1.3.1 Summary of Product characteristics (SmPC)

1.3.1.1 Name of the medicinal product

International Non–Proprietary Name (INN)	Telmisartan Hydrochlorothiazide
Trade mark name	**Cortel-H 80**
Generic Name	Telmisartan and Hydrochlorothiazide Tablets USP

1.3.1.2 ATC and Forensic Classification

Name	ATC Code	Category/Name
Telmisartan	C09CA07	Angiotensin II Antagonists
Hydrochlorothiazide	C03AA03	Thiazides, plain

1.3.1.3 Qualitative and quantitative composition

Sr. No.	Material Name	Spc.	Function	Theo. qty./ Tab. (mg)
Mixing – Telmisartan				
1.	Maize Starch	BP	Disintegrant	121.0
2.	Microcrystalline Cellulose Powder	BP	Diluent	41.60
3.	Crospovidone	USP	Disintegrant	14.00
4.	MCCP (PH 102)	IH	Diluent	155.0
Mixing – Hydrochlorothiazide				
5.	$*Hydrochlorothiazide	BP	Active	12.50
6.	Lactose	BP	Diluent	184.125
7.	Sodium Starch Glycolate	BP	Diluent	12.00
8.	Colour Ponceau 4R Supra	IH	Colouring Agent	0.050
Wet Granulation – Telmisartan				
9.	$Telmisartan	BP	Active	80.00
10.	Sodium Hydroxide Pellets	BP	Alkaliser	10.00
11.	#Purified Water	BP	Solvent	0.019 ml
12.	#Isopropyl Alcohol	BP	Solvent	0.100 ml
13.	Tween-80	BP	Surfactant	0.400
Wet Granulation – Hydrochlorothiazide				
14.	Povidone	BP	Binder	8.000
15.	#Isopropyl Alcohol	BP	Solvent	0.050 ml
Lubrication – Telmisartan				
16.	Meglumine	USP	Stabiliser	10.00
17.	Magnesium Stearate	BP	Lubricant	3.000
18.	Kyron T-314	IH	Disintegrant	20.00
19.	Sodium Carbonate	BP	Preservative	15.00
Lubrication – Hydrochlorothiazide				
20.	Sodium Starch Glycolate	BP	Diluent	11.425
21.	Magnesium Stearate	BP	Lubricant	2.400
Film Coating				
22.	@Instacoat-IC-S-5731 (Pink)	IH	Colouring Agent	15.00
23.	@#Isopropyl Alcohol	BP	Solvent	0.117 ml
24.	@#Dichloromethane	BP	Solvent	0.234 gm

Note: $ = Qty. of active materials shall be vary with assay and LOD.
(Assay considered is 100% and LOD 0%).

-Final qty. shall be compensated with Microcrystalline Cellulose Powder.
* = Overages of these materials will be added to compensate the loss during storage.
# = Quantity of these materials will not be calculated in total weight of tablet.
@ = Overages of coating materials will be added to compensate the loss during coating.
Average weight of coated tablets after coating should be achieved approximately 2.14%
USP - United States Pharmacopeia
BP - British Pharmacopeia
IH - In-house Specification

1.3.1.4 Pharmaceutical Form

Solid Oral dosage form (Oral Tablet)

Description: Pink coloured, elongated shaped, biconvex, film coated tables having break-line on one side and other side plain.

1.3.1.5 Clinical particulars

1.3.1.5.1 Therapeutic indications

Treatment of essential hypertension.

Telmisartan and Hydrochlorothiazide fixed dose combination is indicated in adults whose blood pressure is not adequately controlled on Telmisartan alone.

1.3.1.5.2 Posology and method of administration

Recommended Dose

Telmisartan and Hydrochlorothiazide tablet should be taken in patients whose blood pressure is not adequately controlled by Telmisartan alone. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

-Telmisartan and Hydrochlorothiazide 40/12.5 mg tablets may be administered once daily in patients whose blood pressure is not adequately controlled by Telmisartan 40 mg.

-Telmisartan and Hydrochlorothiazide 80 mg/12.5 mg may be administered once daily in patients whose blood pressure is not adequately controlled by Telmisartan 80 mg.

Mode of administration

Telmisartan and Hydrochlorothiazide tablets are for once-daily oral administration and should be taken with liquid, with or without food.

1.3.1.5.3 Contraindications

-Hypersensitivity to any of the active substances or to any of the excipients in formulation.

-Hypersensitivity to other sulphonamide-derived substances (since hydrochlorothiazide is a sulphonamide-derived medicinal product).

-Second and third trimesters of pregnancy.

-Cholestasis and biliary obstructive disorders.

-Severe hepatic impairment.

-Severe renal impairment (creatinine clearance < 30 ml/min).

-Refractory hypokalaemia, hypercalcaemia.
-The concomitant use of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2)

1.3.1.5.4 Special warnings and precautions for use

Hepatic impairment: Telmisartan and Hydrochlorothiazide should not be given to patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency since Telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for Telmisartan.

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.

Dual blockade of the renin-angiotensin-aldosterone system.

The use of Telmisartan in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

Metabolic and endocrine effects Thiazide therapy may impair glucose tolerance whereas hypoglycaemia may occur in diabetic patients under insulin or antidiabetic therapy and Telmisartan treatment. Therefore, in these patients blood glucose monitoring should be considered: a dose adjustment of insulin or antidiabetics may be required, when indicated. Latent diabetes mellitus may become manifest during thiazide therapy.

1.3.1.5.5 Interaction with other medicinal products and other forms of interaction

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

The combination of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) and is not recommended in other patients.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and Telmisartan and Hydrochloroyhiazide tablets is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia favours the onset of digitalis-induced arrhythmia.

