1. NAME OF THE MEDICINAL PRODUCT

EMBATELTAN A40 PLUS (Telmisartan and Amlodipine Tablets USP (40mg/10mg))

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

3. PHARMACEUTICAL FORM

Oral bilayer uncoated tablet

Product Description: Yellow/White coloured, round shaped, Uncoated, Biconvex, Bilayered tablet having plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of essential hypertension in adults:

Add on therapy
TELMISARTAN AND AMLODIPINE TABLETS USP (40MG/10MG) is indicated in adults whose blood pressure is not adequately controlled on amlodipine 10 mg alone.

Replacement therapy
Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of TELMISARTAN AND AMLODIPINE TABLETS USP (40MG/10MG) containing the same component doses.

4.2 Posology and method of administration

Route of Administration: Oral

Posology

The recommended dose of this medicinal product is one tablet per day.
The maximum recommended dose is one tablet 80 mg telmisartan/10 mg amlodipine per day. This medicinal product is indicated for long term treatment.
Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Add on therapy

TELMISARTAN AND AMLODIPINE TABLETS USP (40MG/10MG) may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg alone.
Individual dose titration with the components (i.e. amlodipine and telmisartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.
Patients treated with 10 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to TELMISARTAN AND AMLODIPINE TABLETS USP (40MG/10MG) once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.
Replacement therapy
Patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Twynsta containing the same component doses in one tablet once daily.

Method of administration

Oral use.
It can be taken with or without food. It is recommended to take TELMISARTAN AND AMLODIPINE TABLETS USP (40MG/10MG) with some liquid.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients
- Second and third trimesters of pregnancy
- Biliary obstructive disorders and severe hepatic impairment
- Shock (including cardiogenic shock)
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)

•Haemodynamically unstable heart failure after acute myocardial infarction

The concomitant use of telmisartan/amlodipine with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)

4.4 Special warnings and precautions for use

Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hepatic impairment

Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Furthermore as with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dose recommendations have not been established. telmisartan/amlodipine should therefore be used with caution in these patients.

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 (RAAS).

Renal impairment and kidney transplantation

When telmisartan/amlodipine is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of telmisartan/amlodipine in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.

Intravascular hypovolaemia

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by e.g. vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of telmisartan. If hypotension occurs with telmisartan/amlodipine, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Heart failure

In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Diabetic patients treated with insulin or antidiabetics

In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required when indicated.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

NSAIDs: Increased risk of renal impairment and loss of antihypertensive effect. If simvastatin is co-administered with amlodipine, do not exceed doses greater than 20 mg daily of simvastatin. Do not co-administer aliskiren with telmisartan and amlodipine tablets in patients with diabetes.

4.6 Pregnancy and Lactation

Pregnancy

There are limited data from the use of telmisartan/amlodipine in pregnant women. Animal

reproductive toxicity studies with telmisartan/amlodipine have not been performed.

Telmisartan
The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy.

Amlodipine
Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery.

Breast-feeding
Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.
Because no information is available regarding the use of telmisartan during breast-feeding, telmisartan/amlodipine is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while breast-feeding a newborn or preterm infant.

Fertility
No data from controlled clinical studies with the fixed dose combination or with the individual components are available.

4.7 Effects on 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.

4.8 Undesirable effects
In the placebo-controlled factorial design study, the most common reasons for discontinuation of therapy with telmisartan and amlodipine tablets were peripheral edema, dizziness, and hypotension, each leading todiscontinuation of ≤ 0.5% of telmisartan and amlodipine tablet-treated patients. Adverse reactions that occurred at a ≥ 2% higher incidence on telmisartan and amlodipine tablets than placebo were peripheral edema (4.8% vs 0%), dizziness (3.0% vs 2.2%), and back pain (2.2% vs 0%).

4.9 Overdose

Symptoms
Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. The most prominent manifestations of telmisartan overdose are expected to be hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported. Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment
The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdose of both telmisartan and amlodipine. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly. Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and Amlodipine are not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers

ATC code: C09DB04

Telmisartan
Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 (AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors.

Amlodipine
Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

5.2 Pharmacokinetic properties

Pharmacokinetic of the fixed dose combination
The rate and extent of absorption of TELMISARTAN AND AMLODIPINE TABLETS USP (40MG/10MG) are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

Absorption
Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.
After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %.
Amlodipine bioavailability is not affected by food ingestion.

Distribution
Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein.
The mean steady state apparent volume of distribution (Vdss) is approximately 500 l.
The volume of distribution of amlodipine is approximately 21 l/kg. In vitro studies have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Biotransformation
Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.
Amlodipine is extensively (approximatively 90%) metabolised by the liver to inactive metabolites.

Elimination
Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination halflife of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, the area

under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.
After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cl_{tot}) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

5.3 Preclinical safety data

Since the non-clinical toxicity profiles of telmisartan and amlodipine are not overlapping, no exacerbation of toxicity was expected for the combination. This has been confirmed in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/10 mg/kg of Telmisartan and amlodipine were tested.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Meglumine
Purified water
Poviodne K 30
Sodium hydroxide pellets
Magnesium stearate
Microcrystalline cellulose
Maize starch
Calcium hydrogen phosphate
Sodium starch glycolate
Colour lake of Ponceau 4R

6.2 Incompatibilities

None.

6.3 Shelf life

24 months from the date of manufacturing

7. Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

8. Nature and contents of container

3X 10 Tablets Alu-Alu blister Pack

9. Marketing authorisation holder

STALLION LABORATORIES PVT.LTD.
C-1B, 305/2, 3, 4&5, G.I.D.C. KERALA (BAVLA),
DIST.: AHMEDABAD,
GUJARAT, INDIA.

10. Marketing authorisation numbers

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11. Date of first authorisation/renewal of the authorization

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12. Date of revision of Text

Not Applicable