SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Teva Lisinopril and Hydrochlorothiazide 10 mg/12.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains lisinopril dihydrate equivalent to lisinopril 10 mg and hydrochlorothiazide 12.5 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Teva Lisinopril and Hydrochlorothiazide 10 mg/12.5 mg Tablets
White oval shaped, slightly arched tablets, debossed “LZ 10” on one side and breakline on the other.
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.

Lisinopril/hydrochlorothiazide fixed dose combination (10 mg lisinopril and 12.5 mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on lisinopril alone (or hydrochlorothiazide alone).

4.2 Posology and method of administration

Posology

The selection of a suitable antihypertensive dose of lisinopril and hydrochlorothiazide will depend upon the clinical evaluation of the patient.

The administration of the fixed combination lisinopril and hydrochlorothiazide is usually recommended after dosage titration with the individual components.
When clinically appropriate, a direct change from monotherapy to fixed combination may be considered.

10 mg/12.5 mg tablets may be administrated in patients whose blood pressure is not adequately controlled by 10 mg lisinopril alone.

A maximum daily dose of 40 mg lisinopril/ 25 mg hydrochlorothiazide should not be exceeded.

Diuretic pre-treatment
The diuretic therapy should be stopped two to three days prior to the start of a treatment with lisinopril/hydrochlorothiazide. If this is not possible, treatment should be started with lisinopril alone, in a 2.5 mg dose.

Special populations
Renal impairment
The combination lisinopril/hydrochlorothiazide is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min). In patients with creatinine clearance between 30 and 80 ml/min it may be used only after titration of the individual components. The recommended initial dose of lisinopril as monotherapy for these patients is 5-10 mg (see section 4.4).

Elderly
Clinical studies on the combination of lisinopril and hydrochlorothiazide have not shown that age is associated with any changes in efficacy or tolerability. See the above section on "Renal impairment".

Paediatric population
Safety and efficacy of lisinopril/hydrochlorothiazide have not been established in children.

Method of administration
Lisinopril/hydrochlorothiazide should be taken once daily.

4.3 Contraindications

- Hypersensitivity to the active substance, any other angiotenzin converting enzyme ACE inhibitors or to any of the excipients listed in section 6.1
- Hypersensitivity to hydrochlorothiazide or other sulphonamide medicinal products
    - History of angioedema relating to previous ACE-inhibitor therapy
    - Hereditary or idiopathic angioedema.
    - Severe renal impairment (creatinine clearance <30 ml/min)
    - Anuria
    - Severe hepatic impairment
    - Second and third trimester of pregnancy (see sections 4.4 and 4.6)
- The concomitant use of Teva Lisinopril and Hydrochlorothiazide Tablets with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1)

- Concomitant use with sacubitril/valsartan therapy. Lisinopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Lisinopril

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving lisinopril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. Regular determination of serum electrolytes should be performed at appropriate intervals in such patients. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be monitored under close medical supervision. Particular considerations applies to patients with ischaemic heart or cerebrovascular disease because an excessive fall in blood pressure could result in myocardial infarction or a cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses. Following restoration of effective blood volume and pressure, reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of lisinopril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, lisinopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal function impairment

See section 4.2.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of lisinopril therapy.

Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or lisinopril may be required.

Patients with renal transplantation
Should not be used, since there is no experience with lisinopril in patients with recent renal transplantation.

Hypersensitivity/angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including lisinopril. This may occur at any time during therapy. In such cases, lisinopril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.
Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of lisinopril. Treatment with lisinopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

The risk of angioedema may also be increased in patients receiving concomitant treatment with ACE inhibitors and a tissue plasminogen activator (see section 4.5).

Anaphylactoid reactions in haemodialysis patients
The use of lisinopril-hydrochlorothiazide is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients undergoing certain haemodialysis procedures (e.g. with the high-flux membranes AN 69 and during low-density lipoproteins (LDL) apheresis with dextran sulphate) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoprotein (LDL) apheresis
In rare occasions, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These symptoms could be avoided by temporarily discontinuation of the treatment with ACE inhibitor before each apheresis.

Desensitisation
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic disease
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving lisinopril-hydrochlorothiazide who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril/hydrochlorothiazide and receive appropriate medical follow-up.

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Lisinopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If lisinopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Race
ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, lisinopril may be less effective in lowering blood pressure in black patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

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

Surgery/anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Serum potassium
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including lisinopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, hypoaldosteronism.
ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt

substitutes), potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).
If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Diabetic patients
In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5).