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 diuretic, natriuretic and antihypertensive effects of thiazide diuretics and the antihypertensive effects of angiotensin II receptor antagonists.

Beta-blockers and diazoxide: The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics or antidepressants.

1.3.1.5.6 Pregnancy and lactation

Pregnancy: There are no adequate data from the use of Telmisartan and Hydrochlorothiazide tablets in pregnant women. Studies in animals have shown reproductive toxicity.

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 antagonists, similar risks may exist for this class of drugs. 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.

Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension.

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding: Because no information is available regarding the use of Telmisartan and Hydrochlorothiazide tablet during breast-feeding, Telmisartan and Hydrochlorothiazide tablet is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Telmisartan and Hydrochlorothiazide tablet during breastfeeding is not recommended. If Telmisartan and Hydrochlorothiazide tablet is used during breastfeeding, doses should be kept as low as possible.

1.3.1.5.7 Effects on ability to drive and use machines

Telmisartan/Hydrochlorothiazide can have influence on the ability to drive and use machines. Dizziness or drowsiness may occasionally occur when taking Telmisartan/Hydrochlorothiazide.

1.3.1.5.8 Undesirable effects

The most commonly reported adverse reaction is dizziness. Serious angioedema may occur rarely (> 1/10,000 to < 1/1,000).

Hepatic function abnormal / liver disorder

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

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.

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.

1.3.1.5.9 Overdose

Symptoms

The most prominent manifestations of telmisartan overdose were hypotension and tachycardia: bradycardia, dizziness, vomiting, increase in serum creatinine and acute renal failure have also been reported. Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and hypovolaemia resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Treatment

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 replacements given quickly.

1.3.1.6 Pharmacological properties

1.3.1.6.1 Pharmacodynamic properties

Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 (AT,) antagonist. Telmisartan selectively binds the AT, receptor. The binding is long-lasting.

Plasma aldosterone levels are decreased by Telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore, it is not expected to potentiate bradykinin-mediated adverse effects.

Hydrochlorothiazide is a thiazide diuretic. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensinaldosterone system, co-administration of Telmisartan tends to reverse the potassium loss associated with these diuretics.

1.3.1.6.2 Pharmacokinetic properties

Absorption

Telmisartan: Following oral administration peak concentrations of telmisartan are reached in 0.5 -1.5 h after dosing. The absolute bioavailability of telmisartan at 40 mg and 160 mg was 42 % and 58 %, respectively. Food slightly reduces the bioavailability of telmisartan with a reduction in the area underthe plasma concentration time curve (AUC) of about 6 % with the 40 mg tablet and about 19% after a 160 mg dose.

Hydrochlorothiazide: Following oral administration peak concentrations of hydrochlorothiazide are reached in approximately 1.0 - 3.0 hours after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60%.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5 %) mainly albumin and alpha 1 - acid glycoprotein. The apparent volume of distribution fortelmisartan is approximately 500 litres indicating additional tissue binding. Hydrochlorothiazide is 68 % protein bound in the plasma and its apparent volume of distribution is 0.83 -1.14 l/kg.

Biotransformation

Telmisartan is metabolised by conjugation to form a pharmacologically inactive acylglucuronide. The glucuronide of the parent compound is the only metabolite that has been identified in humans. After a single dose of 14C-labelled telmisartan the glucuronide represents approximately 11 % of the measured radioactivity in plasma.

Hydrochlorothiazide is not metabolised in man.

Elimination

Telmisartan: Following either intravenous or oral administration of ^{14}C-labelled telmisartan most of the administered dose (>97 %) was eliminated in faeces via biliary excretion. Only

minute amounts were found in urine. Total plasma clearance of Telmisartan after oral administration is >1500 ml/min. Terminal elimination half-life was >20 hours. Hydrochlorothiazide is excreted almost entirely as unchanged substance in urine. About 60 % of the oral dose is eliminated within 48 hours. Renal clearance is about 250 - 300 ml/min. The terminal elimination half-life of hydrochlorothiazide is 10 -15 hours.

1.3.1.6.3 Preclinical safety data

In preclinical safety studies performed with co-administration of Telmisartan and hydrochlorothiazide in normotensive rats and dogs, doses producing exposure comparable to that in the clinical therapeutic range caused no additional findings not already observed with administration of either substance alone. The toxicological findings observed appear to have no relevance to human therapeutic use.

Toxicological findings also well-known from preclinical studies with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists were: a reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit), changes of renal haemodynamics (increased blood urea nitrogen and creatinine), increased plasma renin activity, hypertrophy/hyperplasia of the juxtaglomerular cells and gastric mucosal injury. Gastric lesions could be prevented/ameliorated by oral saline supplementation and group housing of animals. In dogs renal tubular dilation and atrophy were observed. These findings are considered to be due to the pharmacological activity of Telmisartan.

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.

Telmisartan showed no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice. Studies with hydrochlorothiazide have shown equivocal evidence for a genotoxic or carcinogenic effect in some experimental models. However, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

1.3.1.7 Pharmaceutical particulars

1.3.1.7.1 Incompatibilities
Not Applicable

1.3.1.7.2 Shelf life
36 Months

1.3.1.7.3 Special precautions for storage
Store below 30°C.
Protect from light and moisture.

1.3.1.7.4 Nature and contents of container
10 Tablets packed in Alu-Alu Blister pack and such 3 blisters are packed in a carton along with insert.

1.3.1.7.5 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

1.3.1.8 Registrant
Pacmai International Limited

1.3.1.9 Registration Number(s)
B4 - 4768

1.3.1.10 Date of initial or renewed registration
30th April, 2015

1.3.1.11 Date of revision of the text
01/01/2019