ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tolucombi 40 mg/12.5 mg tablets
Tolucombi 80 mg/12.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tolucombi 40 mg/12.5 mg tablets
Each tablet contains 40 mg telmisartan and 12.5 mg hydrochlorothiazide.

Tolucombi 80 mg/12.5 mg tablets
Each tablet contains 80 mg telmisartan and 12.5 mg hydrochlorothiazide.

Excipient(s) with known effect
Each 40 mg/12.5 mg tablet contains 57 mg of lactose (as monohydrate) and 147.04 mg sorbitol (E420).

Each 80 mg/12.5 mg tablet contains 114 mg of lactose (as monohydrate) and 294.08 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Tolucombi 40 mg/12.5 mg tablets:
White to almost white or pinkish white on one side and pink marbled on the opposite side of two-layer biconvex oval tablet, tablet dimensions 15 mm x 7 mm.

Tolucombi 80 mg/12.5 mg tablets
White to almost white or pinkish white on one side and pink marbled on the opposite side of two-layer biconvex oval tablet, tablet dimensions 18 mm x 9 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

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

4.2 Posology and method of administration

Posology

Tolucombi 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.

- Tolucombi 40 mg/12.5 mg may be administered once daily in patients whose blood pressure is not adequately controlled by telmisartan 40 mg.
- Tolucombi 80 mg/12.5 mg may be administered once daily in patients whose blood pressure is

not adequately controlled by telmisartan 80 mg.

Renal impairment

Periodic monitoring of renal function is advised (see section 4.4).

Hepatic impairment

In patients with mild to moderate hepatic impairment the posology should not exceed Tolucombi 40 mg/12.5 mg once daily. Tolucombi is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function (see section 4.4).

Elderly

No dose adjustment is necessary.

Paediatric population

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

Method of administration

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

4.3 Contraindications

- Hypersensitivity to any of the active substances or to any of the excipients listed in section 6.1.
- Hypersensitivity to other sulphonamide-derived substances (since hydrochlorothiazide is a sulphonamide-derived medicinal product).
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Cholestasis and biliary obstructive disorders.
- Severe hepatic impairment.
- Severe renal impairment (creatinine clearance <30 ml/min).
- Refractory hypokalaemia, hypercalcaemia.

The concomitant use of Tolucombi with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

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 (see sections 4.3 and 4.6).

Hepatic impairment
Tolucombi should not be given to patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency (see section 4.3) since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan.

In addition, Tolucombi 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 Tolucombi 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
Tolucombi must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) (see section 4.3). There is no experience regarding the administration of Tolucombi in patients with recent kidney transplantation. Experience with Tolucombi 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.

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 Tolucombi.

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 (see sections 4.5 and 5.1).
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 (see section 4.8).

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 Tolucombi 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 Tolucombi, 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 (see section 4.8).

- 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) (see section 4.5).

- Hyperkalaemia

Conversely, due to the antagonism of the angiotensin II (AT1) receptors by the telmisartan component of Tolucombi, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with Tolucombi, 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 Tolucombi (see section 4.5).

- Hyponatraemia and hypochloraemic alkalosis

There is no evidence that Tolucombi 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 (see section 4.5).

Lactose, sorbitol and sodium

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

Tolucombi 40 mg/12.5 mg contains 147.04 mg sorbitol in each tablet, which is equivalent to 5 mg/kg/day, if the body weight is 29.8 kg. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Tolucombi 80 mg/12.5 mg contains 294.08 mg sorbitol in each tablet, which is equivalent to 5 mg/kg/day, if the body weight is 58.8 kg. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients weighing 58.8 kg or less with hereditary fructose intolerance (HFI) should not take this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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 (see section 4.8). If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a readministration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Choroidal Effusion, Acute Myopia and Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, 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 medicinal product 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.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Acute respiratory toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Tolucombi should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

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 Tolucombi). Coadministration of lithium and Tolucombi is not recommended (see section 4.4). 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 (see section 4.4).

Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporine 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 (see section 4.4).

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when Tolucombi 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 (see section 4.4).

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 (see sections 4.3, 4.4 and 5.1).

Antidiabetic medicinal products (oral agents and insulin)
Dose adjustment of the antidiabetic medicinal products may be required (see section 4.4).

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)
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 medicinal products 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 reactions 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 Fertility, pregnancy and lactation

Pregnancy

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

There are no adequate data from the use of Tolucombi in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

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) (See section 5.3). 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 (see sections 4.3 and 4.4).

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.

Breast-feeding

Because no information is available regarding the use of Tolucombi during breast-feeding, Tolucombi 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 Tolucombi during breast feeding is not recommended. If Tolucombi 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

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

4.8 Undesirable effects

Summary of the safety profile

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

The overall incidence of adverse reactions reported with Tolucombi was comparable to those reported with telmisartan alone in randomised controlled trials involving 1471 patients randomised to receive telmisartan plus hydrochlorothiazide (835) or telmisartan alone (636). Dose-relationship of adverse reactions was not established and they showed no correlation with gender, age or race of the patients.

