



## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE MEDICINAL PRODUCT**

#### **1.1 Product Name**

ARBITEL 80-H

#### **1.2 Strength**

Telmisartan-80

Hydrochlorothiazide-12.5 mg

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each un-coated tablet contains:

Telmisartan Ph.Eur 80 mg

Hydrochlorothiazide Ph.Eur 12.5 mg

### **3. PHARMACEUTICAL FORM**

Tablets.

Biconvex, two layered tablets, oval shaped, uncoated tablets. White to off white layer is of Telmisartan which may contain red specs in between engraved with 'TH3' and red to reddish pink layer of is of hydrochlorothiazide part.

### **4. CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications :**

Treatment of essential hypertension

Telmisartan & Hydrochlorothiazide fixed dose combination is indicated in adults whose blood pressure is not adequately controlled on Telmisartan & Hydrochlorothiazide 80 mg/12.5 mg or adults who have been previously stabilized on telmisartan and hydrochlorothiazide given separately.



#### **4.2 Posology and method of administration:**

##### ***Posology***

Telmisartan & Hydrochlorothiazide should be taken in patients whose blood pressure is not adequately controlled by telmisartan alone. Individual dose titration with each of the two components is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered

- Telmisartan & Hydrochlorothiazide 80 mg/25 mg may be administered once daily in patients whose blood pressure is not adequately controlled by Telmisartan & Hydrochlorothiazide 80 mg/12.5 mg or in patients who have been previously stabilized on telmisartan and hydrochlorothiazide given separately.

Telmisartan & Hydrochlorothiazide is also available at the dose strengths 40 mg/12.5 mg and 80 mg/12.5 mg

##### ***Special populations***

Patients with renal impairment

Periodic monitoring of renal function is advised.

Patients with hepatic impairment

In patients with mild to moderate hepatic impairment the posology should not exceed Telmisartan & Hydrochlorothiazide 40 mg/12.5 mg once daily. Telmisartan & Hydrochlorothiazide is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function.

##### ***Elderly patients***

No dose adjustment is necessary.

##### ***Paediatric population***

The safety and efficacy of Telmisartan & Hydrochlorothiazide in children and adolescents aged below 18 have not been established. No data are available.



***Method of administration***

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

***Precautions to be taken before handling or administering the medicinal product***

Telmisartan & Hydrochlorothiazide should be kept in the sealed blister due to the hygroscopic property of the tablets. Tablets should be taken out of the blister shortly before administration.

**4.3 Contraindications :**

- Hypersensitivity to any of the active substances or to any of the excipients
- 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 hypokalemia, hypercalcaemia.

The concomitant use of Telmisartan & Hydrochlorothiazide with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m<sup>2</sup>)

**4.4 Special warnings and precautions for use:**

***Pregnancy***

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



*Hepatic impairment*

Telmisartan & 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 & 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 & 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 & Hydrochlorothiazide should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min). There is no experience regarding the administration of Telmisartan & Hydrochlorothiazide in patients with recent kidney transplantation. Experience with Telmisartan & 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 azotemia may occur in patients with impaired renal function.

*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 & 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 & 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 & 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 hypokalemia, hyponatraemia, and hypochloremic 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.

#### *- Hypokalemia*

Although hypokalemia may develop with the use of thiazide diuretics, concurrent therapy with telmisartan may reduce diuretic-induced hypokalemia. The risk of hypokalemia 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 Adrenocorticotrophic hormone (ACTH).

#### *- Hyperkalaemia*

Conversely, due to the antagonism of the angiotensin II (AT<sub>1</sub>) receptors by the telmisartan component of Telmisartan & Hydrochlorothiazide, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with Telmisartan & 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 & Hydrochlorothiazide.

- Hyponatraemia and hypochloraemic alkalosis

There is no evidence that Telmisartan & 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

### ***Lactose Monohydrate***

This medicinal product contains lactose monohydrated. Patients with rare hereditary problems of fructose intolerance and/or with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency should not take this medicine.

### ***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 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 acute 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.**

*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 & Hydrochlorothiazide). Co-administration of lithium and Telmisartan & 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 hypokalemia (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 & 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), hypokalemia being a predisposing factor to torsades de pointes.

- class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulphiride, sultopride, Amisulpride, tiapride, pimozide, haloperidol, Droperidol)
- others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloracin, terfenadine, vincamine IV.)



*Digitalis glycosides*

Thiazide-induced hypokalemia or hypomagnesaemia favors the onset of digitalis-induced arrhythmia.

*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.

*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 must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

#### *Beta-blockers and diazoxide*

The hyperglycemic 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 product may potentiate the hypotensive effects of all antihypertensive including telmisartan: Baclofen, amifostine.

