Wilbury Way
Hitchin
Hertfordshire
SG4 0TW
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER

PA1063/052/002

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

Date of first authorisation: 29th May 2015

## 10 DATE OF REVISION OF THE TEXT