Tabulated list 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 Tolucombi.

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

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[1]

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[2]

Skin and subcutaneous tissue disorders
Rare: Angioedema (also with fatal outcome), erythema, pruritus, rash, hyperhidrosis, urticaria

Muscoloskeletal, 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 Tolucombi, 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 cystitis
Rare: Sepsis including fatal outcome[3]

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[3]

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 description, please see sub-section *"Description of selected adverse reactions"*

Hydrochlorothiazide:
Hydrochlorothiazide may cause or exacerbate hypovolaemia which could lead to electrolyte imbalance (see section 4.4).

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

Infections and infestations
Not known: Sialadenitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

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, choroidal effusion, acute myopia, acute angle-closure glaucoma

Vascular disorders

Not known:	Vasculitis necrotizing

Respiratory, thoracic and mediastinal disorders

Very rare:	Acute respiratory distress syndrome (ARDS) (see section 4.4)

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

<u>Description of selected adverse reactions</u>

<u>Hepatic function abnormal / liver disorder</u>
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.

<u>Sepsis</u>
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 (see

section 5.1).

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.

Non-melanoma skin cancer
Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited information available for telmisartan with regard to overdose in humans. The degree to which hydrochlorothiazide is removed by haemodialysis 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 (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 antiarrhythmic 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists and diuretics, ATC code:C09DA07.

Tolucombi 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. Tolucombi once daily produces effective and smooth reductions in blood pressure across the therapeutic dose range.

Mechanism of action
Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 (AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and

other less characterised 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.
An 80 mg dose of telmisartan administered to healthy volunteers almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides have an effect on the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. 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-angiotensin-aldosterone system, co-administration of telmisartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

Clinical efficacy and safety

Treatment of essential hypertension
After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4-8 weeks after the start of treatment and is sustained during long-term therapy. The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by measurements made at the point of maximum effect and immediately prior to the next dose (through to peak ratios consistently above 80 % after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies).

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes of antihypertensive medicinal products (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril).

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.
The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

Cardiovascular prevention
ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, TIA, peripheral arterial disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which is a population at risk for cardiovascular events.

Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years.

Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7 %)

and ramipril (16.5 %) groups. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13). The all-cause mortality rate was 11.6 % and 11.8 % among telmisartan and ramipril treated patients, respectively.

Telmisartan was found to be similarly effective to ramipril in the pre-specified secondary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.99 (97.5 % CI 0.90 - 1.08), p (non-inferiority) = 0.0004], the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo.

TRANSCEND randomized ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to telmisartan 80 mg (n=2954) or placebo (n=2972), both given on top of standard care. The mean duration of follow up was 4 years and 8 months. No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found [15.7 % in the telmisartan and 17.0 % in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p = 0.22)]. There was evidence for a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95 % CI 0.76 - 1.00, p = 0.048)]. There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95 % CI 0.85 - 1.24).

Cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. CV mortality and all cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

In the "Prevention Regimen For Effectively avoiding Second Strokes" (PRoFESS) trial in patients 50 years and older, who recently experienced stroke, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70 % vs. 0.49 % [RR 1.43 (95 % confidence interval 1.00 - 2.06)]; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33 %) vs. patients taking placebo (0.16 %) [RR 2.07 (95 % confidence interval 1.14 - 3.76)]. The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage.
VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest

(hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

The effects of fixed dose combination of telmisartan/HCTZ on mortality and cardiovascular morbidity are currently unknown.

Non-melanoma skin cancer
Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose-response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

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. Telmisartan does not accumulate significantly in plasma on repeated administration.
Hydrochlorothiazide: Following oral administration of Tolucombi 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 l-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 ^{14}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 ^{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.

Linearity/non-linearity
Telmisartan: The pharmacokinetics of orally administered telmisartan are non-linear over doses from 20 – 160 mg with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses.
Hydrochlorothiazide exhibits linear pharmacokinetics.

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 haemodialysis. 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

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 sodium chloride solution 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.
For the foetotoxic potential of the telmisartan/hydrochlorothiazide combination see section 4.6.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate
Mannitol
Meglumine
Povidone (K30)
Red ferric oxide (E172)
Silica, colloidal anhydrous
Sodium hydroxide (E524)
Sodium stearyl fumarate
Sorbitol (E420)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters (OPA/Al/PVC foil//Al foil): 3 years
Blisters (OPA/Al/PE foil with desiccant//Al foil): 2 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blisters (OPA/Al/PVC foil//Al foil): 14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1, 84 x 1, 90 x 1, 98 x 1 and 100 x 1 tablet in a box.
Blisters (OPA/Al/PE foil with desiccant//Al foil): 14 x 1 and 98 x 1 tablet in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

Tolucombi 40 mg/12.5 mg tablets
EU/1/13/821/001

EU/1/13/821/002
EU/1/13/821/003
EU/1/13/821/004
EU/1/13/821/005
EU/1/13/821/006
EU/1/13/821/007
EU/1/13/821/008
EU/1/13/821/009
EU/1/13/821/010
EU/1/13/821/031

Tolucombi 80 mg/12.5 mg tablets
EU/1/13/821/011
EU/1/13/821/012
EU/1/13/821/013
EU/1/13/821/014
EU/1/13/821/015
EU/1/13/821/016
EU/1/13/821/017
EU/1/13/821/018
EU/1/13/821/019
EU/1/13/821/020
EU/1/13/821/032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 March 2013
Date of latest renewal: 8 January 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Tolucombi 80 mg/25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg telmisartan and 25 mg hydrochlorothiazide.