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

#### **4.6 Pregnancy and lactation**

***Pregnancy***

There are no adequate data from the use of Telmisartan & 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 hypo perfusion, 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 & Hydrochlorothiazide during breast-feeding, Telmisartan & Hydrochlorothiazide is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new-born 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 &



Hydrochlorothiazide during breast feeding is not recommended. If Telmisartan & Hydrochlorothiazide is used during breast feeding, doses should be kept as low as possible.

### ***Fertility***

In preclinical studies, no effects of telmisartan and hydrochlorothiazide on male and female fertility were observed.

### **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 such as Telmisartan & Hydrochlorothiazide.

### **4.8 Undesirable effects**

#### ***Summary of the safety profile***

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

The overall incidence and pattern of adverse reactions reported with Telmisartan & Hydrochlorothiazide 80 mg/25 mg was comparable with Telmisartan & Hydrochlorothiazide 80 mg/12.5 mg. A dose-relationship of adverse reactions was not established and they showed no correlation with gender, age or race of the patients.

#### ***Tabulated summary of adverse reactions***

Adverse reactions reported in all clinical trials and occurring more frequently ( $p \leq 0.05$ ) with telmisartan plus hydrochlorothiazide than with placebo are shown below according to system organ class. Adverse reactions known to occur with each component given singly but which have not been seen in clinical trials may occur during treatment with Telmisartan & Hydrochlorothiazide.

Adverse reactions have been ranked under headings of frequency using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to



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<1/100); rare ( $\geq 1/10,000$  to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

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

Infections and infestations	
Rare:	Bronchitis, pharyngitis, sinusitis
Immune system disorders	
Rare:	Exacerbation or activation of systemic lupus erythematosus <sup>1</sup>
Metabolism and nutrition disorders	
Uncommon:	Hypokalaemia
Rare:	Hyperuricaemia, hyponatraemia
Psychiatric disorders	
Uncommon:	Anxiety
Rare:	Depression
Nervous system disorders	
Common:	Dizziness
Uncommon:	Syncope, paraesthesia
Rare:	Insomnia, sleep disorders
Eye disorders	
Rare:	Visual disturbance, vision blurred
Ear and labyrinth disorders	
Uncommon:	Vertigo
Cardiac disorders	
Uncommon:	Tachycardia, arrhythmias
Vascular disorders	



Uncommon:	Hypotension, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea
Rare:	Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders	
Uncommon:	Diarrhoea, dry mouth, flatulence
Rare:	Abdominal pain, constipation, dyspepsia, vomiting, gastritis
Hepatobiliary disorders	
Rare:	Abnormal hepatic function/liver disorder <sup>2</sup>
Skin and subcutaneous tissue disorders	
Rare:	Angioedema (also with fatal outcome), erythema, pruritus, rash, hyperhidrosis, urticaria
Musculoskeletal, connective tissue and bone disorders	
Uncommon:	Back pain, muscle spasms, myalgia
Rare:	Arthralgia, muscle cramps, pain in limb
Reproductive system and breast disorders	
Uncommon:	Erectile dysfunction
General disorders and administration site conditions	
Uncommon:	Chest pain
Rare:	Influenza-like illness, pain
Investigations	
Uncommon:	Blood uric acid increased
Rare:	Blood creatinine increased, blood creatine phosphokinase increased, hepatic enzyme increased



1: Based on post-marketing experience

2: For further description, please see sub-section “*Description of selected adverse reactions*”

*Additional information on individual components*

Adverse reactions previously reported with one of the individual components may be potential adverse reactions with Telmisartan & Hydrochlorothiazide, even if not observed in clinical trials with this product.

***Telmisartan:***

Adverse reactions occurred with similar frequency in placebo and telmisartan treated patients.

The overall incidence of adverse reactions reported with telmisartan (41.4 %) was usually comparable to placebo (43.9 %) in placebo controlled trials. The following adverse reactions listed below have been accumulated from all clinical trials in patients treated with telmisartan for hypertension or in patients 50 years or older at high risk of cardiovascular events.

Infections and infestations	
Uncommon:	Upper respiratory tract infection, urinary tract infection including
Rare:	cystitis Sepsis including fatal outcome <sup>3</sup>
Blood and lymphatic system disorders	
Uncommon:	Anaemia
Rare:	Eosinophilia, thrombocytopenia
Immune system disorders	
Rare:	Hypersensitivity, anaphylactic reactions
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 <sup>3</sup>
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

3: For further descriptions, please see sub-section “*Description of selected adverse reactions*”

***Hydrochlorothiazide:***

Hydrochlorothiazide may cause or exacerbate hypovolaemia which could lead to electrolyte imbalance.