Lithium
The combination of lithium and lisinopril is generally not recommended (see section 4.5).

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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.

Hydrochlorothiazide
Impaired renal function
In patients with renal diseases, thiazides may precipitate azotemia. In patients with impaired renal function, cumulative effects of the medicinal products may occur. If progressive renal insufficiency develops, characterized by an increase in non-protein nitrogen, careful evaluation of the therapy is necessary, and stopping the diuretics therapy should be considered (see section 4.3).

Impaired liver function
Thiazides should be used with caution in patients with impaired hepatic function or liver disease, since minor alterations of fluid and electrolyte balance may induce hepatic coma (see section 4.3).

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. Dosage adjustments of antidiabetic agents or insulin drugs may be required. Blood glucose levels should be monitored closely during the first month of treatment with an ACE inhibitor in diabetic patients treated with oral antidiabetics or insulin. Latent diabetic mellitus may become manifest during thiazide therapy.

Increases of cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. However, lisinopril may increase the excretion of uric acid and thus attenuate the hyperuricemic effect of hydrochlorothiazide.

Electrolyte imbalances
As for any patient treated with diuretics, periodic determination of serum electrolytes at appropriate intervals should be performed.
Thiazides, including hydrochlorothiazide, may cause fluid and electrolyte imbalances (hypokalaemia, hyponatraemia and hypochloremic alkalosis). Warning signals of fluid or electrolyte imbalances are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disorders such as nausea and vomiting. Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does not require treatment. Thiazides have been shown to increase the urinary excretions of magnesium, which may result in hypomagnesaemia.

Although hypokalaemia may develop through the use of thiazide diuretics, concomitant use of lisinopril may decrease diuretic-induced hypokalaemia. The possibility of hypokalaemia is strongest in liver cirrhosis patients, in patients experiencing rapid diuresis, in patients having an inadequate oral intake of electrolytes and in patients concomitantly treated with corticosteroids or ACTH (see section 4.5).

Thiazides may decrease urinary calcium excretion and may cause a slight elevation of serum calcium levels even in the absence of known disorders of calcium metabolism. Marked hypercalcemia may evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out parathyroid function tests.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry.
Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.
Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Acute respiratory toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema

typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Teva Lisinopril and Hydrochlorothiazide should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Other
In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Lisinopril/hydrochlorothiazide
Hypotension and electrolyte/fluid imbalances
Symptomatic hypotension may sometimes occur following the first dose of lisinopril / hydrochlorothiazide. The odds for hypotension in hypertensive patients are greater in the presence of fluid or electrolyte imbalances, such as volume depletion, hyponatraemia, hypochloremic alkalosis, hypomagnesemia or hypokalaemia, that may occur as a result of a diuretic therapy, a low-sodium diet, dialysis or during intercurrent diarrhoea or vomiting. In such patients the serum electrolyte levels must be monitored on a regular basis.
Starting the therapy and adjusting the dosage for patients who are at increased risk for symptomatic hypotension must be done under strict medical supervision.
Special attention should be given to the treatment of patients suffering from ischaemic heart disease or cerebrovascular conditions, because an excessive drop in blood pressure may trigger a myocardial infarction or cerebrovascular accident.
If severe hypotension occurs, the patient must be put into the shock position and promptly administered an intravenous infusion of a physiological saline solution. A transient hypotensive reaction is not a contraindication for future doses. If the blood volume and blood pressure have effectively been restored, therapy may likely be resumed with a lower dosage or may very well be continued simply with one of both components.
As with other vasodilators, caution must be exercised when administering lisinopril / hydrochlorothiazide to patients suffering from aortic stenosis or hypertrophic cardiomyopathy.

Impaired renal function
Thiazides are ineffective in patients with a creatinine clearance of less than 30 ml/min (i.e. a moderate or serious renal insufficiency) (see section 4.3).
Lisinopril/hydrochlorothiazide should not be given to patients with a creatinine clearance of 30-80 ml/minute until dose adjustments of the separate ingredients have shown that there is a need for the doses in the combination preparation.
Some patients without a definite pre-existing renovascular disorder developed slight and transitory increases in blood urea levels and serum creatinine levels when lisinopril was given concomitantly with a diuretic. If this occurs during the use of lisinopril/ hydrochlorothiazide, the treatment should be stopped. Resuming the treatment at a reduced dosage may be possible, if appropriate, one of the components may be used on its own.