Excipient(s) with known effect:
Each tablet contains 114 mg of lactose (as monohydrate) and 294.08 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White to yellowish white on one side and yellow marbled on the opposite side of two-layer biconvex oval tablet, tablet dimensions 18 mm x 9 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

Tolucombi fixed dose combination (80 mg telmisartan/25 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on Tolucombi 80 mg/12.5 mg (80 mg telmisartan/12.5 mg hydrochlorothiazide) or adults who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

4.2 Posology and method of administration

Posology

Tolucombi 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.

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

Tolucombi is also available at the dose strengths 40 mg/12.5 mg and 80 mg/12.5 mg.

Renal impairment

Periodic monitoring of renal function is advised (see section 4.4).

Hepatic impairment

In patients with mild to moderate hepatic impairment the posology should not exceed Tolucombi 40 mg/12.5 mg once daily. Tolucombi is not indicated in patients with severe hepatic impairment.

Thiazides should be used with caution in patients with impaired hepatic function (see section 4.4).

Elderly

No dose adjustment is necessary.

Paediatric population

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

Method of administration

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

4.3 Contraindications

- Hypersensitivity to any of the active substances or to any of the excipients listed in section 6.1.
- Hypersensitivity to other sulphonamide-derived substances (since hydrochlorothiazide is a sulphonamide-derived medicinal product).
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Cholestasis and biliary obstructive disorders.
- Severe hepatic impairment.
- Severe renal impairment (creatinine clearance <30 ml/min).
- Refractory hypokalaemia, hypercalcaemia.

The concomitant use of Tolucombi with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

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 (see sections 4.3 and 4.6).

Hepatic impairment
Tolucombi should not be given to patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency (see section 4.3) since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan.

In addition, Tolucombi 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 Tolucombi 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
Tolucombi must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) (see section 4.3). There is no experience regarding the administration of Tolucombi in

patients with recent kidney transplantation. Experience with Tolucombi 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.

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 Tolucombi.

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 (see sections 4.5 and 5.1).
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 (see section 4.8).

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 Tolucombi 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 Tolucombi, 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 (see section 4.8).

- 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) (see section 4.5).

- Hyperkalaemia

Conversely, due to the antagonism of the angiotensin II (AT1) receptors by the telmisartan component of Tolucombi, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with Tolucombi, 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 Tolucombi (see section 4.5).

- Hyponatraemia and hypochloraemic alkalosis

There is no evidence that Tolucombi 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 (see section 4.5).

Lactose , sorbitol and sodium

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

This medicine contains 294.08 mg sorbitol in each tablet, which is equivalent to 5 mg/kg/day, if the body weight is 58.8 kg. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients weighing 58.8 kg or less with hereditary fructose intolerance (HFI) should not take this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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 (see section 4.8). If a

photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a readministration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Choroidal Effusion, Acute Myopia and Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, 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 medicinal product 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.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Acute respiratory toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Tolucombi should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

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 Tolucombi). Coadministration of lithium and Tolucombi is not recommended (see section 4.4). 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 (see section 4.4).

Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporine 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 (see section 4.4).

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when Tolucombi 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 (see section 4.4).

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 (see sections 4.3, 4.4 and 5.1).

Antidiabetic medicinal products (oral agents and insulin)
Dose adjustment of the antidiabetic medicinal products may be required (see section 4.4).

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)
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 medicinal products 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 reactions 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 Fertility, pregnancy and lactation

Pregnancy

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

There are no adequate data from the use of Tolucombi in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

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) (See section 5.3). 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 (see sections 4.3 and 4.4).

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.

Breast-feeding

Because no information is available regarding the use of Tolucombi during breast-feeding, Tolucombi 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 Tolucombi during breast feeding is not recommended. If Tolucombi 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

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reaction is dizziness. Serious angioedema may occur rarely (≥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 list 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 Tolucombi.

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

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[1]

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[2]

Skin and subcutaneous tissue disorders
Rare: Angioedema (also with fatal outcome), erythema, pruritus, rash, hyperhidrosis, urticaria

Muscoloskeletal, 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 Tolucombi, 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 cystitis
Rare: Sepsis including fatal outcome[3]

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[3]

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 description, please see sub-section *"Description of selected adverse reactions"*

Hydrochlorothiazide:
Hydrochlorothiazide may cause or exacerbate hypovolaemia which could lead to electrolyte imbalance (see section 4.4).

