Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Twilev 2.5 mg/5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Twilev2.5 mg/5 mg film-coated tablets
Each film-coated tablet contains 2.5 mg of ramipril and 5 mg of nebivolol (as 5.45 mg of nebivolol hydrochloride).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Twilev2.5 mg/5 mg film-coated tablets:
Pink, oval, film-coated tablet (length: 12 mm, width: 6 mm)
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension as substitution therapy in adult patients adequately controlled with nebivolol and ramipril given concurrently at the same dose level as in the combination, but with separate tablets.

4.2 Posology and method of administration

Posology

The recommended dose is one tablet per day as a single dose, preferably at the same time of the day.

The fixed dose combination is not suitable for initial therapy. If a change of posology is required, titration should be done with the individual components.

Special populations

Elderly
In view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.

Renal impairment
Daily dose in patients with renal impairment should be based on creatinine clearance (see section 5.2):
- if creatinine clearance is ≥ 60 ml/min, the maximal daily dose of Twilev is 10 mg/5 mg;
- if creatinine clearance is between 10-60 ml/min, the maximal daily dose of Twilev is 5 mg/5 mg;
- in haemodialysed hypertensive patients: ramipril is slightly dialysable and the maximal daily dose of Twilev is 5 mg/5 mg; the medicinal product should be administered few hours after haemodialys is performed.

Hepatic impairment
Twilev is contraindicated in patients with impaired liver function or hepatic insufficiency (see sections 4.3, 4.4)

Paediatric population
The safety and efficacy of Twilev in children and adolescents aged below 18 years have not been established. No data are available. Therefore, use in children and adolescents is not recommended.

Method of administration
Oral use.
Tablets may be taken with or without meals.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or any other ACE (Angiotensin Converting Enzyme) inhibitors or any other beta-blocking agents.

- Liver insufficiency or liver function impairment
- Acute heart failure
- Shock (including cardiogenic shock)
- Episodes of heart failure decompensation (also after acute myocardial infarction) requiring i.v. inotropic therapy
- Sick sinus syndrome, including sino-atrial block
- Second- and third-degree heart block (without a pacemaker)
- History of bronchospasm and bronchial asthma
- Untreated phaeochromocytoma
- Metabolic acidosis
- Symptomatic hypotension
- Symptomatic bradycardia
- Severe peripheral circulatory disturbances
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs)
- Concomitant use with sacubitril/valsartan therapy (see sections 4.4 and 4.5)
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5).
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Twilev must not be used in patients with hypotensive or haemodynamically unstable states.
- The concomitant use of Twilev with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m2) (see sections 4.5 and 5.1)

4.4 Special warnings and precautions for use

Special warnings and precautions related to each monocomponent, as listed below, also to the fixed combination Twilev.

<u>*Nebivolol*</u>

Anaesthesia
Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation. If beta-blockade is interrupted in preparation for surgery, the beta-adrenergic antagonist should be discontinued at least 24 hours beforehand.
Caution should be observed with certain anaesthetics that cause myocardial depression. The patient can be protected against vagal reactions by intravenous administration of atropine.

Cardiovascular
In general, beta-adrenergic antagonists should not be used in patients with untreated congestive heart failure (CHF), unless their condition has been stabilised.
In patients with ischaemic heart disease, treatment with a beta-adrenergic antagonist should be discontinued gradually, i.e. over 1 - 2 weeks. If necessary replacement therapy should be initiated at the same time, to prevent exacerbation of angina pectoris.
Beta-adrenergic antagonists may induce bradycardia: if the pulse rate drops below 50 - 55 bpm at rest and / or the patient experiences symptoms that are suggestive of bradycardia, the dosage should be reduced.
Beta-adrenergic antagonists should be used with caution:
- with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), as aggravation of these disorders may occur;
- with first degree heart block, because of the negative effect of beta-blockers on conduction time;
- with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction: beta-adrenergic antagonists may increase the number and duration of anginal attacks.
Combination of nebivolol with calcium channel antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic drugs, and with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

Metabolic / Endocrinological
Nebivolol does not affect glucose levels in diabetic patients. Care should be taken in diabetic patients however, as nebivolol may mask certain symptoms of hypoglycaemia (tachycardia, palpitations). Beta-blockers could further increase the risk of

severe hypoglycaemia when used concurrently with sulfonylureas. Diabetic patients should be advised to carefully monitor blood glucose levels (see Section 4.5). Beta-adrenergic blocking agents may mask tachycardic symptoms in hyperthyroidism. Abrupt withdrawal may intensify symptoms.

