1. NAME OF THE MEDICINAL PRODUCT

XITHERAM 40/5 AND XITHERAM 80/10 TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Telmisartan Ph.Eur. ……80 mg

Amlodipine Ph. Eur. ……..10 mg

(as Amlodipine Besilate)

Each tablet contains:

Telmisartan Ph.Eur. ……40 mg

Amlodipine Ph. Eur. ……..5 mg

(as Amlodipine Besilate)

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Blue and white oval shaped two-layer tablet engraved with "139" on blue layer and plain on white layer.

4. Clinical particulars

4.1 Therapeutic indications

The Telmisartan and Amlodipine Tablets is an angiotensin II receptor blocker (ARB) and a dihydropyridine calcium channel blocker (DHP-CCB) combination product indicated for the treatment of hypertension alone or with other antihypertensive agents.

Telmisartan and Amlodipine Tablets are indicated as initial therapy in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals.

4.2 Posology and method of administration

Posology

Pediatric population

There are limited data from the use of telmisartan/amlodipine in pregnant women. Animal reproductive toxicity studies with telmisartan/amlodipine have not been performed.

Method of administration

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.

It can be taken with or without food. It is recommended to take Telmisartan and Amlodipine Tablets 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

4.4 Special warnings and precautions for use

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including this medicinal product, e.g. baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol.

Corticosteroids (systemic route)

Reduction of the antihypertensive effect.

Interactions linked to telmisartan

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements

Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss.

Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor

antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Other antihypertensive agents acting on the renin-angiotensin-aldosterone system (RAAS)

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.

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and nonselective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and medicinal products that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and Consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

Ramipril

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC0-24 and Cmax of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Concomitant use to be taken into account

Digoxin

When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49 %) and in trough concentration (20 %) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels to maintain levels within the therapeutic range.

Interactions linked to amlodipine

Concomitant use requiring caution

CYP3A4 inhibitors

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with

hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the coadministration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Grapefruit and grapefruit juice

Administration of Twynsta with grapefruit or grapefruit juice is not recommended since bioavailability may be increased in certain patients resulting in increased blood pressure lowering effects.

Concomitant use to be taken into account

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77 % compared to simvastatin alone. Therefore, the dose of simvastatin in patients on amlodipine should be limited to 20 mg daily.

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.

Breast-feeding

If a mother wants to breastfeed her baby, she should ask her health care provider for advice on the risks and benefits.

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.

4.7 Effects on ability to drive and use machines

XITHERAM 40/5 AND XITHERAM 80/10 TABLETS has moderate influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as syncope, somnolence, dizziness, or vertigo during treatment. Therefore, caution should be recommended when driving a car or using machines. If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines.

4.8 Undesirable effects

Like all medicines, XITHERAM 40/5 AND XITHERAM 80/10 TABLETS can cause side effects, but not everybody gets them. The most common adverse reactions include dizziness and peripheral oedema.

Common Side Effects

The most common adverse reactions include dizziness, peripheral oedema, visual disturbance, altered bowel habits (including diarrhoea and constipation) and ankle swelling.

Uncommon Side Effects

Uncommon side effects are upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis, anaemia, hyperkalemia, dyspnoea, flatulence, hyperhidrosis, renal impairment including acute renal failure, mood change, visual impairment, tinnitus, dyspnoea, rhinitis, alopecia, purpura, skin discolouration, hyperhidrosis, micturition disorder, pollakiuria.

Rare Side Effects

Serious syncope may occur rarely.

Other rare side effects are Confusion, angioedema, drug eruption, toxic skin eruption, urticaria,hepatic function abnormal, liver disorder, stomach discomfort, tachcardia, hypoglycaemia, hypersensitivity, anaphylactic reaction, thrombocytopenia, eosinophilia and sepsis including fatal outcome.

Very Rare Side Effects

Very rare side effects are Leukocytopenia, thrombocytopenia, hypersensitivity, hyperglycaemia, extrapyramidal syndrome, hypertonia, myocardial infarction, arrhythmia, ventricular tachycardia,atrial fibrillation and vasculitis

If You Get Side Effects

Tell your healthcare provider if any of the side effects gets severe or troublesome, or if you notice any side effects not listed in this leaflet.

4.9 Overdose

If overdose occurs the patient should be monitored for evidence of toxicity and standard supportive treatment applied as necessary.

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.
Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.
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 receptor blockers (ARBs) and calcium channel blockers,
ATC code: C09DB04.

Pharmacodynamic effects: Telmisartan and Amlodipine Tablets have been shown to be effective in lowering blood pressure. Telmisartan and Amlodipine Tablets is a combination of two drugs with antihypertensive properties: a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker), amlodipine besylate, and an angiotensin II receptor blocker, telmisartan.