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

Infections and infestations
Not known: Sialadenitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

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, choroidal effusion, acute myopia, acute angle-closure glaucoma

Vascular disorders
Not known: Vasculitis necrotizing

Respiratory, thoracic and mediastinal disorders
Very rare: Acute respiratory distress syndrome (ARDS) (see section 4.4)

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

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 (see section 5.1).

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.

Non-melanoma skin cancer
Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited information available for telmisartan with regard to overdose in humans. The degree to which hydrochlorothiazide is removed by haemodialysis 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 (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 antiarrhythmic 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists and diuretics, ATC code:C09DA07.

Tolucombi 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. Tolucombi once daily produces effective and smooth reductions in blood pressure across the therapeutic dose range.

Mechanism of action
Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 (AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised 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.
An 80 mg dose of telmisartan administered to healthy volunteers almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides have an effect on the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. 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-angiotensin-aldosterone system, co-administration of telmisartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

Clinical efficacy and safety

Treatment of essential hypertension
After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4-8 weeks after the start of treatment and is sustained during long-term therapy. The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by measurements made at the point of maximum effect and immediately prior to the next dose (through to peak ratios consistently above 80 % after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies).

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes of antihypertensive medicinal products (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril).

In a double-blind controlled clinical trial (n=687 patients evaluated for efficacy) in non-responders to the 80 mg/12.5 mg combination, an incremental blood pressure lowering effect of the 80 mg/25 mg combination compared to continued treatment with the 80 mg/12.5 mg combination of 2.7/1.6 mmHg (SBP/DBP) was demonstrated (difference in adjusted mean changes from baseline). In a follow-up trial with the 80 mg/25 mg combination, blood pressure was further decreased (resulting in an overall reduction of 11.5/9.9 mmHg (SBP/DBP).

In a pooled analysis of two similar 8 week double-blind placebo-controlled clinical trials vs. valsartan/hydrochlorothiazide 160 mg/25 mg (n=2121 patients evaluated for efficacy) a significantly greater blood pressure lowering effect of 2.2/1.2 mmHg (SBP/DBP) was demonstrated (difference in adjusted mean changes from baseline, respectively) in favour of telmisartan/hydrochlorothiazide 80 mg/25 mg combination.

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.
The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

Cardiovascular prevention
ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, TIA, peripheral arterial disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which is a population at risk for cardiovascular events.

Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years.

Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7 %) and ramipril (16.5 %) groups. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13). The all-cause mortality rate was 11.6 % and 11.8 % among telmisartan and ramipril treated patients, respectively.

Telmisartan was found to be similarly effective to ramipril in the pre-specified secondary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.99 (97.5 % CI 0.90 - 1.08), p (non-inferiority) = 0.0004], the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo.

TRANSCEND randomized ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to telmisartan 80 mg (n=2954) or placebo (n=2972), both given on top of standard care. The mean duration of follow up was 4 years and 8 months. No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found [15.7 % in the telmisartan and 17.0 % in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p = 0.22)]. There was evidence for a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95 % CI 0.76 - 1.00, p = 0.048)]. There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95 % CI 0.85 - 1.24).

Cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. CV mortality and all cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

In the "Prevention Regimen For Effectively avoiding Second Strokes" (PRoFESS) trial in patients 50 years and older, who recently experienced stroke, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70 % vs. 0.49 % [RR 1.43 (95 % confidence interval 1.00 - 2.06)]; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33 %) vs. patients taking placebo (0.16 %) [RR 2.07 (95 % confidence interval 1.14 - 3.76)]. The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage.
VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the

risk of cardiovascular mortality and morbidity.

The effects of fixed dose combination of telmisartan/HCTZ on mortality and cardiovascular morbidity are currently unknown.

Non-melanoma skin cancer
Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose-response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

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. Telmisartan does not accumulate significantly in plasma on repeated administration.

Hydrochlorothiazide: Following oral administration of Tolucombi 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 l-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 ^{14}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 ^{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.

Linearity/non-linearity
Telmisartan: The pharmacokinetics of orally administered telmisartan are non-linear over doses from 20 – 160 mg with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses.
Hydrochlorothiazide exhibits linear pharmacokinetics.

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 haemodialysis. 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.

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 sodium chloride solution 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.
For the foetotoxic potential of the telmisartan/hydrochlorothiazide combination see section 4.6.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate
Mannitol
Meglumine
Povidone (K30)
Silica, colloidal anhydrous
Sodium hydroxide (E524)
Sodium stearyl fumarate
Sorbitol (E420)
Yellow ferric oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters (OPA/Al/PVC foil//Al foil): 3 years
Blisters (OPA/Al/PE foil with desiccant//Al foil): 2 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blisters (OPA/Al/PVC foil//Al foil): 14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1, 84 x 1, 90 x 1, 98 x 1 and 100 x 1 tablet in a box.
Blisters (OPA/Al/PE foil with desiccant//Al foil): 14 x 1 and 98 x 1 tablet in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/821/021
EU/1/13/821/022

EU/1/13/821/023
EU/1/13/821/024
EU/1/13/821/025
EU/1/13/821/026
EU/1/13/821/027
EU/1/13/821/028
EU/1/13/821/029
EU/1/13/821/030
EU/1/13/821/033

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 March 2013
Date of latest renewal: 8 January 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

KRKA-POLSKA Sp.z. o.o.
ul. Równoległa 5
02-235 Warszawa
Poland

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

TAD Pharma GmbH
Heinz-Lohmann-Straße 5
27472 Cuxhaven
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP shall be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

An updated RMP shall be submitted by CHMP agreed deadline.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tolucombi 40 mg/12.5 mg tablets
telmisartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg telmisartan and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate and sorbitol (E420).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.

