ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tolura 40 mg tablets
Tolura 80 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tolura 40 mg tablets
Each tablet contains 40 mg telmisartan.

Tolura 80 mg tablets
Each tablet contains 80 mg telmisartan.

Excipients with known effect:
40 mg: Each tablet contains 149.8 mg sorbitol (E420) and 57 mg lactose.
80 mg: Each tablet contains 299.7 mg sorbitol (E420) and 114 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

40 mg: white to almost white, biconvex, oval tablets
80 mg: white to almost white, biconvex, capsule shape tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of essential hypertension in adults.

Cardiovascular prevention
Reduction of cardiovascular morbidity in adults with:
- manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or
- type 2 diabetes mellitus with documented target organ damage.

4.2 Posology and method of administration

Posology

Treatment of essential hypertension

The usually effective dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, the dose of telmisartan can be increased to a maximum of 80 mg once daily. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment (see section 5.1). Alternatively, telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide, which has been shown to have an additive blood pressure lowering effect with telmisartan.

Cardiovascular prevention

The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of telmisartan are effective in reducing cardiovascular morbidity.
When initiating telmisartan therapy for the reduction of cardiovascular morbidity, close monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Elderly

No dose adjustment is necessary for elderly patients.

Renal impairment

Limited experience is available in patients with severe renal impairment or haemodialysis. A lower starting dose of 20 mg is recommended in these patients (see section 4.4). No posology adjustment is required for patients with mild to moderate renal impairment. Telmisartan is not removed from blood by haemofiltration and is not dialyzable.

Hepatic impairment

Tolura is contraindicated in patients with severe hepatic impairment (see section 4.3).
In patients with mild to moderate hepatic impairment the posology should not exceed 40 mg once daily (see section 4.4).

Paediatric population

The safety and efficacy of Tolura in children and adolescents aged below 18 years have not been established.
Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

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

Precautions to be taken before handling or administering the medicinal product

Telmisartan should be kept in the sealed blister due to the hygroscopic property of the tablets. Tablets should be taken out of the blister shortly before administration (see section 6.6).

Tolura tablets cannot be divided, therefore they are not suitable for patients who require a dose of 20 mg of telmisartan for the treatment of hypertension or for patients with severe renal impairment or haemodialysis. For these patients, an equivalent product with the same active ingredient is available.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Second and third trimester of pregnancy (see sections 4.4 and 4.6)
- Biliary obstructive disorders
- Severe hepatic impairment

The concomitant use of Tolura 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 blockers should not be initiated during pregnancy. Unless continued angiotensin II receptor blocker 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 blockers should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Hepatic impairment

Tolura is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment (see section 4.3) since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan. Tolura should be used only with caution in patients with mild to moderate hepatic impairment.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation

When Tolura is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Tolura in patients with recent kidney transplantation.
Telmisartan is not removed from blood by haemofiltration and is not dialyzable.

Volume- and/or sodium-depleted patients

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

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 such as telmisartan 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 telmisartan is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

Diabetic patients treated with insulin or antidiabetics

In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

Hyperkalaemia

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

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

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

The main risk factors for hyperkalaemia to be considered are:
- Diabetes mellitus, renal impairment, age (>70 years).
- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor blockers, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.
- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extend trauma).

Close monitoring of serum potassium in at risk patients is recommended (see section 4.5).

Sorbitol

40 mg tablets: This medicine contains 149.8 mg sorbitol in each tablet.
80 mg tablets: This medicine contains 299.7 mg sorbitol in each tablet.

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 with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Lactose

Tolura tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Tolura.

Sodium

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

Ethnic differences

As observed for angiotensin converting enzyme inhibitors, telmisartan and the other angiotensin II receptor blockers are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Ischaemic heart disease

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.

Intestinal angioedema

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

4.5 Interaction with other medicinal products and other forms of interaction

Digoxin

When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia (see section 4.4). The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor blockers, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).

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

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements

Angiotensin II receptor blockers such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor blockers, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor blockers.
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 blockers 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.