Both telmisartan and amlodipine, lower blood pressure by reducing peripheral resistance but through complementary mechanisms.

Clinical efficacy and safety:

Telmisartan

In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an

intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

Amlodipine

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105–114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90–104 mmHg).

Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic

pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in

combination with beta-blockers to patients with either hypertension or angina, no adverse effects of electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

5.2 Pharmacokinetic properties

The pharmacokinetics of amlodipine and telmisartan when combined are similar to the pharmacokinetics of amlodipine and telmisartan when administered separately.

After administering Telmisartan and Amlodipine Tablets USP 80/10 mg tablet with a high-fat meal, the total area under the plasma concentration-time curve (AUC) and Cmax for telmisartan decreased by about 24% and 60%, respectively. For amlodipine, AUC and Cmax

Absorption

Telmisartan

Following oral administration, peak concentrations (Cmax were not altered [see Dosage and Administration of telmisartan are reached in 0.5–1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses.

Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Amlodipine

Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food.

Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady state plasma levels of amlodipine are reached

after 7-8 days of consecutive daily dosing.

Distribution

Telmisartan

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α1- acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.

Amlodipine

The apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Metabolism and Elimination

Telmisartan

Following either intravenous or oral administration of 14C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Amlodipine

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.
Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.
In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light-coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients are Sodium Hydroxide, Povidone, Meglumine, Mannitol, Magnesium stearate, Sodium stearyl fumarate, Iron Oxide Yellow, Iron oxide Black, Brilliant Blue, Colloidal Silicon dioxide and Purified Talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

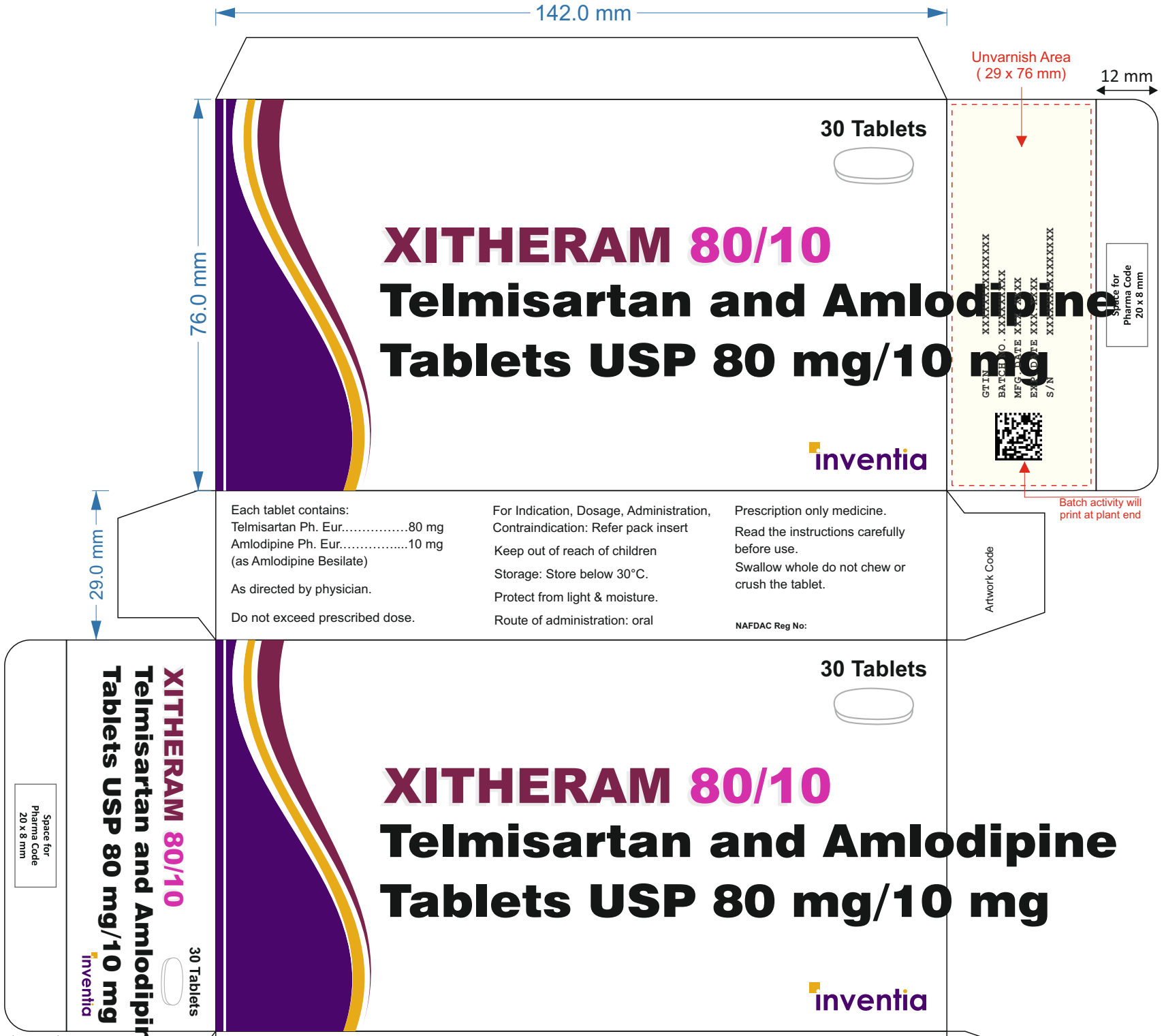
Blister of 10 Tablets. Box containing 30 Tablets. (3 X 10's).