Blister (OPA/Al/PVC foil//Al foil):
14 x 1 tablet
28 x 1 tablet
30 x 1 tablet
56 x 1 tablet
60 x 1 tablet
84 x 1 tablet
90 x 1 tablet
98 x 1 tablet
100 x 1 tablet

Blister (OPA/Al/PE foil with desiccant//Al foil):
14 x 1 tablet
98 x 1 tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/821/001
EU/1/13/821/002
EU/1/13/821/003
EU/1/13/821/004
EU/1/13/821/005
EU/1/13/821/006
EU/1/13/821/007
EU/1/13/821/008
EU/1/13/821/009
EU/1/13/821/010
EU/1/13/821/031

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tolucombi 40 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Tolucombi 40 mg/12.5 mg tablets
telmisartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Only on blisters containing 7 tablets
MON
TUE
WED
THU
FRI
SAT
SUN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tolucombi 80 mg/12.5 mg tablets
telmisartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg telmisartan and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate and sorbitol (E420).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.

Blister (OPA/Al/PVC foil//Al foil):
14 x 1 tablet
28 x 1 tablet
30 x 1 tablet
56 x 1 tablet
60 x 1 tablet
84 x 1 tablet
90 x 1 tablet
98 x 1 tablet
100 x 1 tablet

Blister (OPA/Al/PE foil with desiccant//Al foil):
14 x 1 tablet
98 x 1 tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/821/011
EU/1/13/821/012
EU/1/13/821/013
EU/1/13/821/014
EU/1/13/821/015
EU/1/13/821/016
EU/1/13/821/017
EU/1/13/821/018
EU/1/13/821/019
EU/1/13/821/020
EU/1/13/821/032

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tolucombi 80 mg/12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Tolucombi 80 mg/12.5 mg tablets
telmisartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Only on blisters containing 7 tablets
MON
TUE
WED
THU
FRI
SAT
SUN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tolucombi 80 mg/25 mg tablets
telmisartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg telmisartan and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate and sorbitol (E420).
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.

Blister (OPA/Al/PVC foil//Al foil):
14 x 1 tablet
28 x 1 tablet
30 x 1 tablet
56 x 1 tablet
60 x 1 tablet
84 x 1 tablet
90 x 1 tablet
98 x 1 tablet
100 x 1 tablet

Blister (OPA/Al/PE foil with desiccant//Al foil):
14 x 1 tablet
98 x 1 tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/821/021
EU/1/13/821/022
EU/1/13/821/023
EU/1/13/821/024
EU/1/13/821/025
EU/1/13/821/026
EU/1/13/821/027
EU/1/13/821/028
EU/1/13/821/029
EU/1/13/821/030
EU/1/13/821/033

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tolucombi 80 mg/25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Tolucombi 80 mg/25 mg tablets
telmisartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Only on blisters containing 7 tablets
MON
TUE
WED
THU
FRI
SAT
SUN

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tolucombi 40 mg/12.5 mg tablets
Tolucombi 80 mg/12.5 mg tablets
Tolucombi 80 mg/25 mg tablets
telmisartan/hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tolucombi is and what it is used for

Tolucombi is a combination of two active substances, telmisartan and hydrochlorothiazide in one tablet. Both of these substances help to control high blood pressure.

- Telmisartan belongs to a group of medicines called angiotensin II receptor antagonists. Angiotensin II is a substance produced in your body which causes your blood vessels to narrow thus increasing your blood pressure. Telmisartan blocks the effect of angiotensin II so that the blood vessels relax, and your blood pressure is lowered.

- Hydrochlorothiazide belongs to a group of medicines called thiazide diuretics, which cause your urine output to increase, leading to a lowering of your blood pressure.

High blood pressure, if not treated, can damage blood vessels in several organs, which could lead sometimes to heart attack, heart or kidney failure, stroke, or blindness. There are usually no symptoms of high blood pressure before damage occurs. Thus it is important to regularly measure blood pressure to verify if it is within the normal range.

Tolucombi (40 mg/12.5 mg, 80 mg/12.5 mg) is used to treat high blood pressure (essential hypertension) in adults whose blood pressure is not controlled enough when telmisartan is used alone.
Tolucombi (80 mg/25 mg) is used to treat high blood pressure (essential hypertension) in adults whose blood pressure is not adequately controlled by Tolucombi 80 mg/12.5 mg or in patients who have been previously stabilised by telmisartan and hydrochlorothiazide given separately.

