Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Telmisartan/Hydrochlorothiazide Rowa 40 mg/12.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg telmisartan and 12.5 mg hydrochlorothiazide.

Excipients with known effect:
Each tablet contains 49.8 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Diameter 9.25 mm approximately. Round bilayer tablet with white and yellow colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.
Telmisartan/Hydrochlorothiazide Rowa fixed dose combination (40 mg telmisartan/12.5 mg hydrochlorothiazide (HCTZ)) is indicated in adults whose blood pressure is not adequately controlled on telmisartan alone.

4.2 Posology and method of administration

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

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

Elderly
No dose adjustment is necessary for elderly patients.

Renal impairment
Experience in patients with mild to moderate renal impairment is modest but has not suggested adverse renal effects and dose adjustment is not considered necessary. Periodic monitoring of renal function is advised (see section 4.4). Due to the hydrochlorothiazide component, the fixed dose combination is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see section 4.3).
Telmisartan is not removed from blood by haemofiltration and is not dialysable

Hepatic impairment
In patients with mild to moderate hepatic impairment Telmisartan/Hydrochlorothiazide Rowa should be administered with caution. For telmisartan, the posology should not exceed 40 mg once daily. The fixed dose combination is contraindicated in patients with severe hepatic impairment (see section 4.3).. Thiazides should be used with caution in patients with impaired hepatic function (see section 4.4).

Paediatric population
The safety and efficacy of the fixed dose combination has not been established in patients aged below 18 years. Use of Telmisartan/Hydrochlorothiazide Rowa is not recommended in children and adolescents.

Method of administration
<invented name> tablets are for once-daily oral administration and should be swallowed whole with liquid. Telmisartan/Hydrochlorothiazide Rowa can be taken with or without food.

Precautions to be taken before handling or administering the medicinal product
Telmisartan/Hydrochlorothiazide Rowa 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).

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 HCTZ 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, anuria).
- Refractory hypokalaemia, hypercalcaemia.

The concomitant use of telmisartan/HCTZ 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

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
Telmisartan/HCTZ must not be given to patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency (see section 4.3) since telmisartan is mostly eliminated in the bile. These patients can be expected to have reduced hepatic clearance for telmisartan.

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

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

Renal impairment and kidney transplantation
Telmisartan/HCTZ 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 telmisartan/HCTZ in patients with recent kidney transplantation. Experience with telmisartan/HCTZ 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 diureticassociated azotaemia may occur in patients with impaired renal function.
Telmisartan is not removed from blood by haemofiltration and is not dialysable.

Volume and/or sodium depleted patients
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, especially volume and/or sodium depletion, should be corrected before the administration of telmisartan/HCTZ.

Isolated cases of hyponatraemia accompanied by neurological symptoms (nausea, progressive disorientation, apathy) have been observed with the use of HCTZ.

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 telmisartan/HCTZ 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 the medicinal product, 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 the medicinal product, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with telmisartan/HCTZ, risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes should be co-administered cautiously with telmisartan/HCTZ (see section 4.5).

Hypochloraemic alkalosis
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).

Ethnic differences

As with all other angiotensin II receptor blockers, 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.

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.

General

Hypersensitivity reactions to HCTZ 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 HCTZ.

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 re-administration 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 drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

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 (see section 4.8)..

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, Telmisartan/Hydrochlorothiazide Rowa should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Intestinal angioedema

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

Excipients:

Lactose

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

Sodium

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

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 blockers (including telmisartan/HCTZ). Co-administration of lithium and telmisartan/HCTZ 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 HCTZ-telmisartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of HCTZ on serum potassium (see section 4.4).

Iodinatedcontrastproducts:
In the event of dehydration caused by diuretics, there is an increased risk of acute functional renal failure, particularly during use of high doses of iodinated contrast products. Rehydration before administration of the iodinated product is required.

Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporin or other medicinal products such as heparin sodium).
If these medicinal products are to be prescribed with the HCTZ-telmisartan combination, monitoring of potassium plasma levels is advised. Based on the experience with the use of other medicinal products that blunt the reninangiotensin 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 telmisartan/HCTZ is administered with these 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 antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- class III antiarrhythmics (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 HCTZ.

Cholestyramine and colestipol resins:
Absorption of HCTZ is impaired in the presence of anionic exchange resins.

Non-steroidal anti-inflammatory medicinal products
NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dose 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 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 AUC0-24 and Cmax 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 HCTZ.

Medicinal products used in the treatment for gout (e.g. probenecid, sulfinpyrazone and allopurinol)
Dose adjustment of uricosuric medications may be necessary as HCTZ may raise the level of serum uric acid. Increase in dose of probenecid or sulfinpyrazone may be necessary. Coadministration 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 dose adjusted accordingly.

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

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

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

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of angiotensinII receptor antagonists is not recommended during the first trimester ofpregnancy (see section 4.4). The use of angiotensin II receptor antagonists iscontraindicated during the second and third trimesters of pregnancy (see sections4.3 and 4.4).