Diuretics (thiazide or loop diuretics)

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

To be taken into account with concomitant use

Other antihypertensive agents

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

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

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

Corticosteroids (systemic route)

Reduction of the antihypertensive effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of angiotensin II receptor blockers is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II receptor blockers 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 Tolura 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 blockers, similar risks may exist for this class of drugs. Unless continued angiotensin II receptor blocker 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 blockers should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor blocker 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 blockers 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 blockers should be closely observed for hypotension (see sections 4.3 and 4.4).

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machinery it should be taken into account that syncope or vertigo may occasionally occur when taking antihypertensive therapy such as Tolura.

4.8 Undesirable effects

Summary of the safety profile

Serious adverse drug reactions include anaphylactic reaction and angioedema which may occur rarely (≥1/10,000 to <1/1,000), and acute renal failure.

The overall incidence of adverse reactions reported with telmisartan was usually comparable to placebo (41.4 % vs 43.9 %) in controlled trials in patients treated for hypertension. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients. The safety profile of telmisartan in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

The adverse reactions listed below have been accumulated from controlled clinical trials in patients treated for hypertension and from post-marketing reports. The listing also takes into account serious adverse reactions and adverse reactions leading to discontinuation reported in three clinical long-term studies including 21642 patients treated with telmisartan for the reduction of cardiovascular morbidity for up to six years.

Tabulated list of adverse reactions

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

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

Infections and infestations

Uncommon:	Urinary tract infection, cystitis, upper respiratory tract infection including pharyngitis and sinusitis
Rare:	Sepsis including fatal outcome[1]

Blood and lymphatic system disorders

Uncommon:	Anaemia
Rare:	Eosinophilia, thrombocytopenia

Immune system disorders

Rare:	Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders

Uncommon:	Hyperkalaemia
Rare:	Hypoglycaemia (in diabetic patients), hyponatraemia

Psychiatric disorders

Uncommon:	Insomnia, depression
Rare:	Anxiety

Nervous system disorders

Uncommon:	Syncope
Rare:	Somnolence

Eye disorders

Rare:	Visual impairment

Ear and labyrinth disorders

Uncommon:	Vertigo

Cardiac disorders

Uncommon:	Bradycardia
Rare:	Tachycardia

Vascular disorders

Uncommon:	Hypotension[2], orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon:	Dyspnoea, cough
Very rare:	Interstitial lung disease[4]

Gastrointestinal disorders

Uncommon:	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting
Rare:	Dry mouth, abdominal discomfort, dysgeusia

Hepato-biliary disorders

Rare:	Hepatic function abnormal/liver disorder[3]

Skin and subcutaneous tissue disorders

	Uncommon:	Pruritus, hyperhidrosis, rash
	Rare:	Angioedema (including fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption

Muscoloskeletal and connective tissue disorders

Uncommon:	Back pain (e.g. sciatica), muscle spasms, myalgia,
Rare:	Arthralgia, pain in extremity, tendon pain (tendonitis like symptoms)

Renal and urinary disorders

Uncommon:	Renal impairment (including acute kidney injury)

General disorders and administration site conditions

Uncommon:	Chest pain, asthenia (weakness)
Rare:	Influenza-like illness

Investigations

Uncommon:	Blood creatinine increased
Rare:	Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

1, 2, 3, 4: for further description, please see sub-section *"Description of selected adverse reactions"*

Description of selected 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 also section 5.1).

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

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

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.

Intestinal angioedema
Cases of intestinal angioedema have been reported after the use of angiotensin II receptor blockers (see section 4.4).

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 with regard to overdose in humans.

Symptoms

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

Management

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II receptor blockers (ARBs), plain, ATC code: C09CA07.

Mechanism of action

Telmisartan is an orally active and specific angiotensin II receptor (type AT_1) blocker. 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.

In human, an 80 mg dose of telmisartan 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.

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 to 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 trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies. There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure (SBP). In this respect data concerning diastolic blood pressure (DBP) are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The contribution of the medicinal product's diuretic and natriuretic effect to its hypotensive activity has still to be defined. 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 (**ON**going **T**elmisartan **A**lone and in Combination with **R**amipril **G**lobal **E**ndpoint **T**rial) 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 **H**eart **O**utcomes **P**revention **E**valuation 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. For more detailed information see above under the heading "Cardiovascular prevention".
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.