2. What you need to know before you take Tolucombi

Do not take Tolucombi
- if you are allergic to telmisartan or any other ingredients of this medicine (listed in section 6).
- if you are allergic to hydrochlorothiazide or to any other sulfonamide-derived medicines.
- if you are more than 3 months pregnant. (It is also better to avoid Tolucombi in early pregnancy-see pregnancy section.)

- if you have severe liver problems such as cholestasis or biliary obstruction (problems with drainage of the bile from liver and the gall bladder) or any other severe liver disease.
- if you have severe kidney disease.
- if your doctor determines that you have low potassium levels or high calcium levels in your blood that do not get better with treatment.
- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

If any of the above applies to you, tell your doctor or pharmacist before taking Tolucombi.

Warnings and precautions
Talk to your doctor before taking Tolucombi if you are suffering or have ever suffered from any of the following conditions or illnesses:
- Low blood pressure (hypotension), likely to occur if you are dehydrated (excessive loss of body water) or have salt deficiency due to diuretic therapy (water tablets), low-salt diet, diarrhoea, vomiting, or haemodialysis.
- Kidney disease or kidney transplant.
- Renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- Liver disease.
- Heart trouble.
- Diabetes.
- Gout.
- Raised aldosterone levels (water and salt retention in the body along with imbalance of various blood minerals).
- Systemic lupus erythematosus (also called “lupus” or “SLE”) a disease where the body’s immune system attacks the body.
- The active substance hydrochlorothiazide can cause an unusual reaction, resulting in a decrease in vision and eye pain. These could be symptoms of fluid accumulation in the vascular layer of the eye (choroidal effusion) or an increase of pressure in your eye and can happen within hours to weeks of taking Tolucombi. This can lead to permanent vision impairment, if not treated.
- If you have had skin cancer or if you develop an unexpected skin lesion during the treatment. Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking Tolucombi.
- If you experienced breathing or lung problems (including inflammation or fluid in the lungs) following hydrochlorothiazide intake in the past. If you develop any severe shortness of breath or difficulty breathing after taking Tolucombi, seek medical attention immediately.

Talk to your doctor before taking Tolucombi, if you are taking:
- digoxin.
- any of the following medicines used to treat high blood pressure:
    - an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems.
    - aliskiren.

You must tell your doctor if you think you are (or might become) pregnant. Tolucombi is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

Treatment with hydrochlorothiazide may cause electrolyte imbalance in your body. Typical symptoms of fluid or electrolyte imbalance include dry mouth, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, nausea (feeling sick), vomiting, tired muscles, and an abnormally fast heart rate (faster than 100 beats per minute). If you experience any of these you should tell your doctor.

You should also tell your doctor, if you experience an increased sensitivity of the skin to the sun with symptoms of sunburn (such as redness, itching, swelling, blistering) occurring more quickly than normal.

In case of surgery or anaesthetics, you should tell your doctor that you are taking Tolucombi.

Tolucombi may be less effective in lowering the blood pressure in black patients.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.
See also information under the heading “Do not take Tolucombi”.

Children and adolescents
The use of Tolucombi in children and adolescents up to the age of 18 years is not recommended.

Other medicines and Tolucombi
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may need to change the dose of these other medications or take other precautions. In some cases you may have to stop taking one of the medicines. This applies especially to the medicines listed below taken at the same time with Tolucombi:

- Lithium containing medicines to treat some types of depression.
- Medicines associated with low blood potassium (hypokalaemia) such as other diuretics, ('water tablets'), laxatives (e.g. castor oil), corticosteroids (e.g. prednisone), ACTH (a hormone), amphotericin (an antifungal medicine), carbenoxolone (used to treat mouth ulcers), penicillin G sodium (an antibiotic), and salicylic acid and derivatives.
- Medicines that may increase blood potassium levels such as potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, ACE inhibitors, cyclosporin (an immunosuppressant drug) and other medicinal products such as heparin sodium (an anticoagulant).
- Medicines that are affected by changes of the blood potassium level such as heart medicines (e.g. digoxin) or medicines to control the rhythm of your heart (e.g. quinidine, disopyramide, amiodarone, sotalol), medicines used for mental disorders (e.g. thioridazine, chlorpromazine, levomepromazine) and other medicines such as certain antibiotics (e.g. sparfloxacine, pentamidine) or certain medicines to treat allergic reactions (e.g. terfenadine).
- Medicines for the treatment of diabetes (insulins or oral agents such as metformin).
- Cholestyramine and colestipol, medicines for lowering blood fat levels.
- Medicines to increase blood pressure, such as noradrenaline.
- Muscle relaxing medicines, such as tubocurarine.
- Calcium supplements and/or vitamin D supplements.
- Anti-cholinergic medicines (medicines used to treat a variety of disorders such as gastrointestinal cramps, urinary bladder spasm, asthma, motion sickness, muscular spasms, Parkinson's disease and as an aid to anaesthesia) such as atropine and biperiden.
- Amantadine (medicine used to treat Parkinson’s disease and also used to treat or prevent certain illnesses caused by viruses).
- Other medicines used to treat high blood pressure, corticosteroids, painkillers (such as non-steroidal anti-inflammatory drugs [NSAIDs]), medicines to treat cancer, gout, or arthritis.
- If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not take Tolucombi” and “Warnings and precautions”).
- Digoxin.