Prior diuretic therapy
The diuretic therapy should be discontinued for 2-3 days prior to initiation with lisinopril-hydrochlorothiazide. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

Risk of hypokalaemia
The combination of an ACE-inhibitor with a thiazide does not exclude the occurrence of hypokalaemia. Regular checks of potassium should take place.

Neutropenia/agranulocytosis

The fixed-dose combination of lisinopril and hydrochlorothiazide should be withdrawn if neutropenia (neutrophils less than 1000/mm3) is detected or suspected.

Anti-doping test
The hydrochlorothiazide contained in this medication could produce a positive analytic result in an anti-doping test.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions between lisinopril/ hydrochlorothiazide tablets, other ACE-inhibitors or products containing hydrochlorothiazide have been reported.

Lisinopril

Dual blockade of the renin-angiotensin-aldosterone system
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).
The combination of lisinopril/ hydrochlorthiazide with medicinal products containing aliskiren is contraindicated in patients with diabetes mellitus or impaired renal function (GFR < 60 ml/min/1.73m^2) and is not recommended in other patient groups (see sections 4.3 and 4.4).

Diuretics
When a diuretic is added to the therapy of a patient receiving lisinopril, the antihypertensive effect is usually additive.
Patients already on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure when lisinopril is added. The possibility of symptomatic hypotension with lisinopril can be minimised by discontinuing the diuretic prior to initiation of treatment with lisinopril (see section 4.4).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes
The potassium excreting effect of thiazide diuretics is usually attenuated by the potassium sparing effect of lisinopril. Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with lisinopril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when lisinopril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of lisinopril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Ciclosporin
Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Concomitant administration of ACE inhibitors and ciclosporin increases the risk of renal failure.

Heparin
Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid = 3g/day
Chronic administration of NSAIDs (including selective cyclooxygenase-2 inhibitors) may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors may exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

Gold
Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Other antihypertensive medicinal products
Concomitant use of these medicinal products may increase the hypotensive effects of lisinopril. Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

Tricyclic antidepressants/antipsychotics/anaesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics
Sympathomimetics may reduce the hypotensive effect of ACE-inhibitors; patients must be monitored carefully.

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicinal products (insulins, oral hypoglycaemic agents) may cause an increased blood glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Nitrates, acetylsalicylic acid, thrombolytics and/or beta blockers
Lisinopril may be used concomitantly with acetylsalicylic acid (cardiological doses), thrombolytics, beta blockers and/or nitrates.

Allopurinol
Concomitant administration of ACE inhibitors and allopurinol increases the risk of renal failure and may lead to an increased risk of leucopenia.

Lovastatin
Concomitant administration of ACE inhibitors and lovastatin increases the risk of hyperkalaemia.

Procainamide, cytostatics immunosuppressives

Concomitant administration with ACE inhibitors may lead to an increased risk of leucopenia (see section 4.4).

Haemodialysis
Lisinopril/hydrochlorothiazide is not indicated in patients requiring dialysis as a high incidence of anaphylactoid reactions have been reported in patients dialysed with high-flux membranes and treated concomitantly with an ACE inhibitor. This combination should be avoided.

Medicines increasing the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (mammalian target of rapamycin) (e.g. sirolimus, everolimus, temsirolimus), NEP (neutral endopeptidase)-inhibitors (e.g. racecadotril), vildagliptin or a tissue plasminogen activator may lead to an increased risk for angioedema (see section 4.4)

Hydrochlorothiazide

Other kaliuretic medicines, amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropine (ACTH) , salicylic acid derivatives or stimulating laxatives
Hydrochlorothiazide may cause electrolyte imbalances, especially hypokalaemia.

Calcium salts/vitamin D
Increased serum calcium levels as a result of decreased excretion may occur if concomitantly administered with thiazide diuretics. If additional intake of calcium supplements or vitamin D is required, serum calcium levels should be checked regularly and the dose adjusted accordingly.

Cardiac glycosides
There is increased risk of digitalis intoxication (e.g. increased ventricular excitability) together with thiazide induced hypokalaemia.

Cholestyramine resin and colestipol
These may delay or reduce the absorption of hydrochlorothiazide. Therefore, sulphonamide diuretics should be taken at least 1 hour before or 4-6 hours after intake of these agents.

Non-depolarizing muscle relaxants (i.e. tubocurarine chloride)
The effect of these medications may be potentiated by hydrochlorothiazide.