Adverse reactions of unknown frequency reported with the use of hydrochlorothiazide alone include:



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Infections and infestations	
Not known:	Sialadenitis
Blood and lymphatic system disorders	
Not known:	Aplastic anaemia, haemolytic anaemia, bone marrow failure, leukopenia, neutropenia, agranulocytosis, thrombocytopenia
Immune system disorders	
Not known:	Anaphylactic reactions, hypersensitivity
Endocrine disorders	
Not known:	Diabetes mellitus inadequate control
Metabolism and nutrition disorders	
Not known:	Anorexia, appetite decreased, electrolyte imbalance, hypercholesterolemia, hyperglycaemia, hypovolaemia
Psychiatric disorders	
Not known:	Restlessness
Nervous system disorders	
Not known:	Light-headedness
Eye disorders	
Not known:	Xanthopsia, acute myopia, acute angle-closure glaucoma
Vascular disorders	
Not known:	Vasculitis necrotizing
Gastrointestinal disorders	
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
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

#### *Description of selected adverse reactions*

##### 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:**

There is limited information available for telmisartan with regard to overdose in humans. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

#### ***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 (hypokalemia, hypochloreaemic) and hypovolaemia resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalemia 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 hemodialysis. 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.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties:**

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, ATC code: C09DA07

It is a combination of an angiotensin II receptor antagonist, telmisartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. Telmisartan & Hydrochlorothiazide once daily produces effective and smooth reductions in blood pressure across the therapeutic dose range.



Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 (AT<sub>1</sub>) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT<sub>1</sub> receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT<sub>1</sub> receptor. Telmisartan selectively binds the AT<sub>1</sub> receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT<sub>2</sub> and other less characterized AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. 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.

### **5.2 Pharmacokinetic properties:**

Concomitant administration of hydrochlorothiazide and telmisartan does not appear to affect the pharmacokinetics of either substance in healthy subjects.

#### ***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 under the plasma concentration time curve (AUC) of about 6 % with the 40 mg tablet and about 19 % after a 160 mg dose. By 3 hours after administration plasma concentrations are similar whether telmisartan is taken fasting or with food. The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. The pharmacokinetics of orally administered telmisartan are non-linear over doses from 20 – 160 mg with greater than proportional increases of plasma concentrations (C<sub>max</sub> and AUC) with increasing doses. Telmisartan does not accumulate significantly in plasma on repeated administration.

**Hydrochlorothiazide:** Following oral administration of Telmisartan & Hydrochlorothiazide 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 for telmisartan 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 <sup>14</sup>C-labelled telmisartan the glucuronide represents approximately 11 % of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Hydrochlorothiazide is not metabolised in man.

***Elimination***

Telmisartan: Following either intravenous or oral administration of <sup>14</sup>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.



*Special populations*

*Elderly*

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. In clinical trials however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary. There was a trend towards higher plasma concentrations of hydrochlorothiazide in female than in male subjects. This is not considered to be of clinical relevance.

*Renal impairment*

Renal excretion does not contribute to the clearance of telmisartan. Based on modest experience in patients with mild to moderate renal impairment (creatinine clearance of 30 – 60 ml/min, mean about 50 ml/min) no dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemodialysis. In patients with impaired renal function the rate of hydrochlorothiazide elimination is reduced. In a typical study in 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 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:

No additional preclinical studies have been performed with the Fixed Dose Combination product 80 mg/25 mg. Previous preclinical safety studies performed with co-administration of telmisartan and hydrochlorothiazide in normotensive rats and dogs, in 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 offspring's 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

Name of Excipients	Specifications
Mannitol (Pearlitol SD 200)**	Ph.Eur
Meglumine	Ph.Eur
Sodium Hydroxide	Ph.Eur
Povidone K-30	Ph.Eur
Purified Water	Ph.Eur
Crospovidone Type A/ Kollidon CL	Ph.Eur
Magnesium Stearate	Ph.Eur
Lactose Monohydrate**	Ph.Eur
Microcrystalline Cellulose (Avicel PH 101)	Ph.Eur
Ferric Oxide (Red)	USPNF
Maize Starch	Ph.Eur

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

24 months from the date of manufacturing.

### 6.4 Special precautions for storage

Store below 30 °C. Protect from light. Keep out from the reach of children.

### 6.5 Nature and contents of container

Alu - Alu blister pack of 10 tablets, such 3 blisters are packed in a carton along with pack Insert.

**MICRO LABS LIMITED, INDIA**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**ARBITEL 80-H (Telmisartan 80 mg & Hydrochlorothiazide 12.5 mg Tablets)**

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**7. Marketing Authorization Holder**

**Manufactured by:**

**MICRO LABS LIMITED 92,**

**SIPCOT**

**HOSUR – 635126 INDIA**

**8. Marketing Authorization Number**

Not applicable

**9. Date of first authorization/renewal of authorization**

Not applicable

**10. Date of revision of text**

April 2017