Tolucombi may increase the blood pressure lowering effect of other medicines used to treat high blood pressure or of medicines with blood pressure lowering potential (e.g. baclofen, amifostine). Furthermore, low blood pressure may be aggravated by alcohol, barbiturates, narcotics or antidepressants. You may notice this as dizziness when standing up. You should consult with your doctor if you need to adjust the dose of your other medicine while taking Tolucombi.

The effect of Tolucombi may be reduced when you take NSAIDs (non steroidal anti-inflammatory medicines, e.g. acetylsalicyl acid or ibuprofen).

Tolucombi with food and alcohol

You can take Tolucombi with or without food.
Avoid taking alcohol until you have talked to your doctor. Alcohol may make your blood pressure fall more and/or increase the risk of you becoming dizzy or feeling faint.

Pregnancy and breast-feeding

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Tolucombi before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Tolucombi. Tolucombi is not recommended during pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Tolucombi is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed.

Driving and using machines
Some people feel dizzy or tired when taking Tolucombi. If you feel dizzy or tired, do not drive or operate machinery.

Tolucombi contains lactose, sorbitol and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Tolucombi 40 mg/12.5 mg contains 147.04 mg sorbitol in each tablet, which is equivalent to 5 mg/kg/day, if the body weight is 29.8 kg.

Tolucombi 80 mg/12.5 mg and Tolucombi 80 mg/25 mg contain 294.08 mg sorbitol in each tablet, which is equivalent to 5 mg/kg/day, if the body weight is 58.8 kg.
Patients weighing 58.8 kg or less must take into consideration that sorbitol is a source of fructose and if your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Tolucombi

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of Tolucombi is one tablet a day. Try to take a tablet at the same time each day. You can take Tolucombi with or without food. The tablets should be swallowed with some water or other non-alcoholic drink. It is important that you take Tolucombi every day until your doctor tells you otherwise.

If your liver is not working properly, the usual dose should not exceed 40 mg/12.5 mg once a day.

If you take more Tolucombi than you should

If you accidentally take too many tablets you may experience symptoms such as low blood pressure and rapid heartbeat. Slow heartbeat, dizziness, vomiting, reduced kidney function including kidney failure, have also been reported. Due to the hydrochlorothiazide component, markedly low blood pressure and low blood levels of potassium can also happen, which may result in nausea, sleepiness and muscle cramps and/or irregular heartbeat associated with the concomitant use of drugs such as digitalis or certain anti-arrhythmic treatments. Contact your doctor, pharmacist, or your nearest hospital emergency department immediately.

If you forget to take Tolucombi
If you forget to take a dose, do not worry. Take it as soon as you remember then carry on as before. If you do not take your tablet on one day, take your normal dose on the next day. ***Do not*** take a double dose to make up for forgotten individual doses.

If you have further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious and need immediate medical attention:

You should see your doctor immediately if you experience any of the following symptoms:

Sepsis* (often called "blood poisoning"), is a severe infection with whole-body inflammatory response, rapid swelling of the skin and mucosa (angioedema); blistering and peeling of the top layer of skin (toxic epidermal necrolysis); these side effects are rare (may affect up to 1 in 1,000 people) or of unknown frequency (toxic epidermal necrolysis) but are extremely serious and patients should stop taking the medicine and see their doctor immediately.
If these effects are not treated they could be fatal. Increased incidence of sepsis has been observed with telmisartan only, however can not be ruled out for Tolucombi.

Possible side effects of Tolucombi:

Common side effects (may affect up to 1 in 10 people):
Dizziness.

Uncommon side effects (may affect up to 1 in 100 people):
Decreased blood potassium levels, anxiety, fainting (syncope), sensation of tingling, pins and needles (paraesthesia), feeling of spinning (vertigo), fast heart beat (tachycardia), heart rhythm disorders, low blood pressure, a sudden fall in blood pressure when you stand up, shortness of breath (dyspnoea), diarrhoea, dry mouth, flatulence, back pain, muscle spasm, muscle pain, erectile dysfunction (inability to get or keep an erection), chest pain, increased blood uric acid levels.

Rare side effects (may affect up to 1 in 1,000 people):
Inflammation of the lung (bronchitis), activation or worsening of systemic lupus erythematosus (a disease where the body's immune system attacks the body, which causes joint pain, skin rashes and fever); sore throat, inflamed sinuses; feeling sad (depression), difficulty falling asleep (insomnia), impaired vision, difficulty breathing, abdominal pain, constipation, bloating (dyspepsia), feeling sick (vomiting), inflammation of the stomach (gastritis), abnormal liver function (Japanese patients are more likely to experience this side effect), redness of the skin (erythema), allergic reactions such as itching or rash, increased sweating, hives (urticaria), joint pain (arthralgia) and pain in extremities, muscle cramps, flu-like-illness, pain, low levels of sodium, increased levels of creatinine, hepatic enzymes or creatine phosphokinase in the blood.