Respiratory
In patients with chronic obstructive pulmonary disorders, beta-adrenergic antagonists should be used with caution as airway constriction may be aggravated.

Other
Patients with a history of psoriasis should take beta-adrenergic antagonists only after careful consideration.
Beta-adrenergic antagonists may increase the sensitivity to allergens and the severity of anaphylactic reactions.

Ramipril

Special populations
Pregnancy
ACE inhibitors such as ramipril or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors/AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Patients at particular risk of hypotension

• *Patients with strongly activated renin-angiotensin-aldosterone system*

Patients with strongly activated renin-angiotensin-aldosterone system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase.

Significant activation of renin-angiotensin-aldosterone system is to be anticipated and medical supervision including blood pressure monitoring is necessary, for example in:

- patients with severe hypertension
- patients with decompensated congestive heart failure
- patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve)
- patients with unilateral renal artery stenosis with a second functional kidney
- patients in whom fluid or salt depletion exists or may develop (including patients with diuretics)
- patients with liver cirrhosis and/or ascites
- patients undergoing major surgery or during anaesthesia with agents that produce hypotension

Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload).

• *Dual blockade of the renin-angiotensin-aldosterone system (RAAS)*

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

• *Transient or persistent heart failure post MI*

• *Patients at risk of cardiac or cerebral ischemia in case of acute hypotension*

The initial phase of treatment requires special medical supervision.

Surgery
It is recommended that treatment with angiotensin converting enzyme inhibitors such as ramipril should be discontinued where possible one day before surgery.

Monitoring of renal function
Renal function should be assessed before and during treatment. Particularly careful monitoring is required in patients with renal impairment (see section 4.2). There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant.

Angioedema
Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8). This risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) may be increased in patients taking concomitant medications which may cause angioedema such as mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, everolimus, sirolimus), vildagliptin or neprilysin (NEP) inhibitors (such as racecadotril). The combination of ramipril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see sections 4.3 and 4.5).

In case of angioedema, ramipril must be discontinued.
Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of the symptoms.

Intestinal angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting).

Anaphylactic reactions during desensitization
The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. A temporary discontinuation of Twilev should be considered prior to desensitization.

Electrolyte Monitoring: Hyperkalaemia
Hyperkalaemia has been observed in some patients treated with ACE inhibitors including ramipril. Patients at risk for development of hyperkalaemia include those with renal insufficiency, age (> 70 years), uncontrolled diabetes mellitus, or those using potassium salts, potassium retaining diuretics and other plasma potassium increasing active substances, or conditions such as dehydration, acute cardiac decompensation, metabolic acidosis. If concomitant use of the abovementioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Electrolyte Monitoring: Hyponatraemia
Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatraemia has been observed in some patients treated with ramipril. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatraemia.

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, as well as thrombocytopenia and anaemia, have been rarely seen and bone marrow depression has also been reported. It is recommended to monitor the white blood cell count to permit detection of a possible leucopoenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma), and all those treated with other medicinal products that can cause changes in the blood picture (see sections 4.5 and 4.8).

Ethnic differences
ACE inhibitors cause higher rate of angioedema in black patients than in non-black patients.
As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black people than in non-black patients, possibly because of a higher prevalence of hypertension with low renin level in the black hypertensive population.

Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

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

4.5 Interaction with other medicinal products and other forms of interaction

No clinical study evaluating drug interactions has been performed using Twilev. Interactions that have been identified in studies with individual components of Twilev (nebivolol or ramipril) may occur with Twilev. When nebivolol 10 mg once-daily was co-administered with ramipril 5 mg once-daily for 10 days, no clinically relevant pharmacokinetic interaction was observed between the individual components.

Pharmacokinetic interactions

Effects of other medicinal products on Twilev
As nebivolol metabolism involves the CYP2D6 isoenzyme, co-administration with substances inhibiting this enzyme, especially paroxetine, fluoxetine, thioridazine and quinidine may lead to increased plasma levels of nebivolol associated with an increased risk of excessive bradycardia and adverse events.
Co-administration of cimetidine increased the plasma levels of nebivolol, without changing the clinical effect.
Co-administration of ranitidine did not affect the pharmacokinetics of nebivolol. Provided nebivolol is taken with the meal, and an antacid between meals, the two treatments can be co-prescribed.
Combining nebivolol with nicardipine slightly increased the plasma levels of both drugs, without changing the clinical effect.
Co-administration of alcohol, furosemide or hydrochlorothiazide did not affect the pharmacokinetics of nebivolol.

Effects of Twilev on other medicinal products
Nebivolol does not affect the pharmacokinetics of warfarin.

Pharmacodynamic interactions

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

- Concomitant use contraindicated:

Sacubitril/valsartan
The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see sections 4.3 and 4.4). Treatment with ramipril must not be started until 36 hours after taking the last dose of sacubitril/valsartan. Sacubitril/valsartan must not be started until 36 hours after the last dose of ramipril.

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

- Concomitant use not recommended:

Class I antiarrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone): effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased (see section 4.4).

Calcium channel antagonists of verapamil / diltiazem type: negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients with beta-blocker treatment may lead to profound hypotension and atrio-ventricular block (see section 4.4).
Centrally-acting antihypertensives (clonidine, guanfacine, moxonidine, methyldopa, rilmenidine): concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation) (see section 4.4). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

- Concomitant use requiring caution:

Class III antiarrhythmic drugs (Amiodarone): effect on atrio-ventricular conduction time may be potentiated.

Anaesthetics - volatile halogenated: concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension (see section 4.4). As a general rule, avoid sudden withdrawal of beta-blocker treatment. The anaesthesiologist should be informed when the patient is receiving nebivolol.

Baclofen (antispastic agent), amifostine (antineoplastic adjunct): concomitant use with antihypertensives is likely to increase the fall in blood pressure, therefore the dosage of the antihypertensive medication should be adjusted accordingly.

Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, trimethoprim and in fixed dose combination with sulfamethoxazole, tacrolimus,ciclosporin):
Hyperkalaemia may occur, therefore close monitoring of serum potassium is required.

Other antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, acute alcohol intake, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin):
Potentiation of the risk of hypotension is to be anticipated.

- Concomitant use to be taken into account:

Digitalis glycosides: concomitant use may increase atrio-ventricular conduction time. Clinical trials with nebivolol have not shown any clinical evidence of an interaction. Nebivolol does not influence the kinetics of digoxin.

Calcium antagonists of the dihydropyridine type (amlodipine, felodipine, lacidipine, nifedipine, nicardipine, nimodipine, nitrendipine): concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Antipsychotics, antidepressants (tricyclics, barbiturates and phenothiazines): concomitant use may enhance the hypotensive effect of the beta-blockers (additive effect).

Vasopressor sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine):
Concomitant use may reduce the antihypertensive effect of nebivolol and ramipril. Beta-adrenergic agents may lead to unopposed alpha-adrenergic activity of sympathomimetic agents with both alpha- and beta-adrenergic effects (risk of hypertension, severe bradycardia and heart block).
Blood pressure monitoring is recommended.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell count:
Increased likelihood of haematological reactions (see section 4.4).

Lithium salts:
Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium level must be monitored.

Antidiabetic agents including insulin:
Although nebivolol does not affect glucose level, concomitant use may mask certain symptoms of hypoglycaemia (palpitations, tachycardia). However, hypoglycaemic reactions may occur due to ramipril. Blood glucose monitoring is recommended. The concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia (see Section 4.4).

Non-steroidal anti-inflammatory drugs and acetylsalicylic acid:
Reduction of the antihypertensive effect of ramipril is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and to an increase in kalaemia. NSAIDs have no effect on the blood pressure lowering effect of nebivolol.

mTOR inhibitors or DPP-IV inhibitors:
An increased risk of angioedema is possible in patients taking concomitant medications such as mTOR inhibitors (e.g.temsirolimus, everolimus, sirolimus) or vildagliptin. Caution should be used when starting therapy (see section 4.4).

Neprilysin (NEP) inhibitors:
An increased risk of angioedema has been reported with concomitant use of ACE inhibitors and NEP inhibitor such as

racecadotril (see section 4.4).

Nebivolol does not affect the pharmacodynamics of warfarin.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no available data from the use of Twilev in pregnant women.
Animal studies are insufficient with respect to reproductive toxicity of Twilev (see section 5.3).
Based on the available data on monocomponents, Twilev is not recommended during the first trimester of pregnancy (see section 4.4) and is contraindicated during the second and third trimesters of pregnancy (see section 4.3).

Ramipril

Ramipril is not recommended during the first trimester of pregnancy (see section 4.4) and is contraindicated during the second and third trimesters of pregnancy (see section 4.3).

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. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor/Angiotensin II Receptor Antagonist (AIIRA) therapy exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (See section 5.3 "Preclinical safety data"). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).

Nebivolol
Nebivolol has pharmacological effects that may cause harmful effects on pregnancy and / or the foetus / newborn. In general, beta-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, $beta_1$-selective adrenoceptor blockers are preferable.
Nebivolol should not be used during pregnancy unless clearly necessary. If treatment with nebivolol is considered necessary, the uteroplacental blood flow and the foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.
Breast-feeding
Twilev is not recommended during lactation.

Ramipril

Because insufficient information is available regarding the use of ramipril during breast-feeding (see section 5.2), ramipril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Nebivolol

Animal studies have shown that nebivolol is excreted in breast milk. It is not known whether this drug is excreted in human milk. Most beta-blockers, particularly lipophilic compounds like nebivolol and its active metabolites, pass into breast milk although to a variable extent. A risk to the newborns/infants cannot be excluded. Therefore, mothers receiving nebivolol should not breastfeed.

Fertility
There are no clinical data on fertility with the use of Twilev.

Ramipril

Ramipril did not affect fertility in an animal study (see Section 5.3: Fertility was not impaired either in male or in female rats).

Nebivolol

Nebivolol had no effect on rat fertility except at doses several-fold higher than the human maximum recommended dose when adverse effects on male and female reproductive organs in rats and mice were observed (see section 5.3). The effect of nebivolol on human fertility is unknown.

4.7 Effects on ability to drive and use machines

No studies on the effects of Twilev on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines it should be taken into account that dizziness, drowsiness, and fatigue may occasionally occur.

4.8 Undesirable effects

Summary of safety profile
Adverse reactions from the individual components nebivolol and ramipril in clinical trials, post-authorisation safety studies and spontaneous reporting are summarised in the below table.

Tabulated list of adverse reactions
The following terminologies have been used in order to classify the occurrence of undesirable effects:
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)

Table 1: Overview of adverse reactions with the single components of Twilev

MedDRA System Organ Class	**Adverse reactions**	**Frequency**	
		Nebivolol	**Ramipril**
Blood and lymphatic system disorders	Decrease in haemoglobin	-	Rare
	Red blood cell count decrease	-	Rare
	White blood cell count decreased (including neutropenia or agranulocyto	-	Rare
	Eosinophilia	-	Uncommon
	Platelet count decreased	-	Rare
	Bone marrow failure	-	Not known
	Pancytopenia	-	Not known
	Haemolitic anaemia	-	Not known
Immune system disorders	Antinuclear antibody increased	-	Not known
	Drug hypersensitivity, including anaphylactic or anaphylactoid reactions	Not known	Not known
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	-	Not known
Metabolism and nutrition disorders	Blood potassium increased	-	Common
	Blood sodium decreased	-	Not known
	Decreased appetite	-	Uncommon
Psychiatric disorders	Depression	Uncommon	Uncommon

	Nightmares	Uncommon	-
	Anxiety	-	Uncommon
	Nervousness	-	Uncommon
	Restlessness	-	Uncommon
	Sleep disorder including somnolence	-	Uncommon
	Confusional state	-	Rare
	Disturbance in attention	-	Not known
Nervous system disorders	Dizziness	Common	Common
	Headache	Common	Common
	Paraesthesia	Common	Uncommon
	Syncope	Very rare	Common
	Vertigo	-	Uncommon
	Ageusia	-	Uncommon
	Dysgeusia	-	Uncommon
	Tremor	-	Rare
	Balance disorder	-	Rare
	Cerebral ischaemia including ischaemic stroke and transient ischaemic attack	-	Not known
	Psychomotor skills impaired	-	Not known
	Burning sensation	-	Not known
	Parosmia	-	Not known
Eye disorders	Impaired vision including blurred vision	Uncommon	Uncommon
	Conjunctivitis	-	Rare
Ear and labyrinth disorders	Hearing impaired	-	Rare
	Tinnitus	-	Rare
Cardiac disorders	Bradycardia	Uncommon	-
	Heart Failure	Uncommon	-
	slowed AV conduction / AV-block	Uncommon	-
	Myocardial ischaemia including angina pectoris or myocardial infarction	-	Uncommon
	Tachycardia	-	Uncommon
	Arrythmia	-	Uncommon
	Palpitations	-	Uncommon
	Oedema peripheral	-	Uncommon
Vascular disorders	Hypotension	Uncommon	Common
	(increase of) intermittent claudication	Uncommon	-
	Orthostatic blood pressure decreased	-	Common
	Flushing	-	Uncommon
	Vascular stenosis	-	Rare
	Hypoperfusion	-	Rare
	Vasculitis	-	Rare
	Raynaud's phenomenon	-	Not known
Respiratory, thoracic and mediastinal disorders	Bronchospasm including asthma aggravated	Uncommon	Uncommon
	Cough	-	Common
	Dyspnoea	Common	Common
	Bronchitis	-	Common
	Sinusitis	-	Common
	Nasal congestion	-	Uncommon
Gastrointestinal disorders	Gastrointestinal inflammation	-	Common
	Abdominal discomfort	-	Common

	Constipation	Common	Uncommon
	Diarrhoea	Common	Common
	Dyspepsia	Uncommon	Common
	Flatulence	Uncommon	-
	Nausea	Common	Common
	Vomiting	Uncommon	Common
	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors)	-	Uncommon
	Pancreatic enzymes increased	-	Uncommon
	Small bowel angioedema	-	Uncommon
	Abdominal pain upper including gastritis	-	Uncommon
	Dry mouth	-	Uncommon
	Glossitis	-	Rare
	Aphthous stomatitis	-	Not known
Hepatobiliary disorders	Hepatic enzymes and/or bilirubin conjugated increased	-	Uncommon
	Jaundice cholestatic	-	Rare
	Hepatocellular damage	-	Rare
	Acute hepatic failure	-	Not known
	Cholestatic or cytolytic hepatitis (fatal outcome has been very exceptiona	-	Not known
Skin and subcutaneous tissue disorders	Angioedema	Not known	Uncommon
	Pruritus	Uncommon	Uncommon
	Psoriasis aggravated	Very rare	Not known
	Rash erythematous	Uncommon	
	Rash in particular maculo-papular	-	Common
	Urticaria	Not known	Rare
	Hyperhidrosis	-	Uncommon
	Exfoliative dermatitis	-	Rare
	Onycholysis	-	Rare
	Photosensitivity reaction	-	Very rare
	Toxic epidermal necrolysis	-	Not known
	Stevens-Johnson syndrome	-	Not known
	Erythema multiforme	-	Not known
	Pemphigus	-	Not known
	Dermatitis psoriasiform	-	Not known
	Pemphigoid or lichenoid exanthema or enanthem	-	Not known
	Alopecia	-	Not known
Musculoskeletal and connective tissue disorders	Myalgia	-	Common
	Muscle spasms	-	Common
	Arthralgia	-	Uncommon
Renal and urinary disorders	Renal impairment including renal failure acute	-	Uncommon
	Urine output increased	-	Uncommon
	Worsening of a pre-existing proteinuria	-	Uncommon
	Blood urea increased	-	Uncommon
	Blood creatinine increased	-	Uncommon
Reproductive system and breast disorders	Erectile dysfunction	Uncommon	Uncommon
	Libido decreased	-	Uncommon
	Gynaecomastia	-	Not known
General	Chest pain	-	Common

disorders and administration site conditions			
	Fatigue	Common	Common
	Pyrexia	-	Uncommon
	Asthenia	-	Rare
	Oedema	Common	-

The following adverse reactions have also been reported with some beta-adrenergic antagonists: hallucinations, psychoses, confusion, cold / cyanotic extremities, Raynaud phenomenon, dry eyes, and oculo-mucocutaneous toxicity of the practolol-type.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

There is no information on overdose with Twilev in humans.

Overdose symptoms related to each monocomponent and appropriate treatments as listed below also apply to the fixed combination Twilev.

Ramipril

Symptoms
Symptoms associated with overdose of ACE inhibitors may include excessive peripheral vasodilation (with marked hypotension, shock), bradycardia, electrolyte disturbances and renal failure.

Treatment
The patient should be closely monitored and the treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. Ramiprilat, the active metabolite of ramipril is poorly removed from the general circulation by haemodialysis.

Nebivolol

Symptoms
Symptoms of overdosage with beta-blockers are: bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

Treatment
In case of overdosage or hypersensitivity, the patient should be kept under close supervision and be treated in an intensive care ward. Blood glucose levels should be checked. Absorption of any drug residues still present in the gastro-intestinal tract can be prevented by gastric lavage and the administration of activated charcoal and a laxative. Artificial respiration may be required. Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma / plasma substitutes and, if necessary, catecholamines. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 µg/minute, or dobutamine, starting with a dose of 2.5 µg/minute, until the required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of glucagon 50 - 100 µg/kg i.v. may be considered. If required, the injection should be repeated within one hour, to be followed -if required- by an i.v. infusion of glucagon 70 µg/kg/h. In extreme cases of treatment-resistant bradycardia, a pacemaker may be inserted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE inhibitors, other combinations, ATC code: not yet assigned

Twilev is a combination of ramipril, an angiotensin-converting enzyme (ACE) inhibitor and nebivolol (as nebivolol hydrochloride), a highly selective β1-blocker with vasodilatory activity mediated by nitric oxide (NO). The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than each component alone.

Ramipril/Nebivolol

Clinical efficacy and safety
An open-label, interventional, Phase IV study (MEIN/22/NeRam-Hyp/001; ARTEMISIA study) evaluated the efficacy and safety of the extemporaneous combination of nebivolol 5 mg and ramipril 2.5 mg, 5 mg or 10 mg in hypertensive patients whose blood pressure was uncontrolled under monotherapy with nebivolol 5 mg or ramipril 5 mg monotherapy. After 12 weeks of treatment, the extemporaneous combination provided a statistically significant mean reduction of -19.2 (± 8.62) mmHg and -16.3 (± 7.99) mmHg of mean sitting systolic and diastolic blood pressure, respectively, versus baseline (i.e. values measured after 4 weeks of monotherapy with either nebivolol 5 mg or ramipril 5 mg). The extemporaneous combination of nebivolol 5 mg and ramipril 2.5 mg, 5 mg or 10 mg once daily was safe and well-tolerated and in line with the well-known safety profile of the two monotherapies.

Ramipril

Mechanism of action
Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.
Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients. However, reduced efficacy is not observed in trials involving combination therapy.

Pharmacodynamic effects
Antihypertensive properties:
Administration of ramipril causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow and glomerular filtration rate. Administration of ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.
In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral administration. The peak effect of a single dose is usually reached 3 to 6 hours after oral administration. The antihypertensive effect of a single dose usually lasts for 24 hours.
The maximum antihypertensive effect of continued treatment with ramipril is generally apparent after 3 to 4 weeks. It has been shown that the antihypertensive effect is sustained under long term therapy lasting 2 years.
Abrupt discontinuation of ramipril does not produce a rapid and excessive rebound increase in blood pressure.

Nebivolol

Mechanism of action
Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) andRSSS-nebivolol (or l-nebivolol). It combines two pharmacological activities:
It is a competitive and highly selective β1-receptor antagonist: this effect is attributed to the SRRR-enantiomer (d-enantiomer).
It has vasodilating properties due to an interaction with the L-arginine / nitric oxide pathway.

Pharmacodynamic effects
Single and repeated doses of nebivolol reduce heart rate and blood pressure at rest and during exercise, both in normotensive subjects and in hypertensive patients. The antihypertensive effect is maintained during chronic treatment.
At therapeutic doses, nebivolol is devoid of alpha-adrenergic antagonism.
During acute and chronic treatment with nebivolol in hypertensive patients, systemic vascular resistance is decreased. Despite heart rate reduction, reduction in cardiac output during rest and exercise may be limited due to an increase in stroke volume. The clinical relevance of these haemodynamic differences as compared to other beta1 receptor antagonists has not been fully established.

In hypertensive patients, nebivolol increases the NO-mediated vascular response to acetylcholine (ACh) which is reduced in patients with endothelial dysfunction.

In vitro and *in vivo* experiments in animals showed that nebivolol has no intrinsic sympathomimetic activity.
In vitro and *in vivo* experiments in animals showed that at pharmacological doses nebivolol has no membrane stabilising action.

In healthy volunteers, nebivolol has no significant effect on maximal exercise capacity or endurance.
Available preclinical and clinical evidence in hypertensive patients has not shown that nebivololhas a detrimental effect on erectile function.

5.2 Pharmacokinetic properties

One bioequivalence study in healthy volunteers was carried out to compare Twilev10 mg/5 mg film-coated tablets versus the two single agents given as extemporaneous combination, demonstrating bioequivalence in terms of AUC and Cmax parameters.
Absorption
Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract: peak plasma concentrations of ramipril are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite ramiprilat after oral administration of 2.5 mg and 5 mg ramipril is 45 %.
Peak plasma concentrations of ramiprilat, the sole active metabolite of ramipril are reached 2-4 hours after ramipril intake.
Steady state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.
Both nebivolol enantiomers are rapidly absorbed after oral administration. The absorption of nebivolol is not affected by food; nebivolol can be given with or without meals.
The oral bioavailability of nebivolol averages 12% in fast metabolisers and is virtually complete in slow metabolisers. At steady state and at the same dose level, the peak plasma concentration of unchanged nebivolol is about 23 times higher in poor metabolisers than in extensive metabolisers. When unchanged drug plus active metabolites are considered, the difference in peak plasma concentrations is 1.3 to 1.4 fold. Because of the variation in rates of metabolism, the dose of nebivolol should always be adjusted to the individual requirements of the patient: poor metabolisers therefore may require lower doses.

Distribution
The serum protein binding of ramipril is about 73 % and that of ramiprilat about 56 %.
In plasma, both nebivolol enantiomers are predominantly bound to albumin.
Plasma protein binding is 98.1% for SRRR-nebivolol and 97.9% for RSSS-nebivolol.

Biotransformation
Ramipril is almost completely metabolised to ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat.
Nebivolol is extensively metabolised, partly to active hydroxy-metabolites. Nebivolol is metabolised via alicyclic and aromatic hydroxylation, N-dealkylation and glucuronidation; in addition, glucuronides of the hydroxy-metabolites are formed. The metabolism of nebivolol by aromatic hydroxylation is subject to the CYP2D6 dependent genetic oxidative polymorphism.

Elimination
Excretion of the metabolites of ramipril is primarily renal.
Plasma concentrations of ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations. After multiple once-daily doses of ramipril, the effective half-life of ramiprilat was 13-17 hours for the 5-10 mg doses and longer for the lower 2.5 mg dose. This difference is related to the saturable capacity of the enzyme to bind ramiprilat.
In fast metabolisers, elimination half-lives of the nebivolol enantiomers average 10 hours. In slow metabolisers, they are 3 - 5 times longer. In fast metabolisers, plasma levels of the RSSS-enantiomer are slightly higher than for the SRRR-enantiomer. In slow metabolisers, this difference is larger. In fast metabolisers, elimination half-lives of the hydroxymetabolites of both enantiomers average 24 hours, and are about twice as long in slow metabolisers.
Steady-state plasma levels in most subjects (fast metabolisers) are reached within 24 hours for nebivolol and within a few days for the hydroxy-metabolites.
One week after administration, 38% of the dose is excreted in the urine and 48% in the faeces. Urinary excretion of unchanged nebivolol is less than 0.5% of the dose.

Linearity/non-linearity

Plasma concentrations of nebivolol are dose-proportional between 1 and 30 mg. The pharmacokinetics of nebivolol are not affected by age.

Special population
Patients with renal impairment (see section 4.2)
Renal excretion of ramiprilat is reduced in patients with impaired renal function, and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in subjects with normal renal function.

Patients with hepatic impairment
In patients with impaired liver function, the metabolism of ramipril to ramiprilat was delayed, due to diminished activity of hepatic esterases, and plasma ramipril levels in these patients were increased. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function.

Lactation
A single oral dose of ramipril produced an undetectable level of ramipril and its metabolite in breast milk. However, the effect of multiple doses is not known.

5.3 Preclinical safety data

No animal studies on the combination nebivolol/ramipril have been performed.

Ramipril

Oral administration of ramipril has been found to be devoid of acute toxicity in rodents and dogs.
Studies involving chronic oral administration have been conducted in rats, dogs and monkeys.
Indications of plasma electrolyte shifts and changes in blood picture have been found in the 3 species.
As an expression of the pharmacodynamic activity of ramipril, pronounced enlargement of the juxtaglomerular apparatus has been noted in the dog and monkey from daily doses of 250 mg/kg/d.
Rats, dogs and monkeys tolerated daily doses of 2, 2.5 and 8 mg/kg/d respectively without harmful effects. Irreversible kidney damage has been observed in very young rats given a single dose of ramipril. Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties.
Fertility was not impaired either in male or in female rats.
The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight or higher.
Extensive mutagenicity testing using several test systems has yielded no indication that ramipril possesses mutagenic or genotoxic properties.

Nebivolol

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity, carcinogenic potential, toxicity to reproduction and development. Adverse effects on the reproductive function were only recorded at high doses, exceeding by several fold the maximum recommended human dose (see Section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Croscarmellose sodium
Maize starch
Hypromellose
Polysorbate 80
Sodium stearyl fumarate

Film Coating:
OPADRY Pink, for Twilev2.5 mg/5 mg, composed of:
Hypromellose

Titanium dioxide (E171)
Macrogol
Red iron oxide (E172)
Carmine (E120)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Tablets are provided in oPA/Alu/PVC//Alu blisters.

Pack sizes of 14, 28, 30, 56, 60, 84, 90 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare
1611 Luxembourg
Luxembourg

8 MARKETING AUTHORISATION NUMBER

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