Paediatric population

The safety and efficacy of telmisartan in children and adolescents aged below 18 years have not been established.

The blood pressure lowering effects of two doses of telmisartan were assessed in 76 hypertensive, largely overweight patients aged 6 to < 18 years (body weight ≥ 20 kg and ≤ 120 kg, mean 74.6 kg), after taking telmisartan 1 mg/kg (n = 29 treated) or 2 mg/kg (n = 31 treated) over a four-week treatment period. By inclusion the presence of secondary hypertension was not investigated. In some of the investigated patients the doses used were higher than those recommended in the treatment of hypertension in the adult population, reaching a daily dose comparable to160 mg, which was tested in adults. After adjustment for age group effects mean SBP changes from baseline (primary objective) were -14.5 (1.7) mmHg in the telmisartan 2 mg/kg group, -9.7 (1.7) mmHg in the telmisartan 1 mg/kg group, and -6.0 (2.4) in the placebo group. The adjusted DBP changes from baseline were -8.4 (1.5) mmHg, -4.5 (1.6) mmHg and -3.5 (2.1) mmHg respectively. The change was dose dependent. The safety data from this study in patients aged 6 to < 18 years appeared generally similar to that observed in adults. The safety of long term treatment of telmisartan in children and adolescents was not evaluated.

An increase in eosinophils reported in this patient population has not been recorded in adults. Its clinical significance and relevance is unknown.

These clinical data do not allow to make conclusions on the efficacy and safety of telmisartan in hypertensive paediatric population.

5.2 Pharmacokinetic properties

Absorption
Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately

6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Linearity/non-linearity
The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. C_{max} and to a lesser extent AUC increase disproportionately at doses above 40 mg.

Distribution
Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{dss}) is approximately 500 l.

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

Elimination
Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cl_{tot}) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Paediatric population
The pharmacokinetics of two doses of telmisartan were assessed as a secondary objective in hypertensive patients (n = 57) aged 6 to < 18 years after taking telmisartan 1 mg/kg or 2 mg/kg over a four-week treatment period. Pharmacokinetic objectives included the determination of the steady-state of telmisartan in children and adolescents, and investigation of age-related differences. Although the study was too small for a meaningful assessment of the pharmacokinetics of children under 12 years of age, the results are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for C_{max}.

Gender
Differences in plasma concentrations were observed, with C_{max} and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.

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

Renal impairment
In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient patients and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

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

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

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

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

No effects of telmisartan on male or female fertility were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone (K30)
Meglumine
Sodium hydroxide
Lactose monohydrate
Sorbitol (E420)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

OPA/Al/PVC Al blister. Each blister contains 7 or 10 tablets.

Pack sizes: 14, 28, 30, 56, 84, 90, 98 and 100 tablets 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)

Tolura 40 mg tablets
14 tablets: EU/1/10/632/008
28 tablets: EU/1/10/632/009
30 tablets: EU/1/10/632/010
56 tablets: EU/1/10/632/011
84 tablets: EU/1/10/632/012
90 tablets: EU/1/10/632/013
98 tablets: EU/1/10/632/014
100 tablets: EU/1/10/632/023

Tolura 80 mg tablets
14 tablets: EU/1/10/632/015
28 tablets: EU/1/10/632/016
30 tablets: EU/1/10/632/017
56 tablets: EU/1/10/632/018
84 tablets: EU/1/10/632/019
90 tablets: EU/1/10/632/020
98 tablets: EU/1/10/632/021
100 tablets: EU/1/10/632/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 June 2010
Date of latest renewal: 19 March 2015

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 AUTHORIZATION

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 manufacturers responsible for batch release

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

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

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 AUTHORIZATION

- **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)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON/BOX

1. NAME OF THE MEDICINAL PRODUCT

Tolura 40 mg tablets

telmisartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg telmisartan.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate and sorbitol (E420). Read the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

tablet

14 tablets
28 tablets
30 tablets
56 tablets
84 tablets
90 tablets
98 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before 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

Do not store above 30°C.
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)