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. <APPLICANT/MANUFACTURER>

Inventia Healthcare Limited
F1-F1/1-F75/1, Additional Ambernath M.I.D.C.,
Ambernath (East) Thane 421 506, Maharashtra State, INDIA
Tel.: 912516614000
Fax: 912516614100



Product Name : XITHERAM 80/10 Telmisartan and Amlodipine Tablets USP 80 mg/10 mg	**Packaging Material :** Carton (Reverse Tuck in Flap)	**Size :** 142 x 29 x 76 mm (L x W x H)	
Location : Ambernath	**Artwork No.:-**	**Pack Size:** 3 x 10 Tablets	**Country:** Nigeria
Substrate : ITC Cyber XL Board with Matt UV varnish, Embossing on brand name in main panel [2D Bar code area should be Unvarnished]		**Specification :** 300 GSM	**Drawing No.:** C-100-2105-2446-R1
Tec. Spc. Ref. No.: ATET/80/10/TS/097		**Pharma Code:-**	**SAP Code:-**

No. of Colour : 05 PANTONE 683 C PANTONE 2617 C PANTONE 124 C PANTONE 2385 C PANTONE Black C

Any other Requirement : Cut crease require on creasing lines of both the tuck in flap & both the tuck in panel and not on both collar flap. Laser made die cut to be used

Version No.: 1.0	**Change History :** New Artwork	**Date:** 12-09-2022

Signature and Date				
Department	**Client**	**Packaging Development - R&D**	**Regulatory Affairs**	**Corporate Quality**

Pack Length 135 mm

Pack Width 72 mm

Print Repeat 36 mm

Unwinding Direction

XITHERAM 80/10

Telmisartan and Amlodipine Tab

80 mg/10 mg

Manufactured by

inventia

Inventia Healthcare Limited,
F1-F1/1-F75/1, Additional Ambernath M.I.D.C.,
Ambernath (East) Thane 421 506, Maharashtra State, INDIA

NAFDAC Reg No:
Code No.: MH/DRUGS/25/KD/638

Artwork Code

Over Printing Zone

XITHERAM 80/10
Telmisartan and Amlodipine Tab
80 mg/10 mg
Manufactured by
inventia
Inventia Healthcare Limited,
F1-F1/1-F75/1, Additional Ambernath M.I.D.C.,
Ambernath (East) Thane 421 506, Maharashtra State, INDIA
NAFDAC Reg No:
Code No.: MH/DRUGS/25/KD/638
Artwork Code
Over Printing Zone

6 mm | 2 mm | 3 mm | 2 mm | Printing Area 101 mm | 20 mm | 2 mm | 3 mm | 2 mm | 4 mm | 2 mm | 3 mm | 2 mm | 20 mm | Printing Area 101 mm | 2 mm | 3 mm | 2 mm | 6 mm

Foil Width 286 mm

Product Name :XITHERAM 80/10 Telmisartan and Amlodipine Tablets USP 80 mg/10 mg		**Packaging Material :** Foil	**Country:** Nigeria
Location : Ambernath	**Artwork No.:-----**	**Pack Size:** 10's	**Tec. Spc. Ref. No.:**
Alu Foil Width : 286 mm / Pack Size : 72 x 135 mm / Repeat Length : 36 mm		**Substrate :** DSO	**Layout No.:** F 2010 000724 R0
Specification : 0.025 mm		Any other Requirement : NC Coating	**Tec. Spc. Ref. No.:** ATET/40/5/TS/097
No. of Colour : 02	PANTONE 2385 C	PANTONE Black C	
Version No.: 1.0	**Change History :** New Artwork		**Date:** 12-09-2022

Signature and Date				
Department	**Client**	**Packaging Development - R&D**	**Regulatory Affairs**	**Corporate Quality**