SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TELSWIFT H 40 (Telmisartan 40mg and Hydrochlorothiazide 12.5mg Tablets)
TELSWIFT H 80 (Telmisartan 80mg and Hydrochlorothiazide 12.5mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Telswift H 40 (Telmisartan 40mg and Hydrochlorothiazide 12.5mg Tablets)
Each uncoated tablet contains:

Telmisartan Ph.Eur.	40 mg
Hydrochlorothiazide Ph.Eur.	12.5 mg

Color: Iron Oxide Red

Telswift H 80 (Telmisartan 80mg and Hydrochlorothiazide 12.5mg Tablets) Each uncoated tablet contains:

Telmisartan Ph.Eur.	80 mg
Hydrochlorothiazide Ph.Eur.	12.5 mg

Color: Iron Oxide Red

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Uncoated Tablets.

Telswift H 40 (Telmisartan 40mg and Hydrochlorothiazide 12.5mg Tablets)
Uncoated, bilayered (one layer off white colored and one layer pink colored) biconvex capsule, capsule shaped tablets with both sided plain.

Telswift H 80 (Telmisartan 80mg and Hydrochlorothiazide 12.5mg Tablets)
Uncoated, bilayered (one layer off white colored and one layer pink colored) biconvex capsule, capsule shaped tablets with both sided plain.

4. Clinical Particulars

4.1 Therapeutic Indications

Treatment of essential hypertension.

The fixed dose combination (40 mg Telmisartan/12.5mg hydrochlorothiazide and 80 mg Telmisartan/12.5mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on Telmisartan alone.

4.2 Posology and Method of Administration

The usual starting dose of telmisartan is 40 mg once a day; blood pressure response is dose related over the range of 20-80 mg. Patients with depletion of intravascular volume should have the condition corrected or telmisartan tablets should be initiated under close medical supervision.

Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision.

Hydrochlorothiazide is effective in doses of 12.5 mg to 50 mg once daily.
Telmisartan and hydrochlorothiazide tablets may be administered with other antihypertensive agents.
Telmisartan and hydrochlorothiazide tablets may be administered with or without food.

Patients with Renal Impairment

The usual regimens of therapy with Telmisartan and hydrochlorothiazide tablets may be followed as long as the patient's creatinine clearance is > 30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Telmisartan and hydrochlorothiazide tablets are not recommended.

Patients with Hepatic Impairment

Telmisartan and hydrochlorothiazide tablets are not recommended for patients with severe hepatic impairment. Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision using the 40/12.5 mg combination.

Method of administration

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

4.3 Contra-indications

- Telmisartan and hydrochlorothiazide tablets are contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, hydrochlorothiazide, or any other component of this product.
- Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.
- 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/Hydrochlorothiazide 40/12.5mg with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

4.4 Special Warnings and Special Precautions for Use

Fetal toxicity

Pregnancy category d

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue tablets as soon as possible.

These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

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.

Teratogenic effects

No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m² basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m² basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, decreased weight gain. Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hypotension in volume-depleted patients

Initiation of antihypertensive therapy in patients whose renin-angiotensin system are activated such as patients who are intravascular volume- or sodium-depleted, e.g., in patients treated vigorously with diuretics, should only be approached cautiously. These conditions should be corrected prior to administration of Telmisartan

and hydrochlorothiazide tablets. Treatment should be started under close medical supervision. If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

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.

In addition, Telmisartan and hydrochlorothiazide should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
There is no clinical experience with Telmisartan and hydrochlorothiazide in patients with 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

Telmisartan and hydrochlorothiazide must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min). There is no experience regarding the administration of Telmisartan and hydrochlorothiazide in patients with recent kidney transplantation. Experience with Telmisartan and hydrochlorothiazide is modest in the patients with mild to moderate renal impairment, therefore periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function.

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction

Lithium generally should not be given with thiazides.

Intravascular hypovolaemia

Symptomatic hypotension, especially after the first dose, 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 and hydrochlorothiazide.

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 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 and hydrochlorothiazide 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.

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.

An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy; however, at the 12.5 mg dose contained in Telmisartan and hydrochlorothiazide, minimal or no effects were reported.

Hyperuricaemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy.

Electrolyte imbalance

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, asthenia, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

- Hypokalaemia

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with telmisartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greater in patients with cirrhosis of liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or Adrenocorticotropic hormone (ACTH).