14 tablets: EU/1/10/632/008
28 tablets: EU/1/10/632/009
30 tablets: EU/1/10/632/010
56 tablets: EU/1/10/632/011
84 tablets: EU/1/10/632/012
90 tablets: EU/1/10/632/013
98 tablets: EU/1/10/632/014
100 tablets: EU/1/10/632/023

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tolura 40 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

BLISTER/OPA/Al/PVC Al

1. NAME OF THE MEDICINAL PRODUCT

Tolura 40 mg tablets

telmisartan

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

CARTON/BOX

1. NAME OF THE MEDICINAL PRODUCT

Tolura 80 mg tablets

telmisartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg telmisartan.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate and sorbitol (E420). Read the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

tablet

14 tablets
28 tablets
30 tablets
56 tablets
84 tablets
90 tablets
98 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before 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

Do not store above 30°C.
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)

14 tablets: EU/1/10/632/015
28 tablets: EU/1/10/632/016
30 tablets: EU/1/10/632/017
56 tablets: EU/1/10/632/018
84 tablets: EU/1/10/632/019
90 tablets: EU/1/10/632/020
98 tablets: EU/1/10/632/021
100 tablets: EU/1/10/632/024

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tolura 80 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

BLISTER/OPA/Al/PVC Al

1. NAME OF THE MEDICINAL PRODUCT

Tolura 80 mg tablets

telmisartan

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 user

Tolura 40 mg tablets
telmisartan

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 Tolura is and what it is used for
2. What you need to know before you take Tolura
3. How to take Tolura
4. Possible side effects
5. How to store Tolura
6. Contents of the pack and other information

1. What Tolura is and what it is used for

Tolura belongs to a class of medicines known as angiotensin II receptor blockers. Angiotensin II is a substance produced in your body which causes your blood vessels to narrow, thus increasing your blood pressure. Tolura blocks the effect of angiotensin II so that the blood vessels relax, and your blood pressure is lowered.

Tolura is used to treat essential hypertension (high blood pressure) in adults. 'Essential' means that the high blood pressure is not caused by any other condition.

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.

Tolura is also used to reduce cardiovascular events (i.e. heart attack or stroke) in adults who are at risk because they have a reduced or blocked blood supply to the heart or legs, or have had a stroke or have high risk diabetes. Your doctor can tell you if you are at high risk for such events.

2. What you need to know before you take Tolura

Do not take Tolura
- if you are allergic to telmisartan or any other ingredients of this medicine (listed in section 6).
- if you are more than 3 months pregnant. (It is also better to avoid Tolura in early pregnancy – see pregnancy section.)
- if you have severe liver problems such as cholestasis or biliary obstruction (problems with the drainage of the bile from the liver and gall bladder) or any other severe liver disease.
- 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 Tolura.

Warnings and precautions

Talk to your doctor before taking Tolura if you are suffering or have ever suffered from any of the following conditions or illnesses:

- Kidney disease or kidney transplant.
- Renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- Liver disease.
- Heart trouble.
- Raised aldosterone levels (water and salt retention in the body along with imbalance of various blood minerals).
- Low blood pressure (hypotension), likely to occur if you are dehydrated (excessive loss of body water) or have salt deficiency due to e.g. diuretic therapy ('water tablets'), low-salt diet, diarrhoea, or vomiting.
- Elevated potassium levels in your blood.
- Diabetes.

Talk to your doctor before taking Tolura:
- if you are taking digoxin.
- if you are taking 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.

  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 Tolura”.

Talk to your doctor if you experience abdominal pain, nausea, vomiting or diarrhoea after taking Tolura. Your doctor will decide on further treatment. Do not stop taking Tolura on your own.

You must tell your doctor if you think you are (or might become) pregnant. Tolura 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).

In case of surgery or anaesthesia, you should tell your doctor that you are taking Tolura.

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

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

Other medicines and Tolura
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 medicines 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 Tolura:

- Lithium containing medicines to treat some types of depression.
- Medicines that may increase blood potassium levels such as salt substitutes containing potassium, potassium-sparing diuretics (certain 'water tablets'), ACE inhibitors, angiotensin II receptor blockers, NSAIDs (non steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen), heparin, immunosuppressives (e.g. cyclosporin or tacrolimus), and the antibiotic trimethoprim.
- Diuretics ('water tablets'), especially if taken in high doses together with Tolura, may lead to excessive loss of body water and low blood pressure (hypotension).
- If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not take Tolura” and “Warnings and precautions”).
- Digoxin.