There are no adequate data from the use of telmisartan/HCTZ 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 foetotoxicity (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).

There is limited experience with HCTZ during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of HCTZ 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

Breastfeeding

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

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of telmisartan/HCTZ during breast-feeding is not recommended. If telmisartan/HCTZ is used during breast-feeding, doses should be kept as low as possible.

Fertility

No studies on fertility in humans with the fixed dose combination or with the individual components have been performed. In preclinical studies, no effects of telmisartan and HCTZ on male and female fertility were observed.

4.7 Effects on ability to drive and use machines

Telmisartan/Hydrochlorothiazide Rowa can have influence on the ability to drive and use machines. Dizziness, syncope or vertigo may occasionally occur when taking antihypertensive therapy such as telmisartan/HCTZ.

If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery.

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 telmisartan/HCTZ was comparable to those reported with telmisartan alone in randomised controlled trials involving 1471 patients randomised to receive telmisartan plus HCTZ (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 HCTZ than with placebo are shown below according to system organ class. Adverse reactions known to occur with each component given singly but which have not been seen in clinical trials may occur during treatment with telmisartan/HCTZ.
Adverse reactions previously reported with one of the individual components may be potential adverse reactions with Telmisartan/Hydrochlorothiazide Rowa even if not observed in clinical trials

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.

Table 1: Tabulated list of adverse reactions (MedDRA) from placebo-controlled studies and from post-marketing experience

MedDRASystem Organ Class	**AdverseReactions**	**Frequency**		
		Telmisartan/Hydrochlorothiazide Rowa	**Telmisartan[a]**	**Hydrochlorothiazide**
Infectionsand infestations	Sepsis including fatal outcome		rare[2]	
	Bronchitis	rare		
	Pharyngitis	rare		
	Sinusitis	rare		
	Upper respiratory tract infection		uncommon	
	Urinary tract infection		uncommon	
	Cystitis		uncommon	
Neoplasms benign, malignant and unspecified(incl. cystsandpolyps)	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)			not known[2]
Blood and lymphaticsystem disorders	Anaemia		uncommon	
	Eosinophilia		rare	
	Thrombocytopenia		rare	rare
	Thrombocytopenic purpura			rare
	Aplastic anaemia			not known
	Haemolytic anaemia			very rare
	Bone marrow failure			very rare
	Leukopenia			very rare
	Agranulocytosis			very rare
Immunesystem disorders	Anaphylactic reaction,		rare	
	Hypersensitivity		rare	very rare
Metabolismand nutrition	Hypokalaemia	uncommon		very common

disorders				
	Hyperuricaemia	rare		common
	Hyponatraemia	rare	rare	common
	Hyperkalaemia		uncommon	
	Hypoglycaemia (in diabetic patients)		rare	
	Hypomagnesaemia			common
	Hypercalcaemia			rare
	Alkalosis hypochloraemic			very rare
	Decreased appetite			common
	Hyperlipidaemia			very common
	Hyperglycaemia			rare
	Diabetes mellitus inadequate control			rare
Psychiatric disorders	Anxiety	uncommon	rare	
	Depression	rare	uncommon	rare
	Insomnia	rare	uncommon	
	Sleep disorders	rare		rare
Nervoussystem disorders	Dizziness	common		rare
	Syncope	uncommon	uncommon	
	Paraesthesia	uncommon		rare
	Somnolence		rare	
	Headache			rare
Eyedisorders	Visual impairment	rare	rare	rare
	Vision blurred	rare		
	Acute angle closure glaucoma			not known
	Choroidal effusion			not known
Ear and labyrinth disorders	Vertigo	uncommon	uncommon	
Cardiac disorders	Tachycardia	uncommon	rare	
	Arrhythmias	uncommon		rare
	Bradycardia		uncommon	
Vascular disorders	Hypotension	uncommon	uncommon	
	Orthostatic hypotension	uncommon	uncommon	common
	Vasculitis necrotising			very rare
Respiratory, thoracicand mediastinal disorders	Dyspnoea	uncommon	uncommon	
	Respiratory distress	rare		very rare
	Pneumonitis	rare		very rare
	Pulmonary oedema	rare		very rare
	Cough		uncommon	
	Interstitial lung disease		very rare[1,2]	
	Acute respiratory distress syndrome (ARDS) (see section 4.4)			very rare
Gastrointestinal disorders	Diarrhoea	uncommon	uncommon	common
	Dry mouth	uncommon	rare	

