ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 40 mg/5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg telmisartan and 5 mg amlodipine (as amlodipine besilate).

Excipient(s) with known effect:
Each tablet contains 168.64 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Blue and white oval shaped two layer tablets engraved with the product code 51 and the company logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults:

Add on therapy
Onduarp is indicated in adults whose blood pressure is not adequately controlled on amlodipine.

Replacement therapy
Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Onduarp containing the same component doses.

4.2 Posology and method of administration

Posology
The recommended dose of Onduarp is one tablet per day.

The maximum recommended dose is Onduarp 80 mg/10 mg, one tablet per day. Onduarp is indicated for long term treatment.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects (see section 4.5).

Add on therapy
Onduarp 40 mg/5 mg tablets may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg alone.

Individual dose titration with the components (i.e. amlodipine and telmisartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Patients treated with 10 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to Onduarp 40 mg/5 mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Replacement therapy
Patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Onduarp containing the same component doses in one tablet once daily, e.g. to enhance convenience or compliance

Special population

Elderly patients
No dose adjustment is necessary for elderly patients. Little information is available in the very elderly patients.

Patients with renal impairment
No posology adjustment is required for patients with mild to moderate renal impairment. Limited experience is available in patients with severe renal impairment or haemodialysis. Caution is advised when using Onduarp in such patients as amlodipine and telmisartan are not dialysable (see also section 4.4).

Concomitant use of telmisartan with aliskiren is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

Patients with hepatic impairment
In patients with mild to moderate hepatic impairment Onduarp should be administered with caution. For telmisartan the posology should not exceed 40 mg once daily (see section 4.4). Onduarp is contraindicated in patients with severe hepatic impairment (see section 4.3).

Paediatric population

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

Method of administration
Onduarp can be taken with or without food. It is recommended to take Onduarp with some liquid.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Biliary obstructive disorders and severe hepatic impairment
- Shock (including cardiogenic shock)
- Severe hypotension
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction

The concomitant use of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5).

4.4 Special warnings and precautions for use

Pregnancy
Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should

be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see section 4.3 and 4.6).

Hepatic impairment
Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Furthermore as with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dose recommendations have not been established. Onduarp should therefore be used with caution in these patients.

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 Onduarp is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Onduarp in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.

Intravascular hypovolaemia
Symptomatic hypotension, especially after the first dose, 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 telmisartan. If hypotension occurs with Onduarp, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Dual blockade of the renin-angiotensin-aldosterone system
The use of telmisartan in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by administering telmisartan with other blockers of the renin-angiotensin-aldosterone system) is therefore not recommended. Close monitoring of renal function is advisable if co-administration is considered necessary.

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 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.

Unstable angina pectoris, acute myocardial infarction
There are no data to support the use of Onduarp in unstable angina pectoris and during or within one month of a myocardial infarction.

Heart failure
In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see section 5.1).

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. Hyperkalaemia may be fatal 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.

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 antagonists, 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, extensive trauma).

Serum potassium should be monitored closely in these patients (see section 4.5).

Sorbitol
This medicinal product contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take Onduarp.

Other
As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiomyopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

Interactions common to the combination
No drug interaction studies have been performed.

To be taken into account with concomitant use

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

Medicinal products with blood pressure lowering potential
Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including Onduarp, e.g. baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol.

Corticosteroids (systemic route)
Reduction of the antihypertensive effect.

Interactions linked to telmisartan

Contraindicated (see section 4.3)

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
The combination of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4).

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements
Angiotensin II receptor antagonists 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 antagonists, 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 antagonists.
In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and medicinal products 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.

Ramipril
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.

Concomitant use to be taken into account

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.

Interactions linked to amlodipine

Concomitant use requiring caution

CYP3A4 inhibitors
With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively, the plasma concentration of amlodipine increased by 22 % and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

CYP3A4 inducers
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (i.e. rifampicin, *Hypericum perforatum*) may lead to a lower plasma concentration of amlodipine.

Grapefruit and grapefruit juice
Concomitant administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers did not show a significant effect on the pharmacokinetic properties of amlodipine. The concomitant use of amlodipine and grapefruit or grapefruit juice is still not recommended in patients as the bioavailability of amlodipine may increase in some and may result in increased hypotensive effects.

Concomitant use to be taken into account

Simvastatin
Co-administration of multiple doses of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77 % compared to simvastatin alone. Therefore, the dose of simvastatin in patients on amlodipine should be limited to 20 mg daily.

Others
Amlodipine has been safely administered with digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicinal products (aluminium hydroxide, magnesium hydroxide, simeticone), cimetidine, ciclosporin, antibiotics and oral hypoglycaemic medicinal products. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Onduarp in pregnant women. Animal reproductive toxicity studies with Onduarp have not been performed.

Telmisartan

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

Studies with telmisartan in animals have shown reproductive toxicity (see section 5.3).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of medicinal products. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension (see sections 4.3 and 4.4).

Amlodipine

Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery.

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

Fertility
No data from controlled clinical studies with the Fixed Dose Combination or with the individual components are available.

Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted.
In preclinical studies, no effects of telmisartan on male and female fertility were observed.
Similarly, no effects on male and female fertility were reported for amlodipine (see section 5.3).

Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been observed for calcium channel blockers in preclinical and *in vitro* studies. No clinical relevance has been established.

4.7 Effects on ability to drive and use machines

Onduarp has moderate influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as syncope, somnolence, dizziness, or vertigo during treatment (see section 4.8). Therefore, caution should be recommended when driving a car or using machines. If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions include dizziness and peripheral oedema. Serious syncope may occur rarely (less than 1 case per 1,000 patients).

The safety and tolerability of Onduarp has been evaluated in five controlled clinical studies with over 3500 patients, over 2500 of whom received telmisartan in combination with amlodipine.

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), not known (cannot be estimated from the available data).

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

System Organ Class	Common	Uncommon	Rare
Infections and infestations			cystitis
Psychiatric disorders			depression, anxiety, insomnia
Nervous system disorders	dizziness	somnolence, migraine, headache, paraesthesia	syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremor
Ear and labyrinth disorders		vertigo	
Cardiac disorders		bradycardia, palpitations	
Vascular disorders		hypotension, orthostatic hypotension, flushing	
Respiratory, thoracic and mediastinal disorders		cough	
Gastro-intestinal disorders		abdominal pain, diarrhoea, nausea	vomiting, gingival hypertrophy, dyspepsia, dry mouth
Skin and subcutaneous tissue disorders		pruritus	eczema, erythema, rash
Musculoskeletal and connective tissue disorders		arthralgia, muscle spasms (cramps in legs), myalgia	back pain, pain in extremity (leg pain)
Renal and urinary disorders			nocturia
Reproductive system, and breast disorders		erectile dysfunction	

General disorders and administration site conditions	peripheral oedema	asthenia, chest pain, fatigue, oedema	malaise
Investigations		hepatic enzymes increased	blood uric acid increased

Additional information on individual components

Adverse reactions previously reported with one of the individual components (telmisartan or amlodipine) may be potential adverse reactions with Onduarp as well, even if not observed in clinical trials or during the post-marketing period.

Telmisartan

Infections and infestations
- Uncommon: Upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis
- Rare: Sepsis including fatal outcome[1]

Blood and lymphatic system disorders
- Uncommon: Anaemia
- Rare: Thrombocytopenia, eosinophilia

Immune system disorders
- Rare: Hypersensitivity, anaphylactic reaction

Metabolism and nutrition disorders
- Uncommon: Hyperkalaemia
- Rare: Hypoglycaemia (in diabetic patients)

Eye disorders
- Rare: Visual disturbance

Cardiac disorders
- Rare: Tachycardia

Respiratory, thoracic and mediastinal disorders
- Uncommon: Dyspnoea

Gastrointestinal disorders
- Uncommon: Flatulence
- Rare: Stomach discomfort

Hepato-biliary disorders
- Rare: Hepatic function abnormal, liver disorder[2]

Skin and subcutaneous tissue disorders
- Uncommon: Hyperhidrosis
- Rare: Angioedema (with fatal outcome), drug eruption, toxic skin eruption, urticaria

Musculoskeletal and connective tissue disorders
- Rare: Tendon pain (tendinitis like symptoms)

Renal and urinary disorders
Uncommon: Renal impairment including acute renal failure

General disorders and administration site conditions
Rare: Influenza-like illness

Investigations
Uncommon: Blood creatinine increased
Rare: Blood creatine phosphokinase increased, haemoglobin decreased

[1]: the event may be a chance finding or related to a mechanism currently not known
[2]: 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.

Amlodipine

Blood and lymphatic system disorders
Very rare: Leukocytopenia, thrombocytopenia

Immune system disorders
Very rare: Hypersensitivity

Metabolism and nutrition disorders
Very rare: Hyperglycaemia

Psychiatric disorders
Uncommon: Mood change
Rare Confusion

Nervous system disorders
Very rare: Extrapyramidal syndrome

Eye disorders
Uncommon: Visual impairment

Ear and labyrinth disorders
Uncommon: Tinnitus

Cardiac disorders
Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation

Vascular disorders
Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, rhinitis

Gastrointestinal disorders
Uncommon: Change of bowel habit
Very rare: Pancreatitis, gastritis

Hepatobiliary disorders
Very rare: Hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis

Skin and subcutaneous tissue disorders

Uncommon:	Alopecia, purpura, skin discolouration, hyperhidrosis
Very rare:	Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity

Renal and urinary disorders

Uncommon:	Micturition disorder, pollakiuria

Reproductive system and breast disorders

Uncommon:	Gynaecomastia

General disorders and administration site conditions

Uncommon:	Pain

Investigations

Uncommon:	Weight increased, weight decreased

4.9 Overdose

Symptoms

Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. The most prominent manifestations of telmisartan overdose are expected to be hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

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 of both telmisartan and amlodipine.

Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly. Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and Amlodipine are not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers; ATC Code: C09DB04.

Onduarp combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.

The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Onduarp once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Telmisartan

Telmisartan is an orally active and specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse reactions.

In humans, 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.

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 substances 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.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with heart failure
Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Telmisartan/Amlodipine
In an 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study in 1461 patients with mild to severe hypertension (mean seated diastolic blood pressure ≥95 and ≤119 mmHg), treatment with each combination dose of Onduarp resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

Onduarp showed dose-related reductions in systolic/diastolic blood pressure across the therapeutic dose range of −21.8/−16.5 mmHg (40 mg/5 mg), −22.1/−18.2 mmHg (80 mg/5 mg), −24.7/−20.2 mmHg (40 mg/10 mg) and −26.4/−20.1 mmHg (80 mg/10 mg). The reduction in diastolic blood pressure <90 mmHg was achieved in 71.4 %, 74.8 %, 82.1 %, 85.3 % of patients respectively. Values are adjusted for baseline and country.

The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy. In a subset of 1050 patients with moderate to severe hypertension (DBP ≥100 mmHg) 32.7 - 51.8 % responded sufficiently to monotherapy of either telmisartan or amlodipine. The observed mean changes in systolic/diastolic blood pressure with a combination therapy containing amlodipine 5 mg (−22.2/−17.2 mmHg with 40 mg/5 mg; −22.5/−19.1 mmHg with 80 mg/5 mg) were comparable to or greater than those seen with amlodipine 10 mg (−21.0/−17.6 mmHg) and associated with significant lower oedema rates (1.4 % with 40 mg/5 mg; 0.5 % with 80 mg/5 mg; 17.6 % with amlodipine 10 mg).

Automated ambulatory blood pressure monitoring (ABPM) performed in a subset of 562 patients confirmed the results seen with in-clinic systolic and diastolic blood pressure reductions consistently over the entire 24-hours dosing period.

In a further multicentre, randomised, double-blind, active-controlled, parallel group study, a total of 1097 patients with mild to severe hypertension who were not adequately controlled on amlodipine 5 mg received Onduarp (40 mg/5 mg or 80 mg/5 mg) or amlodipine alone (5 mg or 10 mg). After 8 weeks of treatment, each of the combinations was statistically significantly superior to both amlodipine monotherapy doses in reducing systolic and diastolic blood pressures (−13.6/−9.4 mmHg, −15.0/−10.6 mmHg with 40 mg/5 mg, 80 mg/5 mg versus −6.2/−5.7 mmHg, −11.1/−8.0 mmHg with amlodipine 5 mg and 10 mg and higher diastolic blood pressure control rates compared to the respective monotherapies were achieved (56.7 %, 63.8 % with 40 mg/5 mg and 80 mg/5 mg versus 42 %, 56.7 % with amlodipine 5 mg and 10 mg). Oedema rates were significantly lower with 40 mg/5 mg and 80 mg/5 mg compared to amlodipine 10 mg (4.4 % versus 24.9 %, respectively).

In another multicentre, randomised, double-blind, active-controlled, parallel group study, a total of 947 patients with mild to severe hypertension who were not adequately controlled on amlodipine 10 mg received Onduarp (40 mg/10 mg or 80 mg/10 mg) or amlodipine alone (10 mg). After 8 weeks of treatment, each of the combination treatments was statistically significantly superior to amlodipine monotherapy in reducing diastolic and systolic blood pressure (−11.1/−9.2 mmHg, −11.3/ −9.3 mmHg with 40 mg/10 mg, 80 mg/10 mg versus −7.4/−6.5 mmHg with amlodipine 10 mg) and higher diastolic blood pressure normalisation rates compared to monotherapy were achieved (63.7 %, 66.5 % with 40 mg/10 mg, 80 mg/10 mg versus 51.1 % with amlodipine 10 mg).

In two corresponding open-label long-term follow up studies performed over a further 6 months the effect of Onduarp was maintained over the trial period. Furthermore it was shown that some patients not adequately controlled with Onduarp 40 mg/10 mg had additional blood pressure reduction by up-titration to Onduarp 80 mg/10 mg.

The overall incidence of adverse reactions with Onduarp in the clinical trial programme was low with only 12.7 % of patients on treatment experiencing adverse reactions. The most common adverse reactions were peripheral oedema and dizziness, see also section 4.8. The adverse reactions reported were in agreement with those anticipated from the safety profiles of the components telmisartan and amlodipine. No new or more severe adverse reactions were observed. The oedema related events (peripheral oedema, generalised oedema, and oedema) were consistently lower in patients who received Onduarp as compared to patients who received amlodipine 10 mg. In the factorial design trial the oedema rates were 1.3 % with Onduarp 40 mg/5 mg and 80 mg/5 mg, 8.8 % with Onduarp 40 mg/10 mg and 80 mg/10 mg and 18.4 % with Amlodipine 10 mg. In patients not controlled on amlodipine 5 mg the oedema rates were 4.4 % for 40 mg/5 mg and 80 mg/5 mg and 24.9 % for amlodipine 10 mg.

The antihypertensive effect of Onduarp was similar irrespective of age and gender, and was similar in patients with and without diabetes.

Onduarp has not been studied in any patient population other than hypertension. Telmisartan has been studied in a large outcome study in 25,620 patients with high cardiovascular risk (ONTARGET). Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

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

5.2 Pharmacokinetic properties

Pharmacokinetic of the fixed dose combination (FDC)
The rate and extent of absorption of Onduarp are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

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.

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. Amlodipine bioavailability is not affected by food ingestion.

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.

The volume of distribution of amlodipine is approximately 21 l/kg. In vitro studies have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins in hypertensive patients.

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

Amlodipine is extensively (approximatively 90 %) metabolised by the liver to inactive metabolites.

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).

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours consistent with once daily dosing. Steady-state plasma levels are reached after continuous administration for 7-8 days. Ten per cent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Linearity/non-linearity
The small reduction in AUC for telmisartan 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.

Amlodipine exhibits linear pharmacokinetics.

Special populations

Paediatric population (age below 18 years)
No pharmacokinetic data are available in the paediatric population.

Gender
Differences in plasma concentrations of telmisartan 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 in young and elderly patients.
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline with resulting increases in AUC and elimination half-life.

Renal impairment
In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations of telmisartan 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 subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with

renal impairment. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Hepatic impairment
Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability of telmisartan up to nearly 100 %. The elimination half-life of telmisartan is not changed in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40-60 % in AUC.

5.3 Preclinical safety data

Since the non-clinical toxicity profiles of telmisartan and amlodipine are not overlapping, no exacerbation of toxicity was expected for the combination. This has been confirmed in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/10 mg/kg of telmisartan and amlodipine were tested.

Preclinical data available for the components of this fixed dose combination are reported below.

Telmisartan
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 antagonists, 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 antagonists, 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 offspring 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.

Amlodipine
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
In reproductive toxicity studies in rats, delayed parturition, difficult labour and impaired fetal and pup survival were seen at high doses. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the Maximum Recommended Human Dose of 10 mg/day on an mg/m^2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Brilliant blue FCF (E 133)
Ferric oxide black (E172)
Ferric oxide yellow (E172)
Magnesium stearate
Maize starch
Meglumine
Microcrystalline cellulose

Povidone K25
Pregelatinised starch
Sodium hydroxide
Sorbitol (E420)

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 light and moisture.
Remove the tablets from the blister only directly prior to intake.

6.5 Nature and contents of container

Aluminium/aluminium blisters (PA/Al/PVC/Al) in a carton containing 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/11/729/001 (28 tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 November 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 40 mg/10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg telmisartan and 10 mg amlodipine (as amlodipine besilate).

Excipient(s) with known effect:
Each tablet contains 168.64 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Blue and white oval shaped two layer tablets engraved with the product code A2 and the company logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults:

Add on therapy
Onduarp is indicated in adults whose blood pressure is not adequately controlled on amlodipine.

Replacement therapy
Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Onduarp containing the same component doses.

4.2 Posology and method of administration

Posology
The recommended dose of Onduarp is one tablet per day.

The maximum recommended dose is Onduarp 80 mg/10 mg, one tablet per day. Onduarp is indicated for long term treatment.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects (see section 4.5).

Add on therapy
Onduarp 40 mg/10 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10 mg.

Individual dose titration with the components (i.e. amlodipine and telmisartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Patients treated with 10 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to Onduarp 40 mg/5 mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Replacement therapy
Patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Onduarp containing the same component doses in one tablet once daily, e.g. to enhance convenience or compliance

Special population

Elderly patients
No dose adjustment is necessary for elderly patients. Little information is available in the very elderly patients.

Patients with renal impairment
No posology adjustment is required for patients with mild to moderate renal impairment. Limited experience is available in patients with severe renal impairment or haemodialysis. Caution is advised when using Onduarp in such patients as amlodipine and telmisartan are not dialysable (see also section 4.4).

Concomitant use of telmisartan with aliskiren is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

Patients with hepatic impairment
In patients with mild to moderate hepatic impairment Onduarp should be administered with caution. For telmisartan the posology should not exceed 40 mg once daily (see section 4.4). Onduarp is contraindicated in patients with severe hepatic impairment (see section 4.3).

Paediatric population

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

Method of administration
Onduarp can be taken with or without food. It is recommended to take Onduarp with some liquid.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Biliary obstructive disorders and severe hepatic impairment
- Shock (including cardiogenic shock)
- Severe hypotension
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction

The concomitant use of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5).

4.4 Special warnings and precautions for use

Pregnancy
Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should

be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see section 4.3 and 4.6).

Hepatic impairment
Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Furthermore as with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dose recommendations have not been established. Onduarp should therefore be used with caution in these patients.

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 Onduarp is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Onduarp in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.

Intravascular hypovolaemia
Symptomatic hypotension, especially after the first dose, 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 telmisartan. If hypotension occurs with Onduarp, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Dual blockade of the renin-angiotensin-aldosterone system
The use of telmisartan in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by administering telmisartan with other blockers of the renin-angiotensin-aldosterone system) is therefore not recommended. Close monitoring of renal function is advisable if co-administration is considered necessary.

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 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.

Unstable angina pectoris, acute myocardial infarction
There are no data to support the use of Onduarp in unstable angina pectoris and during or within one month of a myocardial infarction.

Heart failure
In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see section 5.1).

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. Hyperkalaemia may be fatal 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.

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 antagonists, 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, extensive trauma).

Serum potassium should be monitored closely in these patients (see section 4.5).

Sorbitol
This medicinal product contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take Onduarp.

Other
As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiomyopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

Interactions common to the combination
No drug interaction studies have been performed.

To be taken into account with concomitant use

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

Medicinal products with blood pressure lowering potential
Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including Onduarp, e.g. baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol.

Corticosteroids (systemic route)
Reduction of the antihypertensive effect.

Interactions linked to telmisartan

Contraindicated (see section 4.3)

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
The combination of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4).

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements
Angiotensin II receptor antagonists 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 antagonists, 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 antagonists.
In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and medicinal products 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.

Ramipril
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.

Concomitant use to be taken into account

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.

Interactions linked to amlodipine

Concomitant use requiring caution

CYP3A4 inhibitors
With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively, the plasma concentration of amlodipine increased by 22 % and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

CYP3A4 inducers
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (i.e. rifampicin, *Hypericum perforatum*) may lead to a lower plasma concentration of amlodipine.

Grapefruit and grapefruit juice
Concomitant administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers did not show a significant effect on the pharmacokinetic properties of amlodipine. The concomitant use of amlodipine and grapefruit or grapefruit juice is still not recommended in patients as the bioavailability of amlodipine may increase in some and may result in increased hypotensive effects.

Concomitant use to be taken into account

Simvastatin
Co-administration of multiple doses of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77 % compared to simvastatin alone. Therefore, the dose of simvastatin in patients on amlodipine should be limited to 20 mg daily.

Others
Amlodipine has been safely administered with digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicinal products (aluminium hydroxide, magnesium hydroxide, simeticone), cimetidine, ciclosporin, antibiotics and oral hypoglycaemic medicinal products. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Onduarp in pregnant women. Animal reproductive toxicity studies with Onduarp have not been performed.

Telmisartan

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

Studies with telmisartan in animals have shown reproductive toxicity (see section 5.3).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of medicinal products. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension (see sections 4.3 and 4.4).

Amlodipine

Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery.

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

Fertility
No data from controlled clinical studies with the Fixed Dose Combination or with the individual components are available.

Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted.
In preclinical studies, no effects of telmisartan on male and female fertility were observed.
Similarly, no effects on male and female fertility were reported for amlodipine (see section 5.3).

Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been observed for calcium channel blockers in preclinical and *in vitro* studies. No clinical relevance has been established.

4.7 Effects on ability to drive and use machines

Onduarp has moderate influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as syncope, somnolence, dizziness, or vertigo during treatment (see section 4.8). Therefore, caution should be recommended when driving a car or using machines. If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions include dizziness and peripheral oedema. Serious syncope may occur rarely (less than 1 case per 1,000 patients).

The safety and tolerability of Onduarp has been evaluated in five controlled clinical studies with over 3500 patients, over 2500 of whom received telmisartan in combination with amlodipine.

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), not known (cannot be estimated from the available data).

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

System Organ Class	Common	Uncommon	Rare
Infections and infestations			cystitis
Psychiatric disorders			depression, anxiety, insomnia
Nervous system disorders	dizziness	somnolence, migraine, headache, paraesthesia	syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremor
Ear and labyrinth disorders		vertigo	
Cardiac disorders		bradycardia, palpitations	
Vascular disorders		hypotension, orthostatic hypotension, flushing	
Respiratory, thoracic and mediastinal disorders		cough	
Gastro-intestinal disorders		abdominal pain, diarrhoea, nausea	vomiting, gingival hypertrophy, dyspepsia, dry mouth
Skin and subcutaneous tissue disorders		pruritus	eczema, erythema, rash
Musculoskeletal and connective tissue disorders		arthralgia, muscle spasms (cramps in legs), myalgia	back pain, pain in extremity (leg pain)
Renal and urinary disorders			nocturia
Reproductive system, and breast disorders		erectile dysfunction	

General disorders and administration site conditions	peripheral oedema	asthenia, chest pain, fatigue, oedema	malaise
Investigations		hepatic enzymes increased	blood uric acid increased

Additional information on individual components

Adverse reactions previously reported with one of the individual components (telmisartan or amlodipine) may be potential adverse reactions with Onduarp as well, even if not observed in clinical trials or during the post-marketing period.

Telmisartan

Infections and infestations
- Uncommon: Upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis
- Rare: Sepsis including fatal outcome[1]

Blood and lymphatic system disorders
- Uncommon: Anaemia
- Rare: Thrombocytopenia, eosinophilia

Immune system disorders
- Rare: Hypersensitivity, anaphylactic reaction

Metabolism and nutrition disorders
- Uncommon: Hyperkalaemia
- Rare: Hypoglycaemia (in diabetic patients)

Eye disorders
- Rare: Visual disturbance

Cardiac disorders
- Rare: Tachycardia

Respiratory, thoracic and mediastinal disorders
- Uncommon: Dyspnoea

Gastrointestinal disorders
- Uncommon: Flatulence
- Rare: Stomach discomfort

Hepato-biliary disorders
- Rare: Hepatic function abnormal, liver disorder[2]

Skin and subcutaneous tissue disorders
- Uncommon: Hyperhidrosis
- Rare: Angioedema (with fatal outcome), drug eruption, toxic skin eruption, urticaria

Musculoskeletal and connective tissue disorders
- Rare: Tendon pain (tendinitis like symptoms)

Renal and urinary disorders
Uncommon: Renal impairment including acute renal failure

General disorders and administration site conditions
Rare: Influenza-like illness

Investigations
Uncommon: Blood creatinine increased
Rare: Blood creatine phosphokinase increased, haemoglobin decreased

[1]: the event may be a chance finding or related to a mechanism currently not known
[2]: 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.

Amlodipine

Blood and lymphatic system disorders
Very rare: Leukocytopenia, thrombocytopenia

Immune system disorders
Very rare: Hypersensitivity

Metabolism and nutrition disorders
Very rare: Hyperglycaemia

Psychiatric disorders
Uncommon: Mood change
Rare: Confusion

Nervous system disorders
Very rare: Extrapyramidal syndrome

Eye disorders
Uncommon: Visual impairment

Ear and labyrinth disorders
Uncommon: Tinnitus

Cardiac disorders
Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation

Vascular disorders
Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, rhinitis

Gastrointestinal disorders
Uncommon: Change of bowel habit
Very rare: Pancreatitis, gastritis

Hepatobiliary disorders
Very rare: Hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis

Skin and subcutaneous tissue disorders

Uncommon:	Alopecia, purpura, skin discolouration, hyperhidrosis
Very rare:	Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity

Renal and urinary disorders

Uncommon:	Micturition disorder, pollakiuria

Reproductive system and breast disorders

Uncommon:	Gynaecomastia

General disorders and administration site conditions

Uncommon:	Pain

Investigations

Uncommon:	Weight increased, weight decreased

4.9 Overdose

Symptoms

Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. The most prominent manifestations of telmisartan overdose are expected to be hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

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 of both telmisartan and amlodipine.

Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly. Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and Amlodipine are not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers; ATC Code: C09DB04.

Onduarp combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.

The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Onduarp once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Telmisartan

Telmisartan is an orally active and specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse reactions.

In humans, 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.

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 substances 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.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with heart failure
Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Telmisartan/Amlodipine
In an 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study in 1461 patients with mild to severe hypertension (mean seated diastolic blood pressure ≥95 and ≤119 mmHg), treatment with each combination dose of Onduarp resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

Onduarp showed dose-related reductions in systolic/diastolic blood pressure across the therapeutic dose range of −21.8/−16.5 mmHg (40 mg/5 mg), −22.1/−18.2 mmHg (80 mg/5 mg), −24.7/−20.2 mmHg (40 mg/10 mg) and −26.4/−20.1 mmHg (80 mg/10 mg). The reduction in diastolic blood pressure <90 mmHg was achieved in 71.4 %, 74.8 %, 82.1 %, 85.3 % of patients respectively. Values are adjusted for baseline and country.

The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy. In a subset of 1050 patients with moderate to severe hypertension (DBP ≥100 mmHg) 32.7 - 51.8 % responded sufficiently to monotherapy of either telmisartan or amlodipine. The observed mean changes in systolic/diastolic blood pressure with a combination therapy containing amlodipine 5 mg (−22.2/−17.2 mmHg with 40 mg/5 mg; −22.5/−19.1 mmHg with 80 mg/5 mg) were comparable to or greater than those seen with amlodipine 10 mg (−21.0/−17.6 mmHg) and associated with significant lower oedema rates (1.4 % with 40 mg/5 mg; 0.5% with 80 mg/5 mg; 17.6 % with amlodipine 10 mg).

Automated ambulatory blood pressure monitoring (ABPM) performed in a subset of 562 patients confirmed the results seen with in-clinic systolic and diastolic blood pressure reductions consistently over the entire 24-hours dosing period.

In a further multicentre, randomised, double-blind, active-controlled, parallel group study, a total of 1097 patients with mild to severe hypertension who were not adequately controlled on amlodipine 5 mg received Onduarp (40 mg/5 mg or 80 mg/5 mg) or amlodipine alone (5 mg or 10 mg). After 8 weeks of treatment, each of the combinations was statistically significantly superior to both amlodipine monotherapy doses in reducing systolic and diastolic blood pressures (−13.6/−9.4 mmHg, −15.0/−10.6 mmHg with 40 mg/5 mg, 80 mg/5 mg versus −6.2/−5.7 mmHg, −11.1/−8.0 mmHg with amlodipine 5 mg and 10 mg and higher diastolic blood pressure control rates compared to the respective monotherapies were achieved (56.7 %, 63.8 % with 40 mg/5 mg and 80 mg/5 mg versus 42 %, 56.7 % with amlodipine 5 mg and 10 mg). Oedema rates were significantly lower with 40 mg/5 mg and 80 mg/5 mg compared to amlodipine 10 mg (4.4 % versus 24.9 %, respectively).

In another multicentre, randomised, double-blind, active-controlled, parallel group study, a total of 947 patients with mild to severe hypertension who were not adequately controlled on amlodipine 10 mg received Onduarp (40 mg/10 mg or 80 mg/10 mg) or amlodipine alone (10 mg). After 8 weeks of treatment, each of the combination treatments was statistically significantly superior to amlodipine monotherapy in reducing diastolic and systolic blood pressure (−11.1/−9.2 mmHg, −11.3/ −9.3 mmHg with 40 mg/10 mg, 80 mg/10 mg versus −7.4/−6.5 mmHg with amlodipine 10 mg) and higher diastolic blood pressure normalisation rates compared to monotherapy were achieved (63.7 %, 66.5 % with 40 mg/10 mg, 80 mg/10 mg versus 51.1 % with amlodipine 10 mg).

In two corresponding open-label long-term follow up studies performed over a further 6 months the effect of Onduarp was maintained over the trial period. Furthermore it was shown that some patients not adequately controlled with Onduarp 40 mg/10 mg had additional blood pressure reduction by up-titration to Onduarp 80 mg/10 mg.

The overall incidence of adverse reactions with Onduarp in the clinical trial programme was low with only 12.7 % of patients on treatment experiencing adverse reactions. The most common adverse reactions were peripheral oedema and dizziness, see also section 4.8. The adverse reactions reported were in agreement with those anticipated from the safety profiles of the components telmisartan and amlodipine. No new or more severe adverse reactions were observed. The oedema related events (peripheral oedema, generalised oedema, and oedema) were consistently lower in patients who received Onduarp as compared to patients who received amlodipine 10 mg. In the factorial design trial the oedema rates were 1.3 % with Onduarp 40 mg/5 mg and 80 mg/5 mg, 8.8 % with Onduarp 40 mg/10 mg and 80 mg/10 mg and 18.4 % with Amlodipine 10 mg. In patients not controlled on amlodipine 5 mg the oedema rates were 4.4 % for 40 mg/5 mg and 80 mg/5 mg and 24.9 % for amlodipine 10 mg.

The antihypertensive effect of Onduarp was similar irrespective of age and gender, and was similar in patients with and without diabetes.

Onduarp has not been studied in any patient population other than hypertension. Telmisartan has been studied in a large outcome study in 25,620 patients with high cardiovascular risk (ONTARGET). Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

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

5.2 Pharmacokinetic properties

Pharmacokinetic of the fixed dose combination (FDC)
The rate and extent of absorption of Onduarp are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

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.

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %. Amlodipine bioavailability is not affected by food ingestion.

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.

The volume of distribution of amlodipine is approximately 21 l/kg. In vitro studies have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins in hypertensive patients.

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

Amlodipine is extensively (approximatively 90 %) metabolised by the liver to inactive metabolites.

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).

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours consistent with once daily dosing. Steady-state plasma levels are reached after continuous administration for 7-8 days. Ten per cent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Linearity/non-linearity
The small reduction in AUC for telmisartan 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.

Amlodipine exhibits linear pharmacokinetics.

Special populations

Paediatric population (age below 18 years)
No pharmacokinetic data are available in the paediatric population.

Gender
Differences in plasma concentrations of telmisartan 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 in young and elderly patients.
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline with resulting increases in AUC and elimination half-life.

Renal impairment
In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations of telmisartan 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 subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with

renal impairment. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Hepatic impairment
Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability of telmisartan up to nearly 100 %. The elimination half-life of telmisartan is not changed in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40–60 % in AUC.

5.3 Preclinical safety data

Since the non-clinical toxicity profiles of telmisartan and amlodipine are not overlapping, no exacerbation of toxicity was expected for the combination. This has been confirmed in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/10 mg/kg of telmisartan and amlodipine were tested.

Preclinical data available for the components of this fixed dose combination are reported below.

Telmisartan
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 antagonists, 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 antagonists, 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 offspring 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.

Amlodipine
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
In reproductive toxicity studies in rats, delayed parturition, difficult labour and impaired fetal and pup survival were seen at high doses. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the Maximum Recommended Human Dose of 10 mg/day on an mg/m^2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Brilliant blue FCF (E 133)
Ferric oxide black (E172)
Ferric oxide yellow (E172)
Magnesium stearate
Maize starch
Meglumine
Microcrystalline cellulose

Povidone K25
Pregelatinised starch
Sodium hydroxide
Sorbitol (E420)

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 light and moisture.
Remove the tablets from the blister only directly prior to intake.

6.5 Nature and contents of container

Aluminium/aluminium blisters (PA/Al/PVC/Al) in a carton containing 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/11/729/002 (28 tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 November 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg telmisartan and 5 mg amlodipine (as amlodipine besilate).

Excipient(s) with known effect:
Each tablet contains 337.28 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Blue and white oval shaped two layer tablets engraved with the product code A3 and the company logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults:

Add on therapy
Onduarp is indicated in adults whose blood pressure is not adequately controlled on amlodipine.

Replacement therapy
Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Onduarp containing the same component doses.

4.2 Posology and method of administration

Posology
The recommended dose of Onduarp is one tablet per day.

The maximum recommended dose is Onduarp 80 mg/10 mg, one tablet per day. Onduarp is indicated for long term treatment.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects (see section 4.5).

Add on therapy
Onduarp 80 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled with Onduarp 40 mg/5 mg.

Individual dose titration with the components (i.e. amlodipine and telmisartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Patients treated with 10 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to Onduarp 40 mg/5 mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Replacement therapy
Patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Onduarp containing the same component doses in one tablet once daily, e.g. to enhance convenience or compliance

Special population

Elderly patients
No dose adjustment is necessary for elderly patients. Little information is available in the very elderly patients.

Patients with renal impairment
No posology adjustment is required for patients with mild to moderate renal impairment. Limited experience is available in patients with severe renal impairment or haemodialysis. Caution is advised when using Onduarp in such patients as amlodipine and telmisartan are not dialysable (see also section 4.4).

Concomitant use of telmisartan with aliskiren is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

Patients with hepatic impairment
In patients with mild to moderate hepatic impairment Onduarp should be administered with caution. For telmisartan the posology should not exceed 40 mg once daily (see section 4.4). Onduarp is contraindicated in patients with severe hepatic impairment (see section 4.3).

Paediatric population

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

Method of administration
Onduarp can be taken with or without food. It is recommended to take Onduarp with some liquid.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Biliary obstructive disorders and severe hepatic impairment
- Shock (including cardiogenic shock)
- Severe hypotension
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction

The concomitant use of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5).

4.4 Special warnings and precautions for use

Pregnancy
Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should

be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see section 4.3 and 4.6).

Hepatic impairment
Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Furthermore as with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dose recommendations have not been established. Onduarp should therefore be used with caution in these patients.

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 Onduarp is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Onduarp in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.

Intravascular hypovolaemia
Symptomatic hypotension, especially after the first dose, 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 telmisartan. If hypotension occurs with Onduarp, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Dual blockade of the renin-angiotensin-aldosterone system
The use of telmisartan in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by administering telmisartan with other blockers of the renin-angiotensin-aldosterone system) is therefore not recommended. Close monitoring of renal function is advisable if co-administration is considered necessary.

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 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.

Unstable angina pectoris, acute myocardial infarction
There are no data to support the use of Onduarp in unstable angina pectoris and during or within one month of a myocardial infarction.

Heart failure
In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see section 5.1).

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. Hyperkalaemia may be fatal 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.

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 antagonists, 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, extensive trauma).

Serum potassium should be monitored closely in these patients (see section 4.5).

Sorbitol
This medicinal product contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take Onduarp.

Other
As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiomyopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

Interactions common to the combination
No drug interaction studies have been performed.

To be taken into account with concomitant use

Other antihypertensive medicinal products

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

Medicinal products with blood pressure lowering potential
Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including Onduarp, e.g. baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol.

Corticosteroids (systemic route)
Reduction of the antihypertensive effect.

Interactions linked to telmisartan

Contraindicated (see section 4.3)

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
The combination of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4).

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements
Angiotensin II receptor antagonists 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 antagonists, 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 antagonists.
In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and medicinal products 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.

Ramipril
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.

Concomitant use to be taken into account

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.

Interactions linked to amlodipine

Concomitant use requiring caution

CYP3A4 inhibitors
With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively, the plasma concentration of amlodipine increased by 22 % and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

CYP3A4 inducers
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (i.e. rifampicin, *Hypericum perforatum*) may lead to a lower plasma concentration of amlodipine.

Grapefruit and grapefruit juice
Concomitant administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers did not show a significant effect on the pharmacokinetic properties of amlodipine. The concomitant use of amlodipine and grapefruit or grapefruit juice is still not recommended in patients as the bioavailability of amlodipine may increase in some and may result in increased hypotensive effects.

Concomitant use to be taken into account

Simvastatin
Co-administration of multiple doses of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77 % compared to simvastatin alone. Therefore, the dose of simvastatin in patients on amlodipine should be limited to 20 mg daily.

Others
Amlodipine has been safely administered with digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicinal products (aluminium hydroxide, magnesium hydroxide, simeticone), cimetidine, ciclosporin, antibiotics and oral hypoglycaemic medicinal products. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Onduarp in pregnant women. Animal reproductive toxicity studies with Onduarp have not been performed.

Telmisartan

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

Studies with telmisartan in animals have shown reproductive toxicity (see section 5.3).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of medicinal products. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).
Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension (see sections 4.3 and 4.4).

Amlodipine

Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery.

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

Fertility
No data from controlled clinical studies with the Fixed Dose Combination or with the individual components are available.

Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted.
In preclinical studies, no effects of telmisartan on male and female fertility were observed.
Similarly, no effects on male and female fertility were reported for amlodipine (see section 5.3).

Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been observed for calcium channel blockers in preclinical and *in vitro* studies. No clinical relevance has been established.

4.7 Effects on ability to drive and use machines

Onduarp has moderate influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as syncope, somnolence, dizziness, or vertigo during treatment (see section 4.8). Therefore, caution should be recommended when driving a car or using machines. If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions include dizziness and peripheral oedema. Serious syncope may occur rarely (less than 1 case per 1,000 patients).

The safety and tolerability of Onduarp has been evaluated in five controlled clinical studies with over 3500 patients, over 2500 of whom received telmisartan in combination with amlodipine.

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), not known (cannot be estimated from the available data).

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

System Organ Class	Common	Uncommon	Rare
Infections and infestations			cystitis
Psychiatric disorders			depression, anxiety, insomnia
Nervous system disorders	dizziness	somnolence, migraine, headache, paraesthesia	syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremor
Ear and labyrinth disorders		vertigo	
Cardiac disorders		bradycardia, palpitations	
Vascular disorders		hypotension, orthostatic hypotension, flushing	
Respiratory, thoracic and mediastinal disorders		cough	
Gastro-intestinal disorders		abdominal pain, diarrhoea, nausea	vomiting, gingival hypertrophy, dyspepsia, dry mouth
Skin and subcutaneous tissue disorders		pruritus	eczema, erythema, rash
Musculoskeletal and connective tissue disorders		arthralgia, muscle spasms (cramps in legs), myalgia	back pain, pain in extremity (leg pain)
Renal and urinary disorders			nocturia
Reproductive system, and breast disorders		erectile dysfunction	
General disorders and administration site conditions	peripheral oedema	asthenia, chest pain, fatigue, oedema	malaise
Investigations		hepatic enzymes increased	blood uric acid increased

Additional information on individual components

Adverse reactions previously reported with one of the individual components (telmisartan or amlodipine) may be potential adverse reactions with Onduarp as well, even if not observed in clinical trials or during the post-marketing period.

Telmisartan

Infections and infestations
- Uncommon: Upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis
- Rare: Sepsis including fatal outcome[1]

Blood and lymphatic system disorders
- Uncommon: Anaemia
- Rare: Thrombocytopenia, eosinophilia

Immune system disorders
- Rare: Hypersensitivity, anaphylactic reaction

Metabolism and nutrition disorders
- Uncommon: Hyperkalaemia
- Rare: Hypoglycaemia (in diabetic patients)

Eye disorders
- Rare: Visual disturbance

Cardiac disorders
- Rare: Tachycardia

Respiratory, thoracic and mediastinal disorders
- Uncommon: Dyspnoea

Gastrointestinal disorders
- Uncommon: Flatulence
- Rare: Stomach discomfort

Hepato-biliary disorders
- Rare: Hepatic function abnormal, liver disorder[2]

Skin and subcutaneous tissue disorders
- Uncommon: Hyperhidrosis
- Rare: Angioedema (with fatal outcome), drug eruption, toxic skin eruption, urticaria

Musculoskeletal and connective tissue disorders
- Rare: Tendon pain (tendinitis like symptoms)

Renal and urinary disorders
- Uncommon: Renal impairment including acute renal failure

General disorders and administration site conditions
- Rare: Influenza-like illness

Investigations
- Uncommon: Blood creatinine increased

Rare: Blood creatine phosphokinase increased, haemoglobin decreased

[1]: the event may be a chance finding or related to a mechanism currently not known

[2]: 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.

Amlodipine

Blood and lymphatic system disorders
Very rare: Leukocytopenia, thrombocytopenia

Immune system disorders
Very rare: Hypersensitivity

Metabolism and nutrition disorders
Very rare: Hyperglycaemia

Psychiatric disorders
Uncommon: Mood change
Rare Confusion

Nervous system disorders
Very rare: Extrapyramidal syndrome

Eye disorders
Uncommon: Visual impairment

Ear and labyrinth disorders
Uncommon: Tinnitus

Cardiac disorders
Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation

Vascular disorders
Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, rhinitis

Gastrointestinal disorders
Uncommon: Change of bowel habit
Very rare: Pancreatitis, gastritis

Hepatobiliary disorders
Very rare: Hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis

Skin and subcutaneous tissue disorders
Uncommon: Alopecia, purpura, skin discolouration, hyperhidrosis
Very rare: Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity

Renal and urinary disorders
Uncommon: Micturition disorder, pollakiuria

Reproductive system and breast disorders
Uncommon: Gynaecomastia

General disorders and administration site conditions
Uncommon: Pain

Investigations
Uncommon: Weight increased, weight decreased

4.9 Overdose

Symptoms
Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. The most prominent manifestations of telmisartan overdose are expected to be hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.
Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment
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 of both telmisartan and amlodipine.
Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly. Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and Amlodipine are not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers; ATC Code: C09DB04.

Onduarp combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.
The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.
Onduarp once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Telmisartan
Telmisartan is an orally active and specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or

block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse reactions.

In humans, 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.

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 substances 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.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with heart failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Telmisartan/Amlodipine

In an 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study in 1461 patients with mild to severe hypertension (mean seated diastolic blood pressure ≥95 and ≤119 mmHg), treatment with each combination dose of Onduarp resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

Onduarp showed dose-related reductions in systolic/diastolic blood pressure across the therapeutic dose range of −21.8/−16.5 mmHg (40 mg/5 mg), −22.1/−18.2 mmHg (80 mg/5 mg), −24.7/−20.2 mmHg (40 mg/10 mg) and −26.4/−20.1 mmHg (80 mg/10 mg). The reduction in diastolic blood pressure <90 mmHg was achieved in 71.6 %, 74.8 %, 82.1 %, 85.3% of patients respectively. Values are adjusted for baseline and country.

The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy. In a subset of 1050 patients with moderate to severe hypertension (DBP ≥100 mmHg) 32.7 - 51.8 % responded sufficiently to monotherapy of either telmisartan or amlodipine. The observed mean changes in systolic/diastolic blood pressure with a combination therapy containing amlodipine 5 mg (−22.2/−17.2 mmHg with 40 mg/5 mg; −22.5/−19.1 mmHg with 80 mg/5 mg) were comparable to or greater than those seen with amlodipine 10 mg (−21.0/−17.6 mmHg) and associated with significant lower oedema rates (1.4% with 40 mg/5 mg; 9.5 % with 80 mg/5 mg; 17.6 % with amlodipine 10 mg).

Automated ambulatory blood pressure monitoring (ABPM) performed in a subset of 562 patients confirmed the results seen with in-clinic systolic and diastolic blood pressure reductions consistently over the entire 24-hours dosing period.

In a further multicentre, randomised, double-blind, active-controlled, parallel group study, a total of 1097 patients with mild to severe hypertension who were not adequately controlled on amlodipine 5 mg received Onduarp (40 mg/5 mg or 80 mg/5 mg) or amlodipine alone (5 mg or 10 mg). After 8 weeks of treatment, each of the combinations was statistically significantly superior to both amlodipine monotherapy doses in reducing systolic and diastolic blood pressures (−13.6/−9.4 mmHg, −15.0/−10.6 mmHg with 40 mg/5 mg, 80 mg/5 mg versus −6.2/−5.7 mmHg, −11.1/−8.0 mmHg with amlodipine 5 mg and 10 mg and higher diastolic blood pressure control rates compared to the respective monotherapies were achieved (56.7 %, 63.8 % with 40 mg/5 mg and 80 mg/5 mg versus 42 %, 56.7 % with amlodipine 5 mg and 10 mg). Oedema rates were significantly lower with 40 mg/5 mg and 80 mg/5 mg compared to amlodipine 10 mg (4.4% versus 24.9 %, respectively).

In another multicentre, randomised, double-blind, active-controlled, parallel group study, a total of 947 patients with mild to severe hypertension who were not adequately controlled on amlodipine 10 mg received Onduarp (40 mg/10 mg or 80 mg/10 mg) or amlodipine alone (10 mg). After 8 weeks of treatment, each of the combination treatments was statistically significantly superior to amlodipine monotherapy in reducing diastolic and systolic blood pressure (−11.1/−9.2 mmHg, −11.3/−9.3 mmHg with 40 mg/10 mg, 80 mg/10 mg versus −7.4/−6.5 mmHg with amlodipine 10 mg) and higher diastolic blood pressure normalisation rates compared to monotherapy were achieved (63.7 %, 66.5 % with 40 mg/10 mg, 80 mg/10 mg versus 51.1 % with amlodipine 10 mg).

In two corresponding open-label long-term follow up studies performed over a further 6 months the effect of Onduarp was maintained over the trial period. Furthermore it was shown that some patients not adequately controlled with Onduarp 40 mg/10 mg had additional blood pressure reduction by up-titration to Onduarp 80 mg/10 mg.

The overall incidence of adverse reactions with Onduarp in the clinical trial programme was low with only 12.7 % of patients on treatment experiencing adverse reactions. The most common adverse reactions were peripheral oedema and dizziness, see also section 4.8. The adverse reactions reported were in agreement with those anticipated from the safety profiles of the components telmisartan and amlodipine. No new or more severe adverse reactions were observed. The oedema related events (peripheral oedema, generalised oedema, and oedema) were consistently lower in patients who received Onduarp as compared to patients who received amlodipine 10 mg. In the factorial design trial the oedema rates were 1.3 % with Onduarp 40 mg/5 mg and 80 mg/5 mg, 8.8 % with Onduarp 40 mg/10 mg and 80 mg/10 mg and 18.4 % with Amlodipine 10 mg. In patients not controlled on amlodipine 5 mg the oedema rates were 4.4 % for 40 mg/5 mg and 80 mg/5 mg and 24.9 % for amlodipine 10 mg.

The antihypertensive effect of Onduarp was similar irrespective of age and gender, and was similar in patients with and without diabetes.

Onduarp has not been studied in any patient population other than hypertension. Telmisartan has been studied in a large outcome study in 25,620 patients with high cardiovascular risk (ONTARGET). Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

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

5.2 Pharmacokinetic properties

Pharmacokinetic of the fixed dose combination (FDC)
The rate and extent of absorption of Onduarp are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

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.

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %. Amlodipine bioavailability is not affected by food ingestion.

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.

The volume of distribution of amlodipine is approximately 21 l/kg. In vitro studies have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins in hypertensive patients.

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

Amlodipine is extensively (approximatively 90 %) metabolised by the liver to inactive metabolites.

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).

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours consistent with once daily dosing. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Linearity/non-linearity
The small reduction in AUC for telmisartan 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.

Amlodipine exhibits linear pharmacokinetics.

Special populations

Paediatric population (age below 18 years)
No pharmacokinetic data are available in the paediatric population.

Gender
Differences in plasma concentrations of telmisartan 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 in young and elderly patients.
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline with resulting increases in AUC and elimination half-life.

Renal impairment
In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations of telmisartan 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 subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Hepatic impairment
Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability of telmisartan up to nearly 100 %. The elimination half-life of telmisartan is not

changed in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40–60 % in AUC.

5.3 Preclinical safety data

Since the non-clinical toxicity profiles of telmisartan and amlodipine are not overlapping, no exacerbation of toxicity was expected for the combination. This has been confirmed in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/10 mg/kg of telmisartan and amlodipine were tested.

Preclinical data available for the components of this fixed dose combination are reported below.

Telmisartan
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 antagonists, 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 antagonists, 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 offspring 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.

Amlodipine
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
In reproductive toxicity studies in rats, delayed parturition, difficult labour and impaired fetal and pup survival were seen at high doses. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the Maximum Recommended Human Dose of 10 mg/day on an mg/m^2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Brilliant blue FCF (E 133)
Ferric oxide black (E172)
Ferric oxide yellow (E172)
Magnesium stearate
Maize starch
Meglumine
Microcrystalline cellulose
Povidone K25
Pregelatinised starch
Sodium hydroxide
Sorbitol (E420)

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 light and moisture.
Remove the tablets from the blister only directly prior to intake.

6.5 Nature and contents of container

Aluminium/aluminium blisters (PA/Al/PVC/Al) in a carton containing 28 tablets or aluminium/aluminium perforated unit dose blisters (PA/Al/PVC/Al) in multipacks containing 360 (4 packs of 90 x 1) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/11/729/003 (28 tablets)
EU/1/11/729/004 (360 (4 x 90 x 1) tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 November 2011
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg telmisartan and 10 mg amlodipine (as amlodipine besilate).

Excipient(s) with known effect:
Each tablet contains 337.28 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Blue and white oval shaped two layer tablets engraved with the product code 54 and the company logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults:

Add on therapy
Onduarp is indicated in adults whose blood pressure is not adequately controlled on amlodipine.

Replacement therapy
Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Onduarp containing the same component doses.

4.2 Posology and method of administration

Posology
The recommended dose of Onduarp is one tablet per day.

The maximum recommended dose is Onduarp 80 mg/10 mg, one tablet per day. Onduarp is indicated for long term treatment.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects (see section 4.5).

Add on therapy
Onduarp 80 mg/10 mg may be administered in patients whose blood pressure is not adequately controlled on Onduarp 40 mg/10 mg or Onduarp 80 mg/5 mg.

Individual dose titration with the components (i.e. amlodipine and telmisartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Patients treated with 10 mg amlodipine who experience any dose limiting adverse reactions such as oedema, may be switched to Onduarp 40 mg/5 mg once daily, reducing the dose of amlodipine without reducing the overall expected antihypertensive response.

Replacement therapy
Patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Onduarp containing the same component doses in one tablet once daily, e.g. to enhance convenience or compliance

Special population

Elderly patients
No dose adjustment is necessary for elderly patients. Little information is available in the very elderly patients.

Patients with renal impairment
No posology adjustment is required for patients with mild to moderate renal impairment. Limited experience is available in patients with severe renal impairment or haemodialysis. Caution is advised when using Onduarp in such patients as amlodipine and telmisartan are not dialysable (see also section 4.4).

Concomitant use of telmisartan with aliskiren is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

Patients with hepatic impairment
In patients with mild to moderate hepatic impairment Onduarp should be administered with caution. For telmisartan the posology should not exceed 40 mg once daily (see section 4.4). Onduarp is contraindicated in patients with severe hepatic impairment (see section 4.3).

Paediatric population

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

Method of administration
Onduarp can be taken with or without food. It is recommended to take Onduarp with some liquid.

4.3 Contraindications

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Biliary obstructive disorders and severe hepatic impairment
- Shock (including cardiogenic shock)
- Severe hypotension
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction

The concomitant use of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.2, 4.4, 4.5).

4.4 Special warnings and precautions for use

Pregnancy
Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should

be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see section 4.3 and 4.6).

Hepatic impairment
Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Furthermore as with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dose recommendations have not been established. Onduarp should therefore be used with caution in these patients.

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 Onduarp is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Onduarp in patients with a recent kidney transplant. Telmisartan and amlodipine are not dialysable.

Intravascular hypovolaemia
Symptomatic hypotension, especially after the first dose, 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 telmisartan. If hypotension occurs with Onduarp, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Dual blockade of the renin-angiotensin-aldosterone system
The use of telmisartan in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.3).

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by administering telmisartan with other blockers of the renin-angiotensin-aldosterone system) is therefore not recommended. Close monitoring of renal function is advisable if co-administration is considered necessary.

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 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.

Unstable angina pectoris, acute myocardial infarction
There are no data to support the use of Onduarp in unstable angina pectoris and during or within one month of a myocardial infarction.

Heart failure
In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see section 5.1).

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. Hyperkalaemia may be fatal 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,.

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 product 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 antagonists, 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, extensive trauma).

Serum potassium should be monitored closely in these patients (see section 4.5).

Sorbitol
This medicinal product contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take Onduarp.

Other
As with any antihypertensive medicinal product, excessive reduction of blood pressure in patients with ischaemic cardiomyopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions between the two components of this fixed dose combinations have been observed in clinical studies.

Interactions common to the combination
No drug interaction studies have been performed.

To be taken into account with concomitant use

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

Medicinal products with blood pressure lowering potential
Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including Onduarp, e.g. baclofen, amifostine, neuroleptics or antidepressants. Furthermore, orthostatic hypotension may be aggravated by alcohol.

Corticosteroids (systemic route)
Reduction of the antihypertensive effect.

Interactions linked to telmisartan

Contraindicated (see section 4.3)

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
The combination of telmisartan with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients (see sections 4.3, 4.4).

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements
Angiotensin II receptor antagonists 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 antagonists, 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 antagonists.
In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and medicinal products 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.

Ramipril
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.

Concomitant use to be taken into account

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.

Interactions linked to amlodipine

Concomitant use requiring caution

CYP3A4 inhibitors
With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively, the plasma concentration of amlodipine increased by 22 % and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

CYP3A4 inducers
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (i.e. rifampicin, *Hypericum perforatum*) may lead to a lower plasma concentration of amlodipine.

Grapefruit and grapefruit juice
Concomitant administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers did not show a significant effect on the pharmacokinetic properties of amlodipine. The concomitant use of amlodipine and grapefruit or grapefruit juice is still not recommended in patients as the bioavailability of amlodipine may increase in some and may result in increased hypotensive effects.

Concomitant use to be taken into account

Simvastatin
Co-administration of multiple doses of amlodipine with simvastatin 80 mg resulted in an increase in exposure to simvastatin up to 77 % compared to simvastatin alone. Therefore, the dose of simvastatin in patients on amlodipine should be limited to 20 mg daily.

Others
Amlodipine has been safely administered with digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicinal products (aluminium hydroxide, magnesium hydroxide, simeticone), cimetidine, ciclosporin, antibiotics and oral hypoglycaemic medicinal products. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Onduarp in pregnant women. Animal reproductive toxicity studies with Onduarp have not been performed.

Telmisartan

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

Studies with telmisartan in animals have shown reproductive toxicity (see section 5.3).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of medicinal products. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension (see sections 4.3 and 4.4).

Amlodipine

Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery.

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

Fertility
No data from controlled clinical studies with the Fixed Dose Combination or with the individual components are available.

Separate reproductive toxicity studies with the combination of telmisartan and amlodipine have not been conducted.
In preclinical studies, no effects of telmisartan on male and female fertility were observed.
Similarly, no effects on male and female fertility were reported for amlodipine (see section 5.3).

Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been observed for calcium channel blockers in preclinical and *in vitro* studies. No clinical relevance has been established.

4.7 Effects on ability to drive and use machines

Onduarp has moderate influence on the ability to drive and use machines. Patients should be advised that they may experience adverse reactions such as syncope, somnolence, dizziness, or vertigo during treatment (see section 4.8). Therefore, caution should be recommended when driving a car or using machines. If patients experience these adverse reactions, they should avoid potentially hazardous tasks such as driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions include dizziness and peripheral oedema. Serious syncope may occur rarely (less than 1 case per 1,000 patients).

The safety and tolerability of Onduarp has been evaluated in five controlled clinical studies with over 3500 patients, over 2500 of whom received telmisartan in combination with amlodipine.

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), not known (cannot be estimated from the available data).

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

System Organ Class	Common	Uncommon	Rare
Infections and infestations			cystitis
Psychiatric disorders			depression, anxiety, insomnia
Nervous system disorders	dizziness	somnolence, migraine, headache, paraesthesia	syncope, peripheral neuropathy, hypoaesthesia, dysgeusia, tremor
Ear and labyrinth disorders		vertigo	
Cardiac disorders		bradycardia, palpitations	
Vascular disorders		hypotension, orthostatic hypotension, flushing	
Respiratory, thoracic and mediastinal disorders		cough	
Gastro-intestinal disorders		abdominal pain, diarrhoea, nausea	vomiting, gingival hypertrophy, dyspepsia, dry mouth
Skin and subcutaneous tissue disorders		pruritus	eczema, erythema, rash
Musculoskeletal and connective tissue disorders		arthralgia, muscle spasms (cramps in legs), myalgia	back pain, pain in extremity (leg pain)
Renal and urinary disorders			nocturia
Reproductive system, and breast disorders		erectile dysfunction	

General disorders and administration site conditions	peripheral oedema	asthenia, chest pain, fatigue, oedema	malaise
Investigations		hepatic enzymes increased	blood uric acid increased

Additional information on individual components

Adverse reactions previously reported with one of the individual components (telmisartan or amlodipine) may be potential adverse reactions with Onduarp as well, even if not observed in clinical trials or during the post-marketing period.

Telmisartan

Infections and infestations
- Uncommon: Upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis
- Rare: Sepsis including fatal outcome[1]

Blood and lymphatic system disorders
- Uncommon: Anaemia
- Rare: Thrombocytopenia, eosinophilia

Immune system disorders
- Rare: Hypersensitivity, anaphylactic reaction

Metabolism and nutrition disorders
- Uncommon: Hyperkalaemia
- Rare: Hypoglycaemia (in diabetic patients)

Eye disorders
- Rare: Visual disturbance

Cardiac disorders
- Rare: Tachycardia

Respiratory, thoracic and mediastinal disorders
- Uncommon: Dyspnoea

Gastrointestinal disorders
- Uncommon: Flatulence
- Rare: Stomach discomfort

Hepato-biliary disorders
- Rare: Hepatic function abnormal, liver disorder[2]

Skin and subcutaneous tissue disorders
- Uncommon: Hyperhidrosis
- Rare: Angioedema (with fatal outcome), drug eruption, toxic skin eruption, urticaria

Musculoskeletal and connective tissue disorders
- Rare: Tendon pain (tendinitis like symptoms)

Renal and urinary disorders
Uncommon: Renal impairment including acute renal failure

General disorders and administration site conditions
Rare: Influenza-like illness

Investigations
Uncommon: Blood creatinine increased
Rare: Blood creatine phosphokinase increased, haemoglobin decreased
[1]: the event may be a chance finding or related to a mechanism currently not known
[2]: 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.

Amlodipine

Blood and lymphatic system disorders
Very rare: Leukocytopenia, thrombocytopenia

Immune system disorders
Very rare: Hypersensitivity

Metabolism and nutrition disorders
Very rare: Hyperglycaemia

Psychiatric disorders
Uncommon: Mood change
Rare: Confusion

Nervous system disorders
Very rare: Extrapyramidal syndrome

Eye disorders
Uncommon: Visual impairment

Ear and labyrinth disorders
Uncommon: Tinnitus

Cardiac disorders
Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia, atrial fibrillation

Vascular disorders
Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, rhinitis

Gastrointestinal disorders
Uncommon: Change of bowel habit
Very rare: Pancreatitis, gastritis

Hepatobiliary disorders
Very rare: Hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis

Skin and subcutaneous tissue disorders

Uncommon:	Alopecia, purpura, skin discolouration, hyperhidrosis
Very rare:	Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity

Renal and urinary disorders

Uncommon:	Micturition disorder, pollakiuria

Reproductive system and breast disorders

Uncommon:	Gynaecomastia

General disorders and administration site conditions

Uncommon:	Pain

Investigations

Uncommon:	Weight increased, weight decreased

4.9 Overdose

Symptoms

Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects. The most prominent manifestations of telmisartan overdose are expected to be hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

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 of both telmisartan and amlodipine.

Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position with elevation of extremities, with salt and volume replacement given quickly. Supportive treatment should be instituted. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Telmisartan and Amlodipine are not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists and calcium channel blockers; ATC Code: C09DB04.

Onduarp combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: an angiotensin II receptor antagonist, telmisartan, and a dihydropyridinic calcium channel blocker, amlodipine.

The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Onduarp once daily produces effective and consistent reductions in blood pressure across the 24-hour therapeutic dose range.

Telmisartan

Telmisartan is an orally active and specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse reactions.

In humans, 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.

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 substances 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.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, leading to reductions in peripheral vascular resistance and in blood pressure. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with heart failure
Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Telmisartan/Amlodipine
In an 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study in 1461 patients with mild to severe hypertension (mean seated diastolic blood pressure ≥95 and ≤119 mmHg), treatment with each combination dose of Onduarp resulted in significantly greater diastolic and systolic blood pressure reductions and higher control rates compared to the respective monotherapy components.

Onduarp showed dose-related reductions in systolic/diastolic blood pressure across the therapeutic dose range of −21.8/−16.5 mmHg (40 mg/5 mg), −22.1/−18.2 mmHg (80 mg/5 mg), −24.7/−20.2 mmHg (40 mg/10 mg) and −26.4/−20.1 mmHg (80 mg/10 mg). The reduction in diastolic blood pressure <90 mmHg was achieved in 71.4 %, 74.8 %, 82.1 %, 85.3 % of patients respectively. Values are adjusted for baseline and country.

The majority of the antihypertensive effect was attained within 2 weeks after initiation of therapy. In a subset of 1050 patients with moderate to severe hypertension (DBP ≥100 mmHg) 32.7 - 51.8 % responded sufficiently to monotherapy of either telmisartan or amlodipine. The observed mean changes in systolic/diastolic blood pressure with a combination therapy containing amlodipine 5 mg (−22.2/−17.2 mmHg with 40 mg/5 mg; −22.5/−19.1 mmHg with 80 mg/5 mg) were comparable to or greater than those seen with amlodipine 10 mg (−21.0/−17.6 mmHg) and associated with significant lower oedema rates (1.4 % with 40 mg/5 mg; 0.5 % with 80 mg/5 mg; 17.6 % with amlodipine 10 mg).

Automated ambulatory blood pressure monitoring (ABPM) performed in a subset of 562 patients confirmed the results seen with in-clinic systolic and diastolic blood pressure reductions consistently over the entire 24-hours dosing period.

In a further multicentre, randomised, double-blind, active-controlled, parallel group study, a total of 1097 patients with mild to severe hypertension who were not adequately controlled on amlodipine 5 mg received Onduarp (40 mg/5 mg or 80 mg/5 mg) or amlodipine alone (5 mg or 10 mg). After 8 weeks of treatment, each of the combinations was statistically significantly superior to both amlodipine monotherapy doses in reducing systolic and diastolic blood pressures (−13.6/−9.4 mmHg, −15.0/−10.6 mmHg with 40 mg/5 mg, 80 mg/5 mg versus −6.2/−5.7 mmHg, −11.1/−8.0 mmHg with amlodipine 5 mg and 10 mg and higher diastolic blood pressure control rates compared to the respective monotherapies were achieved (56.7 %, 63.8 % with 40 mg/5 mg and 80 mg/5 mg versus 42 %, 56.7 % with amlodipine 5 mg and 10 mg). Oedema rates were significantly lower with 40 mg/5 mg and 80 mg/5 mg compared to amlodipine 10 mg (4.4% versus 24.9 %, respectively).

In another multicentre, randomised, double-blind, active-controlled, parallel group study, a total of 947 patients with mild to severe hypertension who were not adequately controlled on amlodipine 10 mg received Onduarp (40 mg/10 mg or 80 mg/10 mg) or amlodipine alone (10 mg). After 8 weeks of treatment, each of the combination treatments was statistically significantly superior to amlodipine monotherapy in reducing diastolic and systolic blood pressure (−11.1/−9.2 mmHg, −11.3/ −9.3 mmHg with 40 mg/10 mg, 80 mg/10 mg versus −7.4/−6.5 mmHg with amlodipine 10 mg) and higher diastolic blood pressure normalisation rates compared to monotherapy were achieved (63.7 %, 66.5 % with 40 mg/10 mg, 80 mg/10 mg versus 51.1 % with amlodipine 10 mg).

In two corresponding open-label long-term follow up studies performed over a further 6 months the effect of Onduarp was maintained over the trial period. Furthermore it was shown that some patients not adequately controlled with Onduarp 40 mg/10 mg had additional blood pressure reduction by up-titration to Onduarp 80 mg/10 mg.

The overall incidence of adverse reactions with Onduarp in the clinical trial programme was low with only 12.7 % of patients on treatment experiencing adverse reactions. The most common adverse reactions were peripheral oedema and dizziness, see also section 4.8. The adverse reactions reported were in agreement with those anticipated from the safety profiles of the components telmisartan and amlodipine. No new or more severe adverse reactions were observed. The oedema related events (peripheral oedema, generalised oedema, and oedema) were consistently lower in patients who received Onduarp as compared to patients who received amlodipine 10 mg. In the factorial design trial the oedema rates were 1.3% with Onduarp 40 mg/5 mg and 80 mg/5 mg, 8.8 % with Onduarp 40 mg/10 mg and 80 mg/10 mg and 18.4 % with Amlodipine 10 mg. In patients not controlled on amlodipine 5 mg the oedema rates were 4.4 % for 40 mg/5 mg and 80 mg/5 mg and 24.9 % for amlodipine 10 mg.

The antihypertensive effect of Onduarp was similar irrespective of age and gender, and was similar in patients with and without diabetes.

Onduarp has not been studied in any patient population other than hypertension. Telmisartan has been studied in a large outcome study in 25,620 patients with high cardiovascular risk (ONTARGET). Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

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

5.2 Pharmacokinetic properties

Pharmacokinetic of the fixed dose combination (FDC)
The rate and extent of absorption of Onduarp are equivalent to the bioavailability of telmisartan and amlodipine when administered as individual tablets.

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.

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %. Amlodipine bioavailability is not affected by food ingestion.

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.

The volume of distribution of amlodipine is approximately 21 l/kg. In vitro studies have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins in hypertensive patients.

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

Amlodipine is extensively (approximatively 90 %) metabolised by the liver to inactive metabolites.

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).

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours consistent with once daily dosing. Steady-state plasma levels are reached after continuous administration for 7-8 days. Ten per cent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Linearity/non-linearity
The small reduction in AUC for telmisartan 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.

Amlodipine exhibits linear pharmacokinetics.

Special populations

Paediatric population (age below 18 years)
No pharmacokinetic data are available in the paediatric population.

Gender
Differences in plasma concentrations of telmisartan 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 in young and elderly patients.
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline with resulting increases in AUC and elimination half-life.

Renal impairment
In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations of telmisartan 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 subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with

renal impairment. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Hepatic impairment
Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability of telmisartan up to nearly 100 %. The elimination half-life of telmisartan is not changed in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40-60 % in AUC.

5.3 Preclinical safety data

Since the non-clinical toxicity profiles of telmisartan and amlodipine are not overlapping, no exacerbation of toxicity was expected for the combination. This has been confirmed in a subchronic (13-week) toxicology study in rats, in which dose levels of 3.2/0.8, 10/2.5 and 40/10 mg/kg of telmisartan and amlodipine were tested.

Preclinical data available for the components of this fixed dose combination are reported below.

Telmisartan
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 antagonists, 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 antagonists, 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.

Amlodipine
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
In reproductive toxicity studies in rats, delayed parturition, difficult labour and impaired fetal and pup survival were seen at high doses. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the Maximum Recommended Human Dose of 10 mg/day on an mg/m^2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Brilliant blue FCF (E 133)
Ferric oxide black (E172)
Ferric oxide yellow (E172)
Magnesium stearate
Maize starch
Meglumine
Microcrystalline cellulose

Povidone K25
Pregelatinised starch
Sodium hydroxide
Sorbitol (E420)

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 light and moisture.
Remove the tablets from the blister only directly prior to intake.

6.5 Nature and contents of container

Aluminium/aluminium blisters (PA/Al/PVC/Al) in a carton containing 28 tablets or aluminium/aluminium perforated unit dose blisters (PA/Al/PVC/Al) in multipacks containing 360 (4 packs of 90 x 1) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/11/729/005 (28 tablets)
EU/1/11/729/006 (36 (4 x 90 x 1) tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 November 2011
Date of latest renewal:

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 manufacturer responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

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**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 40 mg/5 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 40 mg/5 mg tablets
telmisartan/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg telmisartan and 5 mg amlodipine (as amlodipine besilate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

28 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/729/001 (28 tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onduarp 40 mg/5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister of 7 tablets – 40 mg/5 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 40 mg/5 mg tablets
telmisartan/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 40 mg/10 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 40 mg/10 mg tablets
telmisartan/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg telmisartan and 10 mg amlodipine (as amlodipine besilate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

28 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/729/002 (28 tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onduarp 40 mg/10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister of 7 tablets – 40 mg/10 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 40 mg/10 mg tablets
telmisartan/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 80 mg/5 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/5 mg tablets
telmisartan/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg telmisartan and 5 mg amlodipine (as amlodipine besilate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

28 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/729/003 (28 tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onduarp 80 mg/5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF THE MULTIPACKS OF 360 (4 PACKS OF 90 x 1 TABLETS) – WITHOUT BLUE BOX – 80 mg/5 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/5 mg tablets
telmisartan/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg telmisartan and 5 mg amlodipine (as amlodipine besilate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Component of a multipack comprising 4 packs, each containing 90 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/729/004 (360 (4 x 90 x 1) tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onduarp 80 mg/5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL ON MULTIPACKS OF 360 (4 PACKS OF 90 x 1 TABLETS) BUNDLED – INCLUDING THE BLUE BOX – 80 mg/5 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/5 mg tablets
telmisartan/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg telmisartan and 5 mg amlodipine (as amlodipine besilate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 4 packs, each containing 90 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/729/004 (360 (4 x 90 x 1) tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onduarp 80 mg/5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister of 7 tablets – 80 mg/5 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/5 mg tablets
telmisartan/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Unit dose blister of 10 tablets – 80 mg/5 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/5 mg tablets
telmisartan/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 80 mg/10 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/10 mg tablets
telmisartan/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg telmisartan and 10 mg amlodipine (as amlodipine besilate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

28 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/729/005 (28 tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onduarp 80 mg/10 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF THE MULTIPACKS OF 360 (4 PACKS OF 90 x 1 TABLETS) – WITHOUT BLUE BOX – 80 mg/10 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/10 mg tablets
telmisartan/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg telmisartan and 10 mg amlodipine (as amlodipine besilate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Component of a multipack comprising 4 packs, each containing 90 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/729/006 (360 (4 x 90 x 1) tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onduarp 80 mg/10 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER LABEL ON MULTIPACKS OF 360 (4 PACKS OF 90 x 1 TABLETS) BUNDLED – INCLUDING THE BLUE BOX – 80 mg/10 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/10 mg tablets
telmisartan/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg telmisartan and 10 mg amlodipine (as amlodipine besilate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 4 packs, each containing 90 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/729/006 (360 (4 x 90 x 1) tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onduarp 80 mg/10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister of 7 tablets – 80 mg/10 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/10 mg tablets
telmisartan/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Unit dose blister of 10 tablets – 80 mg/10 mg

1. NAME OF THE MEDICINAL PRODUCT

Onduarp 80 mg/10 mg tablets
telmisartan/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user
Onduarp 40 mg/5 mg tablets
Telmisartan/Amlodipine

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 of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Onduarp is and what it is used for

Onduarp tablets contain two active substances called telmisartan and amlodipine. Both of these substances help to control your high blood pressure:
- Telmisartan belongs to a group of substances called "angiotensin-II receptor antagonists". Angiotensin II is a substance produced in the body which causes blood vessels to narrow, thus increasing blood pressure. Telmisartan works by blocking the effect of angiotensin II.
- Amlodipine belongs to a group of substances called "calcium channel blockers". Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening.
This means that both of these active substances work together to help stop your blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

Onduarp is used to treat high blood pressure
- in adult patients whose blood pressure is not controlled enough with amlodipine.
- in adult patients who already receive telmisartan and amlodipine from separate tablets and who wish to take instead the same doses in one tablet for convenience.

High blood pressure, if not treated, can damage blood vessels in several organs, which puts patients at risk of serious events such as 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.

2. What you need to know before you take Onduarp

Do not take Onduarp

- if you are allergic to telmisartan or amlodipine or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to other medicines of the dihydropyridine type (one type of calcium channel blocker).
- if you are more than 3 months pregnant. (It is also better to avoid Onduarp in early pregnancy – see Warnings and precautions and Pregnancy section.)

- if you have severe liver problems or biliary obstruction (problems with drainage of the bile from the liver and gall bladder).
- if you suffer from severe low blood pressure (including shock).
- if you suffer from low heart output because of a serious heart problem.
- if you have diabetes mellitus or impaired kidney function and you are treated with Rasilez.

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

Warnings and precautions

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

- Kidney disease or kidney transplant.
- Narrowing of the blood vessels to one or both kidneys (renal artery stenosis).
- Liver disease.
- Heart trouble.
- Raised aldosterone levels (which lead to 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 diuretic therapy ('water tablets'), low-salt diet, diarrhoea, or vomiting.
- Elevated potassium levels in your blood.
- Diabetes.
- Narrowing of the aorta (aortic stenosis).
- Heart-associated chest pain also at rest or with minimal effort (unstable angina pectoris).
- A heart attack within the last four weeks.

Talk to your doctor before taking Onduarp:
- if you are taking Rasilez, a medicine used to treat high blood pressure.
- if you are taking digoxin.

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

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

Other medicines and Onduarp

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 Onduarp:

- 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 antagonists, renin inhibitors.
- NSAIDs (non steroidal anti-inflammatory medicines, e.g. acetylsalicylic acid or ibuprofen), heparin, immunosuppressives (e.g. cyclosporin or tacrolimus), and the antibiotic trimethoprim.
- Rifampicin, St. John's wort.
- Medicines used for HIV/AIDS (e.g. ritonavir) or for treatment of fungal infections (e.g. ketoconazole).
- Erythromycin (antibiotic).
- Diltiazem (cardiac medicine).

- Simvastatin to treat elevated levels of cholesterol.
- Rasilez, a medicine used to treat high blood pressure.
- Digoxin.

As with other blood pressure lowering medicines, the effect of Onduarp may be reduced when you take NSAIDs (non steroidal anti-inflammatory medicines, e.g. acetylsalicylic acid or ibuprofen) or corticosteroids.

Onduarp 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, neuroleptics or antidepressants). Furthermore low blood pressure may be aggravated by alcohol. You may notice this as dizziness when standing up.

Onduarp with food and drink

See section 3.

Grapefruit juice and grapefruit should not be consumed when you take Onduarp. This is because grapefruit and grapefruit juice may lead to increased blood levels of the active ingredient amlodipine in some patients and may increase the blood pressure lowering effect of Onduarp.

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 Onduarp before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Onduarp. Onduarp 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. Onduarp 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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Some people may experience side effects such as fainting, sleepiness, dizziness or a feeling of spinning (vertigo) when they are treated for high blood pressure. If you experience these side effects, do not drive or use machines.

Onduarp contains sorbitol.
If you have been told by your doctor that you have an intolerance to some sugars, consult your doctor before taking this medicine.

3. How to take Onduarp

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

The recommended dose is one tablet a day. Try to take the tablet at the same time each day.
Remove your Onduarp tablet from the blister only directly prior to intake.

You can take Onduarp with or without food. The tablets should be swallowed with some water or other non-alcoholic drink.

If your liver is not working properly, the usual dose should not exceed one 40 mg/5 mg tablet or one 40 mg/10 mg tablet per day.

If you take more Onduarp than you should
If you accidentally take too many tablets, contact your doctor, pharmacist, or your nearest hospital emergency department immediately. You might experience low blood pressure and rapid heart beat. Slow heart beat, dizziness, reduced kidney function including kidney failure, marked and prolonged low blood pressure including shock and death have also been reported.

If you forget to take Onduarp
If you forget to take a dose, take it as soon as you remember and 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 stop taking Onduarp
It is important that you take Onduarp every day until your doctor tells you otherwise. If you have the impression that the effect of Onduarp is too strong or too weak, talk to your doctor or pharmacist.

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. Increased incidence of sepsis has been observed with telmisartan only, however can not be ruled out for Onduarp.

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

Uncommon side effects (may affect up to 1 to 100 people):
Sleepiness, migraine, headache, tingling or numbness of the hands or feet, feeling of spinning (vertigo), slow heart rate, palpitations (awareness of your heart beat), low blood pressure (hypotension), dizziness on standing up (orthostatic hypotension), flushing, cough, stomach ache (abdominal pain), diarrhoea, feeling sick (nausea), itching, joint pain, muscle cramps, muscle pain, inability to obtain an erection, weakness, chest pain, tiredness, swelling (oedema), increased levels of hepatic enzymes.

Rare side effects (may affect up to 1 in 1,000 people):
Urinary bladder infection, feeling sad (depression), feeling anxious, sleeplessness, fainting, nerve damage in the hands or feet, reduced sense of touch, taste abnormalities, trembling, vomiting, enlarged gums, discomfort in the abdomen, dry mouth, eczema (a skin disorder), redness of skin, rash, back pain, leg pain, urge to urinate during the night, feeling unwell (malaise), increased levels of uric acid in the blood.

The following side effects have been observed with the components telmisartan or amlodipine and may occur also with Onduarp:

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

Uncommon side effects (may affect up to 1 in 100 people):
Urinary tract infections, upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), deficiency in red blood cells (anaemia), high potassium levels in the blood, shortness of breath, bloating, increased sweating, kidney damage including sudden inability of the kidneys to work, increased levels of creatinine.

Rare side effects (may affect up to 1 in 1,000 people):
Increase in certain white blood cells (eosinophilia), low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty of breathing, wheezing, swelling of the face or low blood pressure), low blood sugar levels (in diabetic patients), impaired vision, fast heart beat, upset stomach, abnormal liver function*, hives (urticaria), medicine rash, inflammation of the tendons, flu-like illness (for example muscle pain, feeling generally unwell), decreased haemoglobin (a blood protein), increased levels of creatinine phosphokinase in the blood.

* Most cases of abnormal liver function and liver disorder from post-marketing experience with telmisartan occurred in Japanese patients. Japanese patients are more likely to experience this side effect.

Amlodipine
In patients taking amlodipine alone the following additional side effects have been reported:

Uncommon side effects (may affect up to 1 in 100 people):
Mood changes, impaired vision, ringing in the ears, shortness of breath, sneezing/running nose, change of bowel habit, hair loss, unusual bruising and bleeding (red blood cell damage), skin discolouration, increased sweating, difficulty passing urine, increased need to pass urine especially at night, enlarging of male breasts, pain, weight increased, weight decreased.

Rare side effects (may affect up to 1 in 1,000 people):
Confusion.

Very rare side effects (may affect up to 1 in 10,000 people):
Reduced number of white blood cells (leucopenia), low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), excess sugar in blood, uncontrollable twitching or jerking movements, heart attack, irregular heart beat, inflammation of the blood vessels, inflamed pancreas, inflammation of the stomach lining (gastritis), inflammation of the liver, yellowing of the skin (jaundice), increased levels of hepatic enzymes with jaundice, rapid swelling of skin and mucosa (angioedema), severe skin reactions, hives (urticaria), severe allergic reactions with blistering eruptions of the skin and mucous membranes (exfoliative dermatitis, Stevens-Johnson-Syndrome), increased sensitivity of the skin to sun.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Onduarp

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

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

This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture. Remove your Onduarp tablet from the blister only directly prior to intake.

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 Onduarp contains

- The active substances are telmisartan and amlodipine.
  Each tablet contains 40 mg telmisartan and 5 mg amlodipine (as besylate).

- The other ingredients are colloidal anhydrous silica, brilliant blue FCF (E 133), ferric oxide black (E172), ferric oxide yellow (E172), magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide, sorbitol (E420).

What Onduarp looks like and contents of the pack

Onduarp 40 mg/5 mg tablets are blue and white oval shaped two layer tablets engraved with the product code A1 and the company logo on the other side.

Onduarp is available in a folding box containing 28 tablets in aluminium/aluminium blisters.

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Manufacturer
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This leaflet was last revised in

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

Package leaflet: Information for the user
Onduarp 40 mg/10 mg tablets
Telmisartan/Amlodipine

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 of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Onduarp is and what it is used for

Onduarp tablets contain two active substances called telmisartan and amlodipine. Both of these substances help to control your high blood pressure:
- Telmisartan belongs to a group of substances called "angiotensin-II receptor antagonists". Angiotensin II is a substance produced in the body which causes blood vessels to narrow, thus increasing blood pressure. Telmisartan works by blocking the effect of angiotensin II.
- Amlodipine belongs to a group of substances called "calcium channel blockers". Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening.
This means that both of these active substances work together to help stop your blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

Onduarp is used to treat high blood pressure
- in adult patients whose blood pressure is not controlled enough with amlodipine.
- in adult patients who already receive telmisartan and amlodipine from separate tablets and who wish to take instead the same doses in one tablet for convenience.

High blood pressure, if not treated, can damage blood vessels in several organs, which puts patients at risk of serious events such as 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.

2. What you need to know before you take Onduarp

Do not take Onduarp

- if you are allergic to telmisartan or amlodipine or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to other medicines of the dihydropyridine type (one type of calcium channel blocker).
- if you are more than 3 months pregnant. (It is also better to avoid Onduarp in early pregnancy – see Warnings and precautions and Pregnancy section.)

- if you have severe liver problems or biliary obstruction (problems with drainage of the bile from the liver and gall bladder).
- if you suffer from severe low blood pressure (including shock).
- if you suffer from low heart output because of a serious heart problem.
- if you have diabetes mellitus or impaired kidney function and you are treated with Rasilez.

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

Warnings and precautions

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

- Kidney disease or kidney transplant.
- Narrowing of the blood vessels to one or both kidneys (renal artery stenosis).
- Liver disease.
- Heart trouble.
- Raised aldosterone levels (which lead to 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 diuretic therapy ('water tablets'), low-salt diet, diarrhoea, or vomiting.
- Elevated potassium levels in your blood.
- Diabetes.
- Narrowing of the aorta (aortic stenosis).
- Heart-associated chest pain also at rest or with minimal effort (unstable angina pectoris).
- A heart attack within the last four weeks.

Talk to your doctor before taking Onduarp:
- if you are taking Rasilez, a medicine used to treat high blood pressure.
- if you are taking digoxin.

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

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

Other medicines and Onduarp

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 Onduarp:

- 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 antagonists, renin inhibitors.
- NSAIDs (non steroidal anti-inflammatory medicines, e.g. acetylsalicylic acid or ibuprofen), heparin, immunosuppressives (e.g. cyclosporin or tacrolimus), and the antibiotic trimethoprim.
- Rifampicin, St. John's wort.
- Medicines used for HIV/AIDS (e.g. ritonavir) or for treatment of fungal infections (e.g. ketoconazole).
- Erythromycin (antibiotic).
- Diltiazem (cardiac medicine).

- Simvastatin to treat elevated levels of cholesterol.
- Rasilez, a medicine used to treat high blood pressure.
- Digoxin.

As with other blood pressure lowering medicines, the effect of Onduarp may be reduced when you take NSAIDs (non steroidal anti-inflammatory medicines, e.g. acetylsalicylic acid or ibuprofen) or corticosteroids.

Onduarp 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, neuroleptics or antidepressants). Furthermore low blood pressure may be aggravated by alcohol. You may notice this as dizziness when standing up.

Onduarp with food and drink

See section 3.

Grapefruit juice and grapefruit should not be consumed when you take Onduarp. This is because grapefruit and grapefruit juice may lead to increased blood levels of the active ingredient amlodipine in some patients and may increase the blood pressure lowering effect of Onduarp.

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 Onduarp before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Onduarp. Onduarp 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. Onduarp 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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Some people may experience side effects such as fainting, sleepiness, dizziness or a feeling of spinning (vertigo) when they are treated for high blood pressure. If you experience these side effects, do not drive or use machines.

Onduarp contains sorbitol.
If you have been told by your doctor that you have an intolerance to some sugars, consult your doctor before taking this medicine.

3. How to take Onduarp

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

The recommended dose is one tablet a day. Try to take the tablet at the same time each day.
Remove your Onduarp tablet from the blister only directly prior to intake.

You can take Onduarp with or without food. The tablets should be swallowed with some water or other non-alcoholic drink.

If your liver is not working properly, the usual dose should not exceed one 40 mg/5 mg tablet or one 40 mg/10 mg tablet per day.

If you take more Onduarp than you should
If you accidentally take too many tablets, contact your doctor, pharmacist, or your nearest hospital emergency department immediately. You might experience low blood pressure and rapid heart beat. Slow heart beat, dizziness, reduced kidney function including kidney failure, marked and prolonged low blood pressure including shock and death have also been reported.

If you forget to take Onduarp
If you forget to take a dose, take it as soon as you remember and 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 stop taking Onduarp
It is important that you take Onduarp every day until your doctor tells you otherwise. If you have the impression that the effect of Onduarp is too strong or too weak, talk to your doctor or pharmacist.

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. Increased incidence of sepsis has been observed with telmisartan only, however can not be ruled out for Onduarp.

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

Uncommon side effects (may affect up to 1 in 100 people):
Sleepiness, migraine, headache, tingling or numbness of the hands or feet, feeling of spinning (vertigo), slow heart rate, palpitations (awareness of your heart beat), low blood pressure (hypotension), dizziness on standing up (orthostatic hypotension), flushing, cough, stomach ache (abdominal pain), diarrhoea, feeling sick (nausea), itching, joint pain, muscle cramps, muscle pain, inability to obtain an erection, weakness, chest pain, tiredness, swelling (oedema), increased levels of hepatic enzymes.

Rare side effects (may affect up to 1 in 1,000 people):
Urinary bladder infection, feeling sad (depression), feeling anxious, sleeplessness, fainting, nerve damage in the hands or feet, reduced sense of touch, taste abnormalities, trembling, vomiting, enlarged gums, discomfort in the abdomen, dry mouth, eczema (a skin disorder), redness of skin, rash, back pain, leg pain, urge to urinate during the night, feeling unwell (malaise), increased levels of uric acid in the blood.

The following side effects have been observed with the components telmisartan or amlodipine and may occur also with Onduarp:

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

Uncommon side effects (may affect up to 1 in 100 people):
Urinary tract infections, upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), deficiency in red blood cells (anaemia), high potassium levels in the blood, shortness of breath, bloating, increased sweating, kidney damage including sudden inability of the kidneys to work, increased levels of creatinine.

Rare side effects (may affect up to 1 in 1,000 people):
Increase in certain white blood cells (eosinophilia), low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty of breathing, wheezing, swelling of the face or low blood pressure), low blood sugar levels (in diabetic patients), impaired vision, fast heart beat, upset stomach, abnormal liver function*, hives (urticaria), medicine rash, inflammation of the tendons, flu-like illness (for example muscle pain, feeling generally unwell), decreased haemoglobin (a blood protein), increased levels of creatinine phosphokinase in the blood.

* Most cases of abnormal liver function and liver disorder from post-marketing experience with telmisartan occurred in Japanese patients. Japanese patients are more likely to experience this side effect.

Amlodipine
In patients taking amlodipine alone the following additional side effects have been reported:

Uncommon side effects (may affect up to 1 in 100 people):
Mood changes, impaired vision, ringing in the ears, shortness of breath, sneezing/running nose, change of bowel habit, hair loss, unusual bruising and bleeding (red blood cell damage), skin discolouration, increased sweating, difficulty passing urine, increased need to pass urine especially at night, enlarging of male breasts, pain, weight increased, weight decreased.

Rare side effects (may affect up to 1 in 1,000 people):
Confusion.

Very rare side effects (may affect up to 1 in 10,000 people):
Reduced number of white blood cells (leucopenia), low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), excess sugar in blood , uncontrollable twitching or jerking movements, heart attack, irregular heart beat, inflammation of the blood vessels, inflamed pancreas, inflammation of the stomach lining (gastritis), inflammation of the liver, yellowing of the skin (jaundice), increased levels of hepatic enzymes with jaundice, rapid swelling of skin and mucosa (angioedema), severe skin reactions, hives (urticaria), severe allergic reactions with blistering eruptions of the skin and mucous membranes (exfoliative dermatitis, Stevens-Johnson-Syndrome), increased sensitivity of the skin to sun.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Onduarp

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

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

This medicine does not require any special temperature storage conditions.Store in the original package in order to protect from light and moisture. Remove your Onduarp tablet from the blister only directly prior to intake.

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 Onduarp contains

- The active substances are telmisartan and amlodipine.
  Each tablet contains 40 mg telmisartan and 10 mg amlodipine (as besylate).

- The other ingredients are colloidal anhydrous silica, brilliant blue FCF (E 133), ferric oxide black (E172), ferric oxide yellow (E172), magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide, sorbitol (E420).

What Onduarp looks like and contents of the pack

Onduarp 40 mg/10 mg tablets are blue and white oval shaped two layer tablets engraved with the product code A2 and the company logo on the other side.

Onduarp is available in a folding box containing 28 tablets in aluminium/aluminium blisters.

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Manufacturer
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This leaflet was last revised in

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

Package leaflet: Information for the user
Onduarp 80 mg/5 mg tablets
Telmisartan/Amlodipine

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 of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Onduarp is and what it is used for

Onduarp tablets contain two active substances called telmisartan and amlodipine. Both of these substances help to control your high blood pressure:
- Telmisartan belongs to a group of substances called "angiotensin-II receptor antagonists". Angiotensin II is a substance produced in the body which causes blood vessels to narrow, thus increasing blood pressure. Telmisartan works by blocking the effect of angiotensin II.
- Amlodipine belongs to a group of substances called "calcium channel blockers". Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening.
This means that both of these active substances work together to help stop your blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

Onduarp is used to treat high blood pressure
- in adult patients whose blood pressure is not controlled enough with amlodipine.
- in adult patients who already receive telmisartan and amlodipine from separate tablets and who wish to take instead the same doses in one tablet for convenience.

High blood pressure, if not treated, can damage blood vessels in several organs, which puts patients at risk of serious events such as 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.

2. What you need to know before you take Onduarp

Do not take Onduarp
- if you are allergic to telmisartan or amlodipine or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to other medicines of the dihydropyridine type (one type of calcium channel blocker).
- if you are more than 3 months pregnant. (It is also better to avoid Onduarp in early pregnancy – see Warnings and precautions and Pregnancy section.)
- if you have severe liver problems or biliary obstruction (problems with drainage of the bile from the liver and gall bladder).

- if you suffer from severe low blood pressure (including shock).
- if you suffer from low heart output because of a serious heart problem.
- if you have diabetes mellitus or impaired kidney function and you are treated with Rasilez.

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

Warnings and precautions

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

- Kidney disease or kidney transplant.
- Narrowing of the blood vessels to one or both kidneys (renal artery stenosis).
- Liver disease.
- Heart trouble.
- Raised aldosterone levels (which lead to 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 diuretic therapy ('water tablets'), low-salt diet, diarrhoea, or vomiting.
- Elevated potassium levels in your blood.
- Diabetes.
- Narrowing of the aorta (aortic stenosis).
- Heart-associated chest pain also at rest or with minimal effort (unstable angina pectoris).
- A heart attack within the last four weeks.

Talk to your doctor before taking Onduarp:
- if you are taking Rasilez, a medicine used to treat high blood pressure.
- if you are taking digoxin.

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

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

Other medicines and Onduarp

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 Onduarp:

- 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 antagonists, renin inhibitors.
- NSAIDs (non steroidal anti-inflammatory medicines, e.g. acetylsalicylic acid or ibuprofen), heparin, immunosuppressives (e.g. cyclosporin or tacrolimus), and the antibiotic trimethoprim.
- Rifampicin, St. John's wort.
- Medicines used for HIV/AIDS (e.g. ritonavir) or for treatment of fungal infections (e.g. ketoconazole).
- Erythromycin (antibiotic).
- Diltiazem (cardiac medicine).
- Simvastatin to treat elevated levels of cholesterol.
- Rasilez, a medicine used to treat high blood pressure.

- Digoxin.

As with other blood pressure lowering medicines, the effect of Onduarp may be reduced when you take NSAIDs (non steroidal anti-inflammatory medicines, e.g. acetylsalicylic acid or ibuprofen) or corticosteroids.

Onduarp 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, neuroleptics or antidepressants). Furthermore low blood pressure may be aggravated by alcohol. You may notice this as dizziness when standing up.

Onduarp with food and drink

See section 3.

Grapefruit juice and grapefruit should not be consumed when you take Onduarp. This is because grapefruit and grapefruit juice may lead to increased blood levels of the active ingredient amlodipine in some patients and may increase the blood pressure lowering effect of Onduarp.

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 Onduarp before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Onduarp. Onduarp 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. Onduarp 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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Some people may experience side effects such as fainting, sleepiness, dizziness or a feeling of spinning (vertigo) when they are treated for high blood pressure. If you experience these side effects, do not drive or use machines.

Onduarp contains sorbitol.
If you have been told by your doctor that you have an intolerance to some sugars, consult your doctor before taking this medicine.

3. How to take Onduarp

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

The recommended dose is one tablet a day. Try to take the tablet at the same time each day.
Remove your Onduarp tablet from the blister only directly prior to intake.

You can take Onduarp with or without food. The tablets should be swallowed with some water or other non-alcoholic drink.

If your liver is not working properly, the usual dose should not exceed one 40 mg/5 mg tablet or one 40 mg/10 mg tablet per day.

If you take more Onduarp than you should
If you accidentally take too many tablets, contact your doctor, pharmacist, or your nearest hospital emergency department immediately. You might experience low blood pressure and rapid heart beat. Slow heart beat, dizziness, reduced kidney function including kidney failure, marked and prolonged low blood pressure including shock and death have also been reported.

If you forget to take Onduarp
If you forget to take a dose, take it as soon as you remember and 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 stop taking Onduarp
It is important that you take Onduarp every day until your doctor tells you otherwise. If you have the impression that the effect of Onduarp is too strong or too weak, talk to your doctor or pharmacist.

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. Increased incidence of sepsis has been observed with telmisartan only, however can not be ruled out for Onduarp.

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

Uncommon side effects (may affect up to 1 in 100 people):
Sleepiness, migraine, headache, tingling or numbness of the hands or feet, feeling of spinning (vertigo), slow heart rate, palpitations (awareness of your heart beat), low blood pressure (hypotension), dizziness on standing up (orthostatic hypotension), flushing, cough, stomach ache (abdominal pain), diarrhoea, feeling sick (nausea), itching, joint pain, muscle cramps, muscle pain, inability to obtain an erection, weakness, chest pain, tiredness, swelling (oedema), increased levels of hepatic enzymes.

Rare side effects (may affect up to 1 in 1,000 people):
Urinary bladder infection, feeling sad (depression), feeling anxious, sleeplessness, fainting, nerve damage in the hands or feet, reduced sense of touch, taste abnormalities, trembling, vomiting, enlarged gums, discomfort in the abdomen, dry mouth, eczema (a skin disorder), redness of skin, rash, back pain, leg pain, urge to urinate during the night, feeling unwell (malaise), increased levels of uric acid in the blood.

The following side effects have been observed with the components telmisartan or amlodipine and may occur also with Onduarp:

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

Uncommon side effects (may affect up to 1 in 100 people):
Urinary tract infections, upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), deficiency in red blood cells (anaemia), high potassium levels in the blood, shortness of breath, bloating, increased sweating, kidney damage including sudden inability of the kidneys to work, increased levels of creatinine.

Rare side effects (may affect up to 1 in 1,000 people):
Increase in certain white blood cells (eosinophilia), low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty of breathing, wheezing, swelling of the face or low blood pressure), low blood sugar levels (in diabetic patients), impaired vision, fast heart beat, upset stomach, abnormal liver function*, hives (urticaria), medicine rash, inflammation of the tendons, flu-like illness (for example muscle pain, feeling generally unwell), decreased haemoglobin (a blood protein), increased levels of creatinine phosphokinase in the blood.

* Most cases of abnormal liver function and liver disorder from post-marketing experience with telmisartan occurred in Japanese patients. Japanese patients are more likely to experience this side effect.

Amlodipine
In patients taking amlodipine alone the following additional side effects have been reported:

Uncommon side effects (may affect up to 1 in 100 people):
Mood changes, impaired vision, ringing in the ears, shortness of breath, sneezing/running nose, change of bowel habit, hair loss, unusual bruising and bleeding (red blood cell damage), skin discolouration, increased sweating, difficulty passing urine, increased need to pass urine especially at night, enlarging of male breasts, pain, weight increased, weight decreased.

Rare side effects (may affect up to 1 in 1,000 people):
Confusion.

Very rare side effects (may affect up to 1 in 10,000 people):
Reduced number of white blood cells (leucopenia), low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), excess sugar in blood , uncontrollable twitching or jerking movements, heart attack, irregular heart beat, inflammation of the blood vessels, inflamed pancreas, inflammation of the stomach lining (gastritis), inflammation of the liver, yellowing of the skin (jaundice), increased levels of hepatic enzymes with jaundice, rapid swelling of skin and mucosa (angioedema), severe skin reactions, hives (urticaria), severe allergic reactions with blistering eruptions of the skin and mucous membranes (exfoliative dermatitis, Stevens-Johnson-Syndrome), increased sensitivity of the skin to sun.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Onduarp

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

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

This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture. Remove your Onduarp tablet from the blister only directly prior to intake.

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 Onduarp contains

- The active substances are telmisartan and amlodipine.
  Each tablet contains 80 mg telmisartan and 5 mg amlodipine (as besylate).

- The other ingredients are colloidal anhydrous silica, brilliant blue FCF (E 133), ferric oxide black (E172), ferric oxide yellow (E172), magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide, sorbitol (E420).

What Onduarp looks like and contents of the pack

Onduarp 80 mg/5 mg tablets are blue and white oval shaped two layer tablets engraved with the product code A3 and the company logo on the other side.

Onduarp is available in a folding box containing 28 tablets in aluminium/aluminium blisters and in a folding box containing 360 (4 x 90 x 1) tablets in aluminium/aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

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This leaflet was last revised in

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

Package leaflet: Information for the user
Onduarp 80 mg/10 mg tablets
Telmisartan/Amlodipine

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 of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Onduarp is and what it is used for

Onduarp tablets contain two active substances called telmisartan and amlodipine. Both of these substances help to control your high blood pressure:
- Telmisartan belongs to a group of substances called "angiotensin-II receptor antagonists". Angiotensin II is a substance produced in the body which causes blood vessels to narrow, thus increasing blood pressure. Telmisartan works by blocking the effect of angiotensin II.
- Amlodipine belongs to a group of substances called "calcium channel blockers". Amlodipine stops calcium from moving into the blood vessel wall which stops the blood vessels from tightening.
This means that both of these active substances work together to help stop your blood vessels tightening. As a result, the blood vessels relax and blood pressure is lowered.

Onduarp is used to treat high blood pressure
- in adult patients whose blood pressure is not controlled enough with amlodipine.
- in adult patients who already receive telmisartan and amlodipine from separate tablets and who wish to take instead the same doses in one tablet for convenience.

High blood pressure, if not treated, can damage blood vessels in several organs, which puts patients at risk of serious events such as 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.

2. What you need to know before you take Onduarp

Do not take Onduarp

- if you are allergic to telmisartan or amlodipine or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to other medicines of the dihydropyridine type (one type of calcium channel blocker).
- if you are more than 3 months pregnant. (It is also better to avoid Onduarp in early pregnancy – see Warnings and precautions and Pregnancy section.)

- if you have severe liver problems or biliary obstruction (problems with drainage of the bile from the liver and gall bladder).
- if you suffer from severe low blood pressure (including shock).
- if you suffer from low heart output because of a serious heart problem.
- if you have diabetes mellitus or impaired kidney function and you are treated with Rasilez.

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

Warnings and precautions

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

- Kidney disease or kidney transplant.
- Narrowing of the blood vessels to one or both kidneys (renal artery stenosis).
- Liver disease.
- Heart trouble.
- Raised aldosterone levels (which lead to 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 diuretic therapy ('water tablets'), low-salt diet, diarrhoea, or vomiting.
- Elevated potassium levels in your blood.
- Diabetes.
- Narrowing of the aorta (aortic stenosis).
- Heart-associated chest pain also at rest or with minimal effort (unstable angina pectoris).
- A heart attack within the last four weeks.

Talk to your doctor before taking Onduarp:
- if you are taking Rasilez, a medicine used to treat high blood pressure.
- if you are taking digoxin.

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

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

Other medicines and Onduarp

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 Onduarp:

- 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 antagonists, renin inhibitors.
- NSAIDs (non steroidal anti-inflammatory medicines, e.g. acetylsalicylic acid or ibuprofen), heparin, immunosuppressives (e.g. cyclosporin or tacrolimus), and the antibiotic trimethoprim.
- Rifampicin, St. John's wort.
- Medicines used for HIV/AIDS (e.g. ritonavir) or for treatment of fungal infections (e.g. ketoconazole).
- Erythromycin (antibiotic).
- Diltiazem (cardiac medicine).

- Simvastatin to treat elevated levels of cholesterol.
- Rasilez, a medicine used to treat high blood pressure.
- Digoxin.

As with other blood pressure lowering medicines, the effect of Onduarp may be reduced when you take NSAIDs (non steroidal anti-inflammatory medicines, e.g. acetylsalicylic acid or ibuprofen) or corticosteroids.

Onduarp 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, neuroleptics or antidepressants). Furthermore low blood pressure may be aggravated by alcohol. You may notice this as dizziness when standing up.

Onduarp with food and drink

See section 3.

Grapefruit juice and grapefruit should not be consumed when you take Onduarp. This is because grapefruit and grapefruit juice may lead to increased blood levels of the active ingredient amlodipine in some patients and may increase the blood pressure lowering effect of Onduarp.

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 Onduarp before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Onduarp. Onduarp 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. Onduarp 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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Some people may experience side effects such as fainting, sleepiness, dizziness or a feeling of spinning (vertigo) when they are treated for high blood pressure. If you experience these side effects, do not drive or use machines.

Onduarp contains sorbitol.
If you have been told by your doctor that you have an intolerance to some sugars, consult your doctor before taking this medicine.

3. How to take Onduarp

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

The recommended dose is one tablet a day. Try to take the tablet at the same time each day.
Remove your Onduarp tablet from the blister only directly prior to intake.

You can take Onduarp with or without food. The tablets should be swallowed with some water or other non-alcoholic drink.

If your liver is not working properly, the usual dose should not exceed one 40 mg/5 mg tablet or one 40 mg/10 mg tablet per day.

If you take more Onduarp than you should
If you accidentally take too many tablets, contact your doctor, pharmacist, or your nearest hospital emergency department immediately. You might experience low blood pressure and rapid heart beat. Slow heart beat, dizziness, reduced kidney function including kidney failure, marked and prolonged low blood pressure including shock and death have also been reported.

If you forget to take Onduarp
If you forget to take a dose, take it as soon as you remember and 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 stop taking Onduarp
It is important that you take Onduarp every day until your doctor tells you otherwise. If you have the impression that the effect of Onduarp is too strong or too weak, talk to your doctor or pharmacist.

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. Increased incidence of sepsis has been observed with telmisartan only, however can not be ruled out for Onduarp.

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

Uncommon side effects (may affect up to 1 in 100 people):
Sleepiness, migraine, headache, tingling or numbness of the hands or feet, feeling of spinning (vertigo), slow heart rate, palpitations (awareness of your heart beat), low blood pressure (hypotension), dizziness on standing up (orthostatic hypotension), flushing, cough, stomach ache (abdominal pain), diarrhoea, feeling sick (nausea), itching, joint pain, muscle cramps, muscle pain, inability to obtain an erection, weakness, chest pain, tiredness, swelling (oedema), increased levels of hepatic enzymes.

Rare side effects (may affect up to 1 in 1,000 people):
Urinary bladder infection, feeling sad (depression), feeling anxious, sleeplessness, fainting, nerve damage in the hands or feet, reduced sense of touch, taste abnormalities, trembling, vomiting, enlarged gums, discomfort in the abdomen, dry mouth, eczema (a skin disorder), redness of skin, rash, back pain, leg pain, urge to urinate during the night, feeling unwell (malaise), increased levels of uric acid in the blood.

The following side effects have been observed with the components telmisartan or amlodipine and may occur also with Onduarp:

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

Uncommon side effects (may affect up to 1 in 100 people):
Urinary tract infections, upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), deficiency in red blood cells (anaemia), high potassium levels in the blood, shortness of breath, bloating, increased sweating, kidney damage including sudden inability of the kidneys to work, increased levels of creatinine.

Rare side effects (may affect up to 1 in 1,000 people):
Increase in certain white blood cells (eosinophilia), low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty of breathing, wheezing, swelling of the face or low blood pressure), low blood sugar levels (in diabetic patients), impaired vision, fast heart beat, upset stomach, abnormal liver function*, hives (urticaria), medicine rash, inflammation of the tendons, flu-like illness (for example muscle pain, feeling generally unwell), decreased haemoglobin (a blood protein), increased levels of creatinine phosphokinase in the blood.

* Most cases of abnormal liver function and liver disorder from post-marketing experience with telmisartan occurred in Japanese patients. Japanese patients are more likely to experience this side effect.

Amlodipine
In patients taking amlodipine alone the following additional side effects have been reported:

Uncommon side effects (may affect up to 1 in 100 people):
Mood changes, impaired vision, ringing in the ears, shortness of breath, sneezing/running nose, change of bowel habit, hair loss, unusual bruising and bleeding (red blood cell damage), skin discolouration, increased sweating, difficulty passing urine, increased need to pass urine especially at night, enlarging of male breasts, pain, weight increased, weight decreased.

Rare side effects are (may affect up to 1 in 1,000 people):
Confusion.

Very rare side effects (may affect up to 1 in 10,000 people):
Reduced number of white blood cells (leucopenia), low platelet count (thrombocytopenia), allergic reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), excess sugar in blood , uncontrollable twitching or jerking movements, heart attack, irregular heart beat, inflammation of the blood vessels, inflamed pancreas, inflammation of the stomach lining (gastritis), inflammation of the liver, yellowing of the skin (jaundice), increased levels of hepatic enzymes with jaundice, rapid swelling of skin and mucosa (angioedema), severe skin reactions, hives (urticaria), severe allergic reactions with blistering eruptions of the skin and mucous membranes (exfoliative dermatitis, Stevens-Johnson-Syndrome), increased sensitivity of the skin to sun.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Onduarp

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

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

This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture. Remove your Onduarp tablet from the blister only directly prior to intake.

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 Onduarp contains

- The active substances are telmisartan and amlodipine.
  Each tablet contains 80 mg telmisartan and 10 mg amlodipine (as besylate).

- The other ingredients are colloidal anhydrous silica, brilliant blue FCF (E 133), ferric oxide black (E172), ferric oxide yellow (E172), magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide, sorbitol (E420).

What Onduarp looks like and contents of the pack

Onduarp 80 mg/10 mg tablets are blue and white oval shaped two layer tablets engraved with the product code A4 and the company logo on the other side.

Onduarp is available in a folding box containing 28 tablets in aluminium/aluminium blisters and in a folding box containing 360 (4 x 90 x 1) tablets in aluminium/aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

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This leaflet was last revised in

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