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

Tolura 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 Tolura.

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 Tolura before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Tolura. Tolura is not recommended in early 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. Tolura is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
Some people may experience side effects such as fainting or a feeling of spinning (vertigo) when taking Tolura. If you experience these side effects, do not drive or operate machinery.

Tolura contains lactose, sorbitol (E420) 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.

This medicine contains 149.8 mg sorbitol in each tablet. Sorbitol is a source of fructose. If your doctor has told you that you 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 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 Tolura

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

The recommended dose of Tolura is one tablet a day. Try to take the tablet at the same time each day. You can take Tolura with or without food. The tablets should be swallowed whole with some water or other non-alcoholic drink. It is important that you take Tolura every day until your doctor tells you otherwise. If you have the impression that the effect of Tolura is too strong or too weak, talk to your doctor or pharmacist.

For treatment of high blood pressure, the usual dose of Tolura for most patients is one 40 mg tablet once a day to control blood pressure over the 24 hour period. However, sometimes your doctor may recommend a lower dose of 20 mg or a higher dose of 80 mg. Tolura tablets cannot be divided, therefore they are not suitable for patients who require a dose of 20 mg of telmisartan. For these patients, an equivalent product with the same active ingredient is available. Tolura may also be used in combination with diuretics ('water tablets') such as hydrochlorothiazide which has been shown to have

an additive blood pressure lowering effect with Tolura.

For reduction of cardiovascular events, the usual dose of Tolura is one 80 mg tablet once a day. At the beginning of the preventive therapy with Tolura 80 mg, blood pressure should be frequently monitored.

If your liver is not working properly, the usual dose should not exceed 40 mg once daily.

If you take more Tolura than you should
If you accidentally take too many tablets, contact your doctor, pharmacist, or your nearest hospital emergency department immediately.

If you forget to take Tolura
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 any 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); these side effects are rare (may affect up to 1 in 1,000 people) 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.

Possible side effects of Tolura:

Common side effects (may affect up to 1 in 10 people):
Low blood pressure (hypotension) in users treated for reduction of cardiovascular events.

Uncommon side effects (may affect up to 1 in 100 people):
Urinary tract infections, upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), deficiency in red blood cells (anaemia), high potassium levels, difficulty falling asleep, feeling sad (depression), fainting (syncope), feeling of spinning (vertigo), slow heart rate (bradycardia), low blood pressure (hypotension) in users treated for high blood pressure, dizziness on standing up (orthostatic hypotension), shortness of breath, cough, abdominal pain, diarrhoea, pain in the belly, bloating, vomiting, itching, increased sweating, drug rash, back pain, muscle cramps, muscle pain (myalgia), kidney impairment (including acute kidney failure), pain in the chest, feeling of weakness, and increased level of creatinine in the blood.

Rare side effects (may affect up to 1 in 1,000 people):
Sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatory response which can lead to death), increase in certain white blood cells (eosinophilia), low platelet count (thrombocytopenia), severe allergic reaction (anaphylactic reaction), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), low blood sugar levels (in diabetic patients), feeling anxious, somnolence, impaired vision, fast heart beat (tachycardia), dry mouth, discomfort in the belly, taste disturbance (dysgeusia), abnormal liver function (Japanese patients are more likely to experience this side effect), rapid swelling of the skin and mucosa which can also lead to death (angioedema including fatal outcome), eczema (a skin

disorder), redness of skin, hives (urticaria), severe drug rash, joint pain (arthralgia), pain in extremity, tendon pain, flu-like-illness, decreased haemoglobin (a blood protein), increased levels of uric acid, increased hepatic enzymes or creatine phosphokinase in the blood, low levels of sodium.

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

Not known (frequency cannot be estimated from the available data):
Intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting, and diarrhoea has been reported after the use of similar products.

* 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.

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 Tolura

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.