- Hyperkalaemia

Conversely, due to the antagonism of the angiotensin II (AT_1) receptors by the telmisartan component of Telmisartan and hydrochlorothiazide, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with Telmisartan and hydrochlorothiazide, risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes should be co-administered cautiously with Telmisartan and hydrochlorothiazide.

- Hyponatraemia and hypochloraemic alkalosis

There is no evidence that Telmisartan and hydrochlorothiazide would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

- Hypercalcaemia

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

- Hypomagnesaemia

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Ethnic differences

As with all other angiotensin II receptor antagonists, telmisartan is apparently less effective in lowering blood pressure in black patients than in non blacks, possibly because of higher prevalence of low renin states in the black hypertensive population.

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.

General

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics, including hydrochlorothiazide.

Cases of photosensitivity reactions have been reported with thiazide diuretics. If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute Myopia and Secondary Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Aliskiren
Do not co-administer aliskiren with Telmisartan & Hydrochlorothiazide tablets in patients with diabetes. Avoid use of aliskiren with Telmisartan & Hydrochlorothiazide tablets in patients with renal impairment (GFR <60 mL/min).

Digoxin
When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over-or under-digitalization.

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 (including Telmisartan and hydrochlorothiazide). Lithium should not be used with diuretics, the use of lithium with telmisartan and hydrochlorothiazide is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

Medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid and derivatives).

If these substances are to be prescribed with the hydrochlorothiazide-telmisartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium.

Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporin or other medicinal products such as heparin sodium). If these medicinal products are to be prescribed with the hydrochlorothiazide-telmisartan combination, monitoring of potassium plasma levels is advised. Based on the experience with the use of other medicinal products that blunt the renin-angiotensin system, concomitant use of the above medicinal products may lead to increases in serum potassium and is, therefore, not recommended.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when telmisartan and hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the following torsades de pointes inducing medicinal products (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes.

- class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide)

- class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)

- some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)

- others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine IV.)

Digitalis glycosides

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

Other antihypertensive agents
Telmisartan may increase the hypotensive effect of other antihypertensive agents.

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

Antidiabetic medicinal products (oral agents and insulin)

Dosage adjustment of the antidiabetic medicinal products may be required.

Metformin

Metformin should be used with precaution: risk of lactic acidosis induced by a possible functional renal failure linked to hydrochlorothiazide.
Cholestyramine and colestipol resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

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.

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 AUC_{0-24} and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Pressor amines (e.g. noradrenaline)

The effect of pressor amines may be decreased.

Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine)

The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Medicinal products used in the treatment for gout (e.g. probenecid, sulfinpyrazone and allopurinol)

Dosage adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide may increase the incidence of hypersensitivity reactions of allopurinol.

Calcium salts

Thiazide diuretics may increase serum calcium levels due to the decreased excretion. If calcium supplements or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

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.

Amantadine

Thiazides may increase the risk of adverse effects caused by amantadine.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)

Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

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.

4.6 Pregnancy and Lactation

There are no adequate data from the use of telmisartan and hydrochlorothiazide 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.

Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended

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 gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no

other treatment could be used.

Lactation

Because no information is available regarding the use of telmisartan and hydrochlorothiazide during breast-feeding, telmisartan and hydrochlorothiazide 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 during breast feeding is not recommended. If it is used during breast feeding, doses should be kept as low as possible.

Infections and infestations

Uncommon:	Upper respiratory tract infection, urinary tract infection including cystitis
Rare:	Sepsis including fatal outcome*

Uncommon:	Anaemia
Rare:	Eosinophilia, thrombocytopenia

Immune system disorders

Metabolism and nutrition disorders

Uncommon:	Hyperkalaemia
Rare:	Hypoglycaemia (in diabetic patients)

Cardiac disorders

Uncommon:	Bradycardia

Nervous system disorders

Rare:	Somnolence

Respiratory, thoracic and mediastinal disorders

Uncommon:	Cough
Very rare:	Interstitial lung disease*

Gastrointestinal disorders

Rare:	Stomach discomfort

Skin and subcutaneous tissue disorders

Rare:	Eczema, drug eruption, toxic skin eruption

Musculoskeletal, connective tissue and bone disorders

Rare:	Arthrosis, tendon pain

Renal and urinary disorders

Uncommon:	Renal impairment (including acute renal failure)