Torsades de pointes-inducing medicinal products
Because of the risk of hypokalaemia, the concomitant administration of hydrochlorothiazide and medicinal products that induce torsades de pointes, e.g. some antiarrythmias some antipsychotics and other medications which are known to induce torsades de pointes should be used with caution.

Sotalol
Thiazide-induced hypokalaemia can increase the risk of sotalol-induced arrhythmias.

Diazoxide
The hyperglycaemic effect of diazoxide may be increased by concomitant use with thiazides.

Amantadine
Thiazides may increase the risk of adverse drug reactions occurring during treatment with

amantadine.

Cytotoxic drugs
Thiazides may reducethe renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and increase their myelosuppressive effects.

Ciclosporin
Concomitant use of thiazides and ciclosporin may increase the risk of hyperuricaemia and gout-like complications.

Barbiturates/alcohol/anaesthetics
The concomitant use of thiazides with alcohol, barbiturates or anaesthetics may possibly cause an increase in hypotension.

Adrenergic amines
Hydrochlorothiazide may decrease the response to adrenergic amines, such as noradrenaline. However, the clinical impact of this effect does not justify the exclusion of their use.

Lisinopril/hydrochlorothiazide

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of lisinopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

ACE inhibitors

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

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 antihypertensive 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.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3.) Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose

mothers have taken ACE inhibitors should be closely observed for hypotension (See sections 4.3 and 4.4).

Lisinopril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Hydrochlorothiazide

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding

ACE inhibitors

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

Hydrochlorothiazide

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Teva Lisinopril and Hydrochlorothiazide Tablets during breast-feeding is not recommended. If Teva Lisinopril and Hydrochlorothiazide Tablets is used during breast-feeding, doses should be kept as low as possible. Hypersensivity to sulphonamide-derived drugs, hypokalaemia and nuclear icterus have also been observed.

4.7 Effects on ability to drive and use machines

As with other antihypertensives, lisinopril-hydrochlorothiazide combination products may have a mild to moderate effect on the ability to drive and use machines. Especially at the start of the treatment or when the dose is modified, and also when used in combination with alcohol, but these effects depend on the individual's susceptibility.

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or tiredness may occur.

4.8 Undesirable effects

Clinical studies have shown that the undesirable effects of the combination preparation are similar to the ones already reported with lisinopril and hydrochlorothiazide separately.

The following undesirable effects have been observed and reported during treatment with lisinopril and/or hydrochlorothiazide with the following frequencies: very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10000 to1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).
The most commonly reported ADRs are cough, dizziness, hypotension, and headache which may occur in 1 to 10% of treated patients. In clinical studies, side effects have usually been mild and transient, and in most instances have not required interruption of therapy.

Metabolism and nutrition disorders
uncommon: gout

Nervous system and psychiatric disorders
common: dizziness, which generally responded to dosage reduction and seldom required discontinuation of therapy; headache, fatigue.
uncommon: paraesthesia, asthenia

Respiratory, thoracic and mediastinal disorders
common: dry and persistent cough, which disappeared after discontinuation of therapy.

Cardiac and vascular disorders
common: hypotension including orthostatic hypotension.
uncommon: palpitation, chest pain, muscle spasms and muscle weakness

Gastrointestinal disorders
uncommon: diarrhoea, nausea, vomiting, indigestion, pancreatitis, dry mouth.

Skin and subcutaneous tissue disorders
uncommon: rash, angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx (see section 4.4)

Reproductive system and genitals and breast disorders
uncommon: impotence.

Others
rare: a complex of symptoms, consisting of one or more of the following: fever, vasculitis, myalgia, artralgia or arthritis, positive ANA test; increased ESR, eosinophilia, leukocytosis, rash, photosensibility or other dermatological manifestations.

Laboratory test values
Fluctuations in laboratory values were rarely of clinical importance. Hyperglycaemia, hyperuricaemia, hyperkalemia or hypokalaemia have been reported incidentally. Increases in blood cholesterol and triglyceride concentrations may be observed in thiazide treatment. A slight increase in blood urea level and serum creatinine are usually found in patients without a

history of decreased renal function. When an increase is observed, this will usually disappear after stopping the treatment. Bone marrow depression, which manifests itself as anaemia and/or thrombocytopenia and/or leucopenia, has been reported. Agranulocytosis is reported in rare cases, but a clear relation to the