	Flatulence	uncommon	uncommon	
	Abdominal pain	rare	uncommon	
	Constipation	rare		rare
	Dyspepsia	rare	uncommon	
	Vomiting	rare	uncommon	common
	Gastritis	rare		
	Abdominal discomfort		rare	rare
	Nausea			common
	Pancreatitis			very rare
Hepatobiliary disorders	Abnormal hepatic function/liver disorder	rare[2]	rare[2]	
	Jaundice			rare
	Cholestasis			rare
Skin and subcutaneous tissuedisorders	Angioedema (including fatal outcome)	rare	rare	
	Erythema	rare	rare	
	Pruritus	rare	uncommon	
	Rash	rare	uncommon	common
	Hyperhidrosis	rare	uncommon	
	Urticaria	rare	rare	common
	Eczema		rare	
	Drug eruption		rare	
	Toxic skin eruption		rare	
	Lupus-like syndrome			very rare
	Photosensitivity reaction			rare
	Toxic epidermal necrolysis			very rare
	Erythema multiforme			not known
Muscoloskeletal, connectivetissue and bone disorders	Back pain	uncommon	uncommon	
	Muscle spasms (cramps in leg)	uncommon	uncommon	not known
	Myalgia	uncommon	uncommon	
	Arthralgia	rare	rare	
	Pain in extremity (leg pain)	rare	rare	
	Tendon pain (tendonitis-like symptoms)		rare	
	Systemic lupus erythematosus	rare[1]		very rare
Renal and urinarydisorders	Renal impairment		uncommon	not known
	Acute renal failure		uncommon	uncommon
	Glucosuria			rare
Reproductive system and breastdisorders	Erectile dysfunction	uncommon		common
General disorders and administration site conditions	Chest pain	uncommon	uncommon	

	Influenza-like illness	rare	rare	
	Pain	rare		
	Asthenia (weakness)		uncommon	not known
	Pyrexia			not known
Investigations	Blood uric acid increased	uncommon	rare	
	Blood creatinine increased	rare	uncommon	
	Blood creatine phosphokinase increased	rare	rare	
	Hepatic enzyme increased	rare	rare	
	Haemoglobin decreased		rare	

[1] Based on post-marketing experience
[2] See subsections below for additional information
[a] 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 adverse reactions listed above 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.

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).

Intestinal angioedema
Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists (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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

There is limited information available for telmisartan with regard to overdose in humans. The degree to which HCTZ 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 HCTZ is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and hypovolaemia resulting from excessive diuresis. The most common

signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Treatment
Telmisartan is not removed by haemofiltration and is not dialysable. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II receptor blockers (ARBs) and diuretics, ATC code: C09DA07

Telmisartan/Hydrochlorothiazide Rowa is a combination of an angiotensin II receptor blocker, telmisartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.
Telmisartan/Hydrochlorothiazide Rowa 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 (AT1) blocker. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 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 HCTZ 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 reninangiotensin- aldosterone system, co-administration of telmisartan tends to reverse the potassium loss associated with these diuretics. With HCTZ, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

Pharmacodynamic effects

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 mg 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.

Clinical efficacy and safety

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 25 620 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 = 8 542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8 502), 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. 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.

Epidemiological studies have shown that long-term treatment with HCTZ 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).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with telmisartan/HCTZ in all subsets of the paediatric population in hypertension (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Concomitant administration of HCTZ 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 the fixed dose combination peak concentrations of HCTZ are reached in approximately 1.0 – 3.0 hours after dosing. Based on cumulative renal excretion of HCTZ 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 64% protein bound in the plasma and its apparent volume of distribution is 0.8±0.3 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 as unchanged substance 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 (Cmax and AUC) with increasing doses.
Telmisartan does not accumulate significantly in plasma on repeated administration
Hydrochlorothiazide exhibits linear pharmacokinetics.

Pharmacokinetics in specific populations

Elderly
Pharmacokinetics of telmisartan do not differ between the elderly and younger patients.

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 dose adjustment is necessary. There was a trend towards higher plasma concentrations of HCTZ in female than in male subjects. This is not considered to be of clinical relevance.

Renal impairment
Lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment. In patients with impaired renal function the rate of HCTZ elimination is reduced. In a typical study in patients with a mean creatinine clearance of 90 ml/min the elimination half-life of HCTZ 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 HCTZ 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 blockers were: a reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit), changes of renal haemodynamics (increased blood urea nitrogen and creatinine), increased plasma renin activity, hypertrophy/hyperplasia of the juxtaglomerular cells and gastric mucosal injury. Gastric lesions could be prevented/ameliorated by oral saline supplementation and group housing of animals. In dogs renal tubular dilation and atrophy were observed. These findings are considered to be due to the pharmacological activity of telmisartan.
No effects of telmisartan on male or female fertility were observed.

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 HCTZ 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

Mannitol (E421)
Povidone K 25 (E1201)
Crospovidone (E1202)
Magnesium Stearate (E572)
Meglumine
Sodium Hydroxide (E524)
Lactose Monohydrate
Cellulose Microcrystalline (E460)
Hypromellose (Hydroxypropylmethylcellulose) (E464)
Carboxymethyl starch sodium from potato starch (Type A)
Ferric Oxide Yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 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 moisture and light.

6.5 Nature and contents of container

Telmisartan Hydrochlorothiazide tablets are packaged in Aluminium/aluminium blister packs.

Pack sizes: Blister with 7, 10, 14, 28, 28x1, 30, 30x1, 50, 56, 84, 90, 90x1, 98, 100, 112, 126, 140, 154, 168, 182, 196 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowa Pharmaceuticals Limited,
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

October 2025