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

Telmisartan
In patients taking telmisartan alone the following additional side effects have been reported:

Uncommon side effects (may affect up to 1 in 100 people):
Upper respiratory tract infection (e.g. sore throat, inflamed sinuses, common cold), urinary tract infections, deficiency in red blood cells (anaemia), high potassium levels, slow heart rate (bradycardia), kidney impairment including acute kidney failure, weakness, cough.

Rare side effects (may affect up to 1 in 1,000 people):
Low platelet count (thrombocytopenia), increase in certain white blood cells (eosinophilia), serious allergic reaction (e.g. hypersensitivity, anaphylactic reaction, drug rash), low blood sugar levels (in diabetic patients), upset stomach, eczema (a skin disorder), arthrosis, inflammation of the tendons, decreased haemoglobin (a blood protein), somnolence.

Very rare side effects (may affect up to 1 in 10,000 people):
Progressive scarring of lung tissue (interstitial lung disease)**

* The event may have happened by chance or could be related to a mechanism currently not known.

** Cases of progressive scarring of lung tissue have been reported during intake of telmisartan. However, it is not known whether telmisartan was the cause.

Hydrochlorothiazide
In patients taking hydrochlorothiazide alone the following additional side effects have been reported:

Common side effects (may affect up to 1 in 10 people):
Feeling sick (nausea), low blood magnesium level.

Rare side effects (may affect up to 1 in 1,000 people):
Reduction in blood platelets, which increases risk of bleeding or bruising (small purple-red marks in skin or other tissue caused by bleeding), high blood calcium level, headache.

Very rare side effects (may affect up to 1 in 10,000 people):
Increased pH (disturbed acid-base balance) due to low blood chloride level, acute respiratory distress (signs include severe shortness of breath, fever, weakness, and confusion).

Side effects of unknown frequency (frequency cannot be estimated from the available data):
Inflammation of the salivary gland, skin and lip cancer (Non-melanoma skin cancer), decreases in the number (or even lack) of cells in the blood, including low red and white blood cell count, serious allergic reactions (e.g. hypersensitivity, anaphylactic reaction), decreased or loss of appetite, restlessness, light-headedness, blurred or yellowing of vision, decrease in vision and eye pain (possible signs of fluid accumulation in the vascular layer of the eye (choroidal effusion) or acute myopia or acute-angle closure glaucoma), inflammation of blood vessels (vasculitis necrotising), inflamed pancreas, upset stomach, yellowing of the skin or eyes (jaundice), lupus-like syndrome (a condition mimicking a disease called systemic lupus erythematosus where the body's immune system attacks the body); skin disorders such as inflamed blood vessels in the skin, increased sensitivity to sunlight, rash, redness of the skin, blistering of the lips, eyes or mouth, skin peeling, fever (possible signs of erythema multiforme), weakness, kidney inflammation or impaired kidney function, glucose in the urine (glycosuria), fever, impaired electrolyte balance, high blood cholesterol levels, decreased blood volume, increased levels of glucose, difficulties in controlling blood/ urine levels of glucose in patients with a diagnosis of diabetes mellitus, or fat in the blood.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of

this medicine.

5. How to store Tolucombi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tolucombi contains
- The active substances are telmisartan and hydrochlorothiazide.
  Each tablet contains 40 mg telmisartan and 12.5 mg hydrochlorothiazide.
  Each tablet contains 80 mg telmisartan and 12.5 mg hydrochlorothiazide.
  Each tablet contains 80 mg telmisartan and 25 mg hydrochlorothiazide.
- The other ingredients are: hydroxypropylcellulose, lactose monohydrate, magnesium stearate, mannitol, meglumine, povidone (K30), red ferric oxide (E172) – only in 40 mg/12.5 mg and 80 mg/12.5 mg tablets, silica colloidal anhydrous, sodium hydroxide (E524), sodium stearyl fumarate, sorbitol (E420) and yellow ferric oxide (E172) – only in 80 mg/25 mg tablets. See section 2 "Tolucombi contains lactose, sorbitol and sodium".

What Tolucombi looks like and contents of the pack
40 mg/12.5 mg tablets: White to almost white or pinkish white on one side and pink marbled on the opposite side of two-layer biconvex oval tablet, tablet dimensions 15 mm x 7 mm.
80 mg/12.5 mg tablets: White to almost white or pinkish white on one side and pink marbled on the opposite side of two-layer biconvex oval tablet, tablet dimensions 18 mm x 9 mm.
80 mg/25 mg tablets: White to yellowish white on one side and yellow marbled on the opposite side of two-layer biconvex oval tablet, tablet dimensions 18 mm x 9 mm.

Blisters (OPA/Al/PVC foil//Al foil): 14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1, 84 x 1, 90 x 1, 98 x 1 and 100 x 1 tablet in a box.
Blisters (OPA/Al/PE foil with desiccant//Al foil): 14 x 1 and 98 x 1 tablet in a box.
Not all pack sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu