SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product:
HYTEL CM

Telmisartan, Cilnidipine & Extended-Release Metoprolol Succinate Tablets

2 Qualitative and quantitative compositions:

Each film coated tablet contains:
Telmisartan BP.....40 mg
Metoprolol Succinate BP
Eq. to Metoprolol Tartrate…..... 25 mg
(As extended- release) Cilnidipine…
..... 10 mg
Excipients. .....q.s.
Colour: Ferric oxide Red USP & Titanium dioxide BP For the full list of excipients, see section 6.1.

3. Pharmaceutical form:

Oral tablet.

A brown coloured, round shaped biconvex film coated tablet plain on both side

4. Clinical particulars

4.1 Therapeutic indications

Hytel CM is indicated for the treatment of Hypertension.

4.2 Posology and method of administration

Recommended dose is one tablet daily or as directed by the physician.

Route of administration

For oral administration.

4.3 Contraindications

Hypersensitivity to the active substances, to related derivatives or to any of the excipients listed in section 6.1.

TELMISARTAN

- Second and third trimester of pregnancy.
- Biliary obstructive disorders.
- Severe hepatic impairment.
- The concomitant use of telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)

CILNIDIPINE

- Aortic stenosis, advanced.
- Hypersensitivity to Cilnidipine or other calcium channel antagonists.

METOPROLOL

- Severe asthma or history of severe bronchospasm.
- Atrioventricular block of second or third degree.
- Uncontrolled heart failure.
- Clinically relevant sinus bradycardia.
- Sick-sinus syndrome.
- Severe peripheral arterial disease.
- Cardiogenic shock.
- Hypotension.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Metoprolol is also contraindicated when myocardial infarction is complicated by significant bradycardia, first degree heart block, systolic hypotension (less than 100 mmHg) and/or severe heart failure.

4.4 Special warnings and precautions for use

Telmisartan

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 not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan. Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment.

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.

Renal impairment and kidney transplantation

When Telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended.

There is no experience regarding the administration of Telmisartan in patients with recent kidney transplantation

Intravascular hypovolaemia

Symptomatic hypotension, especially after the first dose of Telmisartan, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Telmisartan.
Volume and/or sodium depletion should be corrected prior to administration of Telmisartan.

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. 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.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin- aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as telmisartan has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

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.

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.

In the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events, hyperkalaemia may be fatal.

Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated.

The main risk factors for hyperkalaemia to be considered are:

- Diabetes mellitus, renal impairment, age (> 70 years)

- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.

- Intercurrent events, in particular dehydratation, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischaemia, rhabdomyolysis, extend trauma).
Close-monitoring of serum potassium in at risk patients is recommended Intestinal

angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea.
Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, telmisartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Cilnidipine

- Angina

- Chronic renal insufficiency

- Congestive heart failure

- Hypotension

- Liver dysfunction, or elevated liver enzymes

- Peripheral edema (confounding physical findings in congestive failure)

Metoprolol

Although cardioselective beta-blockers, including metoprolol, may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers these should be avoided in patients with reversible obstructive airway disease unless there are compelling clinical reasons for their use.
Therapy with a beta2- stimulant may become necessary or current therapy require adjustment.

Metoprolol may aggravate bradycardia and symptoms of peripheral arterial circulatory disorders. If the patient develops increasing bradycardia, (heart rate less than 50 to 55 beats/min) metoprolol should be given in lower doses or gradually withdrawn.

In addition, anaphylactic reactions precipitated by other agents may be particularly severe in patients taking beta-blockers, and may be resistant to normal doses of adrenaline. Whenever possible, beta-blockers, including metoprolol, should be avoided for patients who are at increased risk of anaphylaxis.

Abrupt cessation of therapy with a beta-blocker should be avoided, especially in patients with ischaemic heart disease. When possible, metoprolol should be withdrawn gradually over a period of 10 days, the doses diminishing to 25 mg for the last 6 days. During its withdrawal, the patient should be kept under close surveillance and replacement therapy should be initiated where required.

Beta-blockers, including metoprolol, should not be used in patients with untreated congestive heart failure. This condition should first be stabilised. Additional therapy should also be considered for patients with a history of heart failure or patients who are known to have a poor cardiac reserve, e.g. diuretics and/or digitalisation.

Because of their negative effect on atrioventricular conduction, beta-blockers, including metoprolol, should be given only with caution to patients with first degree atrioventricular block.

Beta-blockers mask some of the clinical signs of thyrotoxicosis. Therefore, metoprolol should be administered with caution to patients having, or suspected of developing, thyrotoxicosis, and both thyroid and cardiac function should be monitored closely.

Metoprolol should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents. In labile and insulin-dependent diabetes it may be necessary to adjust the hypoglycaemic therapy. Metoprolol may mask some of the symptoms of hypoglycaemia by inhibition of sympathetic nerve functions and patients should be warned accordingly. Beta-blockers could further increase the

risk of severe hypoglycaemia when used concurrently with sulfonylureas. Diabetic patients should be advised to carefully monitor blood glucose levels.

In patients with a treated phaeochromocytoma, an alpha-blocker should be given concomitantly.

In patients with significant hepatic dysfunction it may be necessary to adjust the dosage because metoprolol undergoes biotransformation in the liver.

The administration of adrenaline to patients undergoing beta-blockade can result in an increase in blood pressure and bradycardia although this is less likely to occur with beta1-selective drugs.

Metoprolol therapy should be brought to the attention of the anaesthetist prior to general anaesthesia. The benefits of continuing a treatment with a beta-blocker, including metoprolol, should be balanced against the risk of withdrawing it in each patient. When it has been decided to interrupt a beta-blockade in preparation for surgery, therapy should be discontinued for at least 24 hours. Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation. However, the risk of hypertension may be increased. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. In a patient under beta-blockade, the anaesthetic selected should be one exhibiting as little negative inotropic activity as possible (halothane/nitrous oxide). The patient may be protected against vagal reactions by intravenous administration of atropine.

Beta-blockers may increase the number and duration of angina attacks in patients with Prinzmetal's angina (variant angina pectoris). However, relatively selective β1-receptor blockers, such as metoprolol, can be used in such patients, but only with the utmost care.

Patients with anamnestically known psoriasis should take beta-blockers only after careful consideration.

The full oculomucocutaneous syndrome, as described elsewhere with practolol, has not been reported with metoprolol. However, part of this syndrome (dry eyes either alone or, occasionally, with skin rashes) has occurred. In most cases the symptoms cleared when metoprolol treatment was withdrawn. Patients should be observed carefully for potential ocular effects. If such effects occur, discontinuation of metoprolol should be considered.

Lactose

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

Other

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

4.5 Interactions with other medicines and other forms of interactions

Telmisartan

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 in order to maintain levels within the therapeutic range.

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia. The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).

The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above- mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.

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.

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective 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 agents 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.

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.

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume depletion, and in a risk of hypotension when initiating therapy with telmisartan.

To be taken into account with concomitant use

Other antihypertensive agents

The blood pressure lowering effect of telmisartan can be increased by concomitant use of other antihypertensive medicinal products.

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.

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine.
Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic use) Reduction

of the antihypertensive effect. **Cilnidipine**

Cilnidipine is mainly metabolized by drug metabolizing enzymes CYP3A4 and CYP2C19.

Cilnidipine may interact with other antihypertensive agents, aldesleukin, and antipsychotics which may cause hypotension. Interactions may occur with quinidine, carbamazepine, phenytoin, rifampicin, cimetidine, and erythromycin.

Drugs with Antihypertensive Action	Risk of Hypotension	Additive or synergistic action
Digoxin	It has been reported that other calcium antagonists (e.g., nifedipine) increase the concentration of digoxin in the blood. If digoxin intoxication symptoms (nausea vomiting, headache, visual abnormality, arrhythmia etc.) are observed, the dosage of digoxin should be adjusted or discontinued.	Although the mechanism has not been fully elucidated, it is believed that extrarenal clearance of digoxin is reduced.
Cimetidine	May enhance the antihypertensive effect of Cilnidipine.	Cimetidine reduces hepatic blood flow and inhibits CYP3A4 enzymes which metabolize Cilnidipine while decreasing gastric acid and increasing absorption of calcium antagonists.
Rifampicin	The antihypertensive effect of cilnidipine may be attenuated.	Rifampicin induces CYP3A4 and may promote metabolism and clearance of Cilnidipine.
Azole antifungal agents i.e., itraconazole, miconazole, etc.	May enhance the antihypertensive effect of Cilnidipine.	Azole antifungal agent inhibits CYP3A4, a drug metabolizing enzyme of Cilnidipine.
Grapefruit juice	May enhance the antihypertensive effect of Cilnidipine.	Mechanism of action is unknown but components contained in grapefruit juice likely suppress CYP3A4

		activity which metabolizes Cilnidipine.

Metoprolol

The effects of metoprolol and other antihypertensive drugs on blood pressure are usually additive, and care should be taken to avoid hypotension. However, combinations of antihypertensive drugs may often be used with benefit to improve control of hypertension.

As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity, e.g. ergotamine are given concurrently.

Care should also be exercised when beta-blockers are given in combination with sympathetic ganglion blocking agents, other beta blockers (also in the form of eye drops) or MAO inhibitors.

Prazosin

The acute postural hypotension that can follow the first dose of prazosin may be increased in patients already taking a beta-blocker.

Clonidine

If combination treatment with clonidine is to be discontinued metoprolol should be withdrawn several days before clonidine. This is because the hypertension that can follow withdrawal of clonidine may be increased in patients receiving concurrent beta-blocker treatment.

Calcium channel blockers

Calcium channel blockers such as verapamil and diltiazem may potentiate the depressant effects of beta-blockers on blood pressure, heart rate, cardiac contractility and atrioventricular conduction. A calcium channel blocker of the verapamil (phenylalkylamine) type should not be given intravenously to patients receiving metoprolol because there is a risk of cardiac arrest in this situation. Patients taking an oral calcium channel blocker of the verapamil type in combination with metoprolol should be closely monitored.

CYP2D6 inhibitors

Potent inhibitors of this enzyme may increase the plasma concentration of metoprolol. Caution should therefore be exercised when co-administering potent CYP2D6 inhibitors with metoprolol. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluoxetine, paroxetine or bupropion, antipsychotics such as thioridazine, antiarrhythmics such as propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine and medications for stomach ulcers such as cimetidine.

Class I anti-arrhythmic drugs and amiodarone

Amiodarone, propafenone, and other class I anti-arrhythmic agents such as quinidine and disopyramide may potentiate the effects of beta-blockers on heart rate and atrioventricular conduction.

Nitroglycerin

Nitroglycerin may enhance the hypotensive effect of metoprolol. Digitalis

glycosides

Concurrent use of digitalis glycosides may result in excessive bradycardia and/or increase in atrioventricular conduction time.

Sympathomimetics

Metoprolol will antagonise the beta1 effects of sympathomimetic agents but should have little influence on the bronchodilator effects of beta2-agonists at normal therapeutic doses.

Insulin and oral hypoglycaemic drugs

In diabetic patients who use insulin, beta-blocker treatment may be associated with increased or prolonged hypoglycaemia. Beta-blockers may also antagonise the hypoglycaemic effects of sulfonylureas. The risk of either effect is less with a beta1-selective drug such as metoprolol than with a non- selective beta-blocker. However, diabetic patients receiving metoprolol should be monitored to ensure that diabetes control is maintained.

The concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia.

Non-steroidal anti-inflammatory drugs

Concurrent treatment with non-steroidal anti-inflammatory drugs such as indomethacin may decrease the antihypertensive effect of metoprolol.