General disorders and administration site conditions

Uncommon:	Asthenia

Investigations

Rare:	Haemoglobin decreased

HYDROCHLOROTHIAZIDE

Infections and infestations

Not known:	Sialadenitis

Blood and lymphatic system disorders

Rare:	Thrombocytopenia (sometimes with purpura)
Not known:	Aplastic anaemia, haemolytic anaemia, bone marrow failure, leukopenia, neutropenia, agranulocytosis,

Immune system disorders

Not known:	Anaphylactic reactions, hypersensitivity

Endocrine disorders

Not known:	Diabetes mellitus inadequate control

Metabolism and nutrition disorders

Common:	Hypomagnesaemia
Rare:	Hypercalcaemia
Very rare:	Hypochloraemic alkalosis
Not known:	Anorexia, appetite decreased, electrolyte imbalance, hypercholesterolaemia, hyperglycaemia, hypovolaemia

Psychiatric disorders

Not known:	Restlessness

Nervous system disorders

Rare:	Headache

Not known:	Light-headedness
Eye disorders	
Not known	Xanthopsia, acute myopia, acute angle-closure glaucoma
Vascular disorders	
Not known:	Vasculitis necrotizing
Gastrointestinal disorders	
Common:	Nausea
Not known:	Pancreatitis, stomach discomfort
Hepatobiliary disorders	
Not known:	Jaundice hepatocellular, jaundice cholestatic
Skin and subcutaneous tissue disorders	
Not known:	Lupus-like syndrome, photosensitivity reactions, skin vasculitis, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal, connective tissue and bone disorders	
Not known:	Weakness
Renal and urinary disorders	
Not known:	Nephritis interstitial, renal dysfunction, glycosuria
General disorders and administration site conditions	
Not known:	Pyrexia
Investigations	
Not known:	Triglycerides increased

*** 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.

4.9. Overdose

TELMISARTAN

The most likely manifestations of overdosage with telmisartan would be hypotension, dizziness, vomiting, increase in serum creatinine, acute renal failure and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

HYDROCHLOROTHIAZIDE

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and hypovolaemia dehydration 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.

5. Pharmacological Properties

5.1. Pharmacodynamic Properties

TELMISARTAN

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 and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan did not influence plasma aldosterone concentrations. In multiple dose studies, 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).

HYDROCHLOROTHIAZIDE

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

5.2 Pharmacokinetic Properties

TELMISARTAN

Absorption

Following oral administration, peak concentrations (Cmax) 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.

Distribution
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.

Metabolism and Elimination

Following either intravenous or oral administration of ^{14}C-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 appears to be independent of dose.

HYDROCHLOROTHIAZIDE

Absorption
When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Distribution
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Metabolism and Elimination
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours.

SPECIAL POPULATIONS

***Pediatric*:** Telmisartan pharmacokinetics have not been investigated in patients < 18 years of age.

***Geriatric*:** The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.

***Gender*:** Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

***Renal Insufficiency*:** Renal excretion does not contribute to the clearance of telmisartan. With mild-to-moderate renal impairment (creatinine clearance of 30-80 mL/min, mean clearance approximately 50 mL/min), no dosage adjustment is necessary with decreased renal function. Telmisartan is not removed from blood by haemodialysis. In patients with impaired renal function the rate of hydrochlorothiazide elimination is reduced. Patients with a mean creatinine clearance of 90 ml/min the elimination half-life of hydrochlorothiazide was increased. In functionally anephric patients the elimination half-life is about 34 hours.

***Hepatic Insufficiency*:** In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Mannitol
Sodium Hydroxide
Polysorbate 80
Triethanolamine
Povidone
Purified water
Hypromellose
Polyethylene Glycol
Magnesium Stearate
Sodium Starch Glycolate
Iron Oxide Red

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 Months

6.4 Special Precautions for Storage

Store below 30°C. Protect from moisture.

6.5 Nature and Contents of Container

Available in Alu-Alu Blister pack.

Alu Alu Blister pack of 7 tablets using cold form laminate foil and Printed Aluminium foil. Four such blisters of 7 tablets each are packed in a carton along with insert.

6.6 Special precautions for disposal

No special requirements

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Ind Swift Limited
Village Jawaharpur, Off. NH-21 Derabassi, Dist AS Nagar (Mohali), Punjab, India

8. MARKETING AUTHORISATION NUMBER

Registration No.- INDS/IND/006
09345/07109/REN/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

05/06/2015 renewal: Dec 23, 2023

10. DATE OF (PARTIAL) REVISION OF THE TEXT

June 2019