Do not store above 30°C.
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 Tolura contains
- The active substance is telmisartan. Each tablet contains 40 mg telmisartan.

The other ingredients are povidone (K30), meglumine, sodium hydroxide, lactose monohydrate, sorbitol (E420) and magnesium stearate. See section 2: "Tolura contains lactose, sorbitol (E420) and sodium."

What Tolura looks like and contents of the pack
Tolura 40 mg tablets are white to almost white, biconvex, oval tablets.

Tolura is available in blister packs containing 14, 28, 30, 56, 84, 90, 98 and 100 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

Manufacturers
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
KRKA-POLSKA Sp. z o.o., ul. Równoległa 5, 02-235 Warszawa, Poland

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
KRKA Belgium, SA.
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Deutschland
TAD Pharma GmbH
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Eesti
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This leaflet was last revised in

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

Package leaflet: Information for the user

Tolura 80 mg tablets
telmisartan

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 Tolura is and what it is used for
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1. What Tolura is and what it is used for

Tolura belongs to a class of medicines known as angiotensin II receptor blockers. Angiotensin II is a substance produced in your body which causes your blood vessels to narrow, thus increasing your blood pressure. Tolura blocks the effect of angiotensin II so that the blood vessels relax, and your blood pressure is lowered.

Tolura is used to treat essential hypertension (high blood pressure) in adults. 'Essential' means that the high blood pressure is not caused by any other condition.

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.

Tolura is also used to reduce cardiovascular events (i.e. heart attack or stroke) in adults who are at risk because they have a reduced or blocked blood supply to the heart or legs, or have had a stroke or have high risk diabetes. Your doctor can tell you if you are at high risk for such events.

2. What you need to know before you take Tolura

Do not take Tolura
- if you are allergic to telmisartan or any other ingredients of this medicine (listed in section 6).
- if you are more than 3 months pregnant. (It is also better to avoid Tolura in early pregnancy – see pregnancy section.)
- if you have severe liver problems such as cholestasis or biliary obstruction (problems with the drainage of the bile from the liver and gall bladder) or any other severe liver disease.
- 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 Tolura.

Warnings and precautions

Talk to your doctor before taking Tolura if you are suffering or have ever suffered from any of the following conditions or illnesses:

- Kidney disease or kidney transplant.
- Renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- Liver disease.
- Heart trouble.
- Raised aldosterone levels (water and salt retention in the body along with imbalance of various blood minerals).
- Low blood pressure (hypotension), likely to occur if you are dehydrated (excessive loss of body water) or have salt deficiency due to e.g. diuretic therapy ('water tablets'), low-salt diet, diarrhoea, or vomiting.
- Elevated potassium levels in your blood.
- Diabetes.

Talk to your doctor before taking Tolura:
- if you are taking digoxin.
- if you are taking 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.

  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 Tolura”.

Talk to your doctor if you experience abdominal pain, nausea, vomiting or diarrhoea after taking Tolura. Your doctor will decide on further treatment. Do not stop taking Tolura on your own.

You must tell your doctor if you think you are (or might become) pregnant. Tolura 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).

In case of surgery or anaesthesia, you should tell your doctor that you are taking Tolura.

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

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

Other medicines and Tolura
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 medicines 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 Tolura:

- Lithium containing medicines to treat some types of depression.
- Medicines that may increase blood potassium levels such as salt substitutes containing potassium, potassium-sparing diuretics (certain 'water tablets'), ACE inhibitors, angiotensin II receptor blockers, NSAIDs (non steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen), heparin, immunosuppressives (e.g. cyclosporin or tacrolimus), and the antibiotic trimethoprim.
- Diuretics ('water tablets'), especially if taken in high doses together with Tolura, may lead to excessive loss of body water and low blood pressure (hypotension).
- If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not take Tolura” and “Warnings and precautions”).
- Digoxin.

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

Tolura 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 Tolura.

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 Tolura before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Tolura. Tolura is not recommended in early 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. Tolura is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
Some people may experience side effects such as fainting or a feeling of spinning (vertigo) when taking Tolura. If you experience these side effects, do not drive or operate machinery.