Lignocaine

Metoprolol may impair the elimination of lignocaine. General

anaesthetics

Some inhalation anaesthetics may enhance the cardiodepressant effect of beta-blockers.

Hepatic enzyme inducers/inhibitors

Enzyme inducing agents (e.g. rifampicin) may reduce plasma concentrations of metoprolol, whereas enzyme inhibitors (e.g. cimetidine) may increase plasma concentrations.

Alcohol

During concomitant ingestion of alcohol and metoprolol the concentration of blood alcohol may reach higher levels and may decrease more slowly.

4.6 Fertility, pregnancy and lactation

Pregnancy

HYTEL CM is not recommended during pregnancy.

Lactation

The amount of metoprolol ingested via breast milk seems to be negligible with regard to its beta-blocking effects if the mother is treated in doses within the therapeutic range. Because no information is available regarding the use of Telmisartan during breast-feeding, Telmisartan 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

When driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

4.8 Undesirable effects

Telmisartan

Serious adverse reactions include anaphylactic reaction and angioedema which may occur rarely (≥1/10,000 to <1/1,000), and acute renal failure. The overall incidence of adverse reactions reported with telmisartan was usually comparable to placebo (41.4% vs 43.9%) in controlled trials in patients treated for hypertension. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients. The safety profile of telmisartan in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

The adverse reactions listed below have been accumulated from controlled clinical trials in patients treated for hypertension and from post-marketing reports. The listing also takes into account serious adverse reactions and adverse reactions leading to discontinuation reported in three clinical long-term studies including 21,642 patients treated with telmisartan for the reduction of cardiovascular morbidity for up to six years.

Tabulated summary of adverse reactions

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)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations
Uncommon: Upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis
Rare: Sepsis including fatal outcome[1] Blood and the lymphatic system disorders
Uncommon: Anaemia
Rare: Eosinophilia, thrombocytopenia Immune system disorders
Rare: Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders
Uncommon: Hyperkalaemia
Rare: Hypoglycaemia (in diabetic patients)
Psychiatric disorders
Uncommon: Depression, insomnia
Rare: Anxiety
Nervous system disorders
Uncommon: Syncope Rare: Somnolence
Eye disorders
Rare: Visual disturbance Ear and labyrinth disorders
Uncommon: Vertigo Cardiac disorders Uncommon: Bradycardia Rare: Tachycardia
Vascular disorders
Uncommon: Hypotension[2], orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, cough
Very rare: Interstitial lung disease[3]
Gastrointestinal disorders
Uncommon: Abdominal pain, diarrhoea, dyspepsia , flatulence, vomiting Rare: Stomach discomfort, dry mouth, dysgeusia
Hepato-biliary disorders
Rare: Hepatic function abnormal/liver disorder[4] Skin and subcutaneous tissue disorders Uncommon: Hyperhidrosis, pruritus, rash
Rare: Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
Muscoloskeletal and connective tissue disorders
Uncommon: Myalgia, back pain (e.g. sciatica), muscle spasms
Rare: Arthralgia, pain in extremity, tendon pain (tendonitis like symptoms)
Renal and urinary disorders

Uncommon: Renal impairment including acute renal failure General disorders and administration site conditions Uncommon: Chest pain, asthenia (weakness)
Rare: Influenza-like illness
Investigations
Uncommon: Blood creatinine increased
Rare: Blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased, haemoglobin decreased
Description of selected adverse reactions
Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists

1 Sepsis

In the PRoFESS trial, an increased incidence of sepsis was observed with telmisartan compared with placebo. The event may be a chance finding or related to a mechanism currently not known.

2 Hypotension

This adverse reaction was reported as common in patients with controlled blood pressure who were treated with telmisartan for the reduction of cardiovascular morbidity on top of standard care.

3 Interstitial lung disease

Cases of interstitial lung disease have been reported from post-marketing experience in temporal association with the intake of telmisartan. However, a causal relationship has not been established.

4 Hepatic function abnormal / liver disorder

Most cases of hepatic function abnormal / liver disorder from post-marketing experience occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

Cilnidipine Abdominal pain Swelling in the ankles Dizziness
Edema
Pain or irritation in the eyes
Fatigue
Flushing of the face, ears and neck
Headache
Nausea
Pain in the chest area
Palpitations
Drowsiness

Metoprolol

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).

Blood and the lymphatic system disorders	
Very rare	Thrombocytopenia
Psychiatric disorders	
Rare	depression, nightmares
Very rare	personality disorder, hallucinations
Nervous system disorders	
Common	dizziness, headache
Rare	alertness decreased, somnolence or insomnia, paraesthesia
Eye disorders	
Very rare	visual disturbance (eg. blurred vision), dry eyes and/or eye irritation
Ear and labyrinth disorders	
Very rare	tinnitus, and, in doses exceeding those recommended, hearing disorders (eg. hypoacusis or deafness)
Cardiac disorders	
Common	Bradycardia
Rare	heart failure, cardiac arrhythmias, palpitation
Very rare	cardiac conduction disorders, precordial pain,
Vascular disorders	
Common	orthostatic hypotension (occasionally with syncope)
Rare	oedema, Raynaud's phenomenon
Very rare	gangrene in patients with pre-existing severe peripheral circulatory disorders
Respiratory, thoracic and mediastinal disorders	
Common	exertional dyspnoea
Rare	bronchospasm (which may occur in patients without a history of obstructive lung disease)
Very rare	Rhinitis

Gastrointestinal disorders	
Common	nausea and vomiting, abdominal pain
Rare	diarrhoea or constipation
Very rare	dry mouth
Not known	retroperitoneal fibrosis (relationship to metoprolol has not been definitely established)
Hepatobiliary disorders	
Not known	Hepatitis
Skin and subcutaneous tissue disorders	
Rare	skin rash (in the form of urticaria, psoriasiform and dystrophic skin lesions)
Very rare	photosensitivity, hyperhydrosis, alopecia, worsening of psoriasis
Musculoskeletal and connective tissue disorders	
Rare	muscle cramps
Very rare	Arthritis
Reproductive system and breast disorders	
Very rare	disturbances of libido and potency
Not known	Peyronie's disease (relationship to metoprolol has not been definitely established)
General disorders and administration site conditions	
Common	Fatigue
Investigations	
Very rare	weight increase, liver function test abnormal

Post marketing experience

The following adverse reactions have been reported during post-approval use of metoprolol: confusional state, an increase in blood triglycerides and a decrease in high density lipoprotein (HDL). Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via the National Regulatory Authority.

4.9 Overdose

The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Telmisartan is not removed by haemodialysis. 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. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacement given quickly.

In more severe cases an overdosage of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma, convulsions, nausea, vomiting, cyanosis, hypoglycaemia and occasionally hyperkalaemia. The first manifestations of overdosage appear 20 minutes to 2 hours after ingestion of metoprolol. The effects of massive overdose may persist for several days, despite declining plasma concentrations. Patients should be admitted to hospital and, generally, should be managed in an intensive care setting, with continuous monitoring of cardiac function, blood gases, and blood biochemistry. Even apparently well patients who have taken a small overdose should be closely observed for signs of poisoning for at least 4 hours. In the event of a potentially life-threatening oral overdose, use induction of vomiting or gastric lavage (if within 4 hours after ingestion of metoprolol) and/or activated charcoal to remove the drug from the gastrointestinal tract. Metoprolol can not be effectively removed by haemodialysis.

5 Pharmacological properties

5.1 Pharmacodynamics properties

Hytel CM is a combination of three medicines: Cilnidipine, metoprolol and telmisartan. They work by different mechanisms to provide better control of blood pressure when single or dual therapy is not effective. Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Clinidipine is a third generation dihydropyridine calcium antagonist with a slow onset and long duration of action. Calcium antagonists inhibit influx of extracellular calcium ions into the cells

resulting in decreased vascular smooth muscle tone and vasodilation, leading to reduction in blood pressure. Metoprolol has a relatively greater blocking effect on beta1-receptors than on beta2-receptors which are chiefly involved in broncho and vasodilation. The stimulant effect of catecholamines on the heart is reduced or inhibited by metoprolol. This leads to a decrease in heart rate, cardiac contractility and cardiac output.

5.2 Pharmacokinetic properties

Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolutebioavailability for telmisartan is about 50%.

Metoprolol is well absorbed after oral administration, peak plasma concentrations occurring 1.5 -2 hours after dosing. The bioavailability of a single dose is approximately 50%, increasing to approximately 70% during repeated administration.

Cilnidipine presents a very rapid absorption with a maximum peaked concentration after 2 hours.

Its distribution tends to be higher in the liver as well as in kidneys, plasma and other tissues.

Cilnidipine does not present a high accumulation in the tissue after repeated oral administration.

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 500l.

Approximately 10% of metoprolol in plasma is protein bound. Metoprolol crosses the placenta, and is found in breast milk.

Drugs on the group of dihydropyridines such as cilnidipine tend to have a large volume of distribution.

Biotransformation

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Metoprolol is extensively metabolised by enzymes of the cytochrome P450 system in the liver.

The oxidative metabolism of metoprolol is under genetic control with a major contribution of the polymorphic cytochrome P450 isoform 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolisers (PM) phenotype. Approximately 7% of Caucasians and
less than 1% Orientals are PMs.

Elimination

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of > 20 hours. The maximum plasma concentration (Cmax) and, to a smaller extent, the area under the plasma concentration-time curve (AUC) increase disproportionately with dose.

Elimination of Metoprolol is mainly by hepatic metabolism and the average elimination half- life is 3.5 hours (range 1 to 9 hours). Rates of metabolism vary between individuals, with poor metabolisers (approximately 10%) showing higher plasma concentrations and slower elimination than extensive metabolisers. Within individuals, however, plasma concentrations

are stable and reproducible.
Cilnidipine gets eliminated through the urine in a proportion of 20% of the administered dose and 80% is eliminated by the feces.

Hepatic impairment:

Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100 %. The elimination half-life is not changed in patients with hepatic impairment.

5.3 Preclinical safety data

Telmisartan

In preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral sodium chloride solution supplementation.

In both species, increased plasma renin activity and hypertrophy/ hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance.

No clear evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the offsprings such as lower body weight and delayed eye opening was observed.

There was no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice.

6 Pharmaceutical particulars

6.1 List of Excipients:

Microcrystalline Cellulose (PH 101)
Mannitol
Crospovidone XL IO L
HPC 21
Lactose Monohydrate Microcrystalline
Cellulose (PH 102) Sodium Hydroxide
Meglumine
Sodium Bicarbonate
Povidone K 30 Purified
water
Polacrilin Potassium (Kyron T-314)

Sodium lauryl sulphate
Magnesium stearate HPMC
K 100 M
Color Ferric oxide Red
Hydroxypropyl methyl cellulose
Hydrogenated Castor Oil Colloidal
Silicon dioxide DRCOAT FCU
(C/026/218)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

3 x 10 Alu Alu Blister Pack.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7Marketing Authorization Holder and Manufacturing Site Address Marketing Authorization Holder:

Krishna Chemists Limited
P.O. Box:3328-00506,
Nairobi-Kenya.

Manufactured in India by:
4CARE LIFESCIENCE PVT. LTD.
Survey no. 23/3P & 24, opp. Jeans factory,
Daduramvistar, village- Bagdol. Tal.Kathlal,
Dist. Kheda-387630, Gujarat, India.

8Marketing Authorization Number
CTD11405

9.Date of first Registration/ Renewal of the Registration
30/07/2026

10. Date of Revision of the Text
30/07/2026