Tolura contains lactose, sorbitol (E420) 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.

This medicine contains 299.7 mg sorbitol in each tablet.
Sorbitol is a source of fructose. If your doctor has told you that you 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 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 Tolura

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

The recommended dose of Tolura is one tablet a day. Try to take the tablet at the same time each day. You can take Tolura with or without food. The tablets should be swallowed whole with some water or other non-alcoholic drink. It is important that you take Tolura every day until your doctor tells you otherwise. If you have the impression that the effect of Tolura is too strong or too weak, talk to your doctor or pharmacist.

For treatment of high blood pressure, the usual dose of Tolura for most patients is one 40 mg tablet once a day to control blood pressure over the 24 hour period. However, sometimes your doctor may recommend a lower dose of 20 mg or a higher dose of 80 mg. Tolura tablets cannot be divided, therefore they are not suitable for patients who require a dose of 20 mg of telmisartan. For these patients, an equivalent product with the same active ingredient is available. Tolura may also be used in

combination with diuretics ('water tablets') such as hydrochlorothiazide which has been shown to have an additive blood pressure lowering effect with Tolura.

For reduction of cardiovascular events, the usual dose of Tolura is one 80 mg tablet once a day. At the beginning of the preventive therapy with Tolura 80 mg, blood pressure should be frequently monitored.

If your liver is not working properly, the usual dose should not exceed 40 mg once daily.

If you take more Tolura than you should
If you accidentally take too many tablets, contact your doctor, pharmacist, or your nearest hospital emergency department immediately.

If you forget to take Tolura
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 any 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); these side effects are rare (may affect up to 1 in 1,000 people) 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.

Possible side effects of Tolura:

Common side effects (may affect up to 1 in 10 people):
Low blood pressure (hypotension) in users treated for reduction of cardiovascular events.

Uncommon side effects (may affect up to 1 in 100 people):
Urinary tract infections, upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), deficiency in red blood cells (anaemia), high potassium levels, difficulty falling asleep, feeling sad (depression), fainting (syncope), feeling of spinning (vertigo), slow heart rate (bradycardia), low blood pressure (hypotension) in users treated for high blood pressure, dizziness on standing up (orthostatic hypotension), shortness of breath, cough, abdominal pain, diarrhoea, pain in the belly, bloating, vomiting, itching, increased sweating, drug rash, back pain, muscle cramps, muscle pain (myalgia), kidney impairment (including acute kidney failure), pain in the chest, feeling of weakness, and increased level of creatinine in the blood.

Rare side effects (may affect up to 1 in 1,000 people):
Sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatory response which can lead to death), increase in certain white blood cells (eosinophilia), low platelet count (thrombocytopenia), severe allergic reaction (anaphylactic reaction), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), low blood sugar levels (in diabetic patients), feeling anxious, somnolence, impaired vision, fast heart beat (tachycardia), dry mouth, discomfort in the belly, taste disturbance (dysgeusia), abnormal liver function (Japanese patients are more likely to experience this side effect), rapid swelling of the skin

and mucosa which can also lead to death (angioedema including fatal outcome), eczema (a skin disorder), redness of skin, hives (urticaria), severe drug rash, joint pain (arthralgia), pain in extremity, tendon pain, flu-like-illness, decreased haemoglobin (a blood protein), increased levels of uric acid, increased hepatic enzymes or creatine phosphokinase in the blood, low levels of sodium.

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

Not known (frequency cannot be estimated from the available data):
Intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting, and diarrhoea has been reported after the use of similar products.

*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.

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 Tolura

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.

Do not store above 30°C.
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 Tolura contains
- The active substance is telmisartan. Each tablet contains 80 mg telmisartan.

The other ingredients are povidone (K30), meglumine, sodium hydroxide, lactose monohydrate, sorbitol (E420) and magnesium stearate. See section 2: “Tolura contains lactose,sorbitol (E420) and sodium.”

What Tolura looks like and contents of the pack
Tolura 80 mg tablets are white to almost white, biconvex, capsule shape tablets.

Tolura is available in blister packs containing 14, 28, 30, 56, 84, 90, 98 and 100 tablets.
Not all pack sizes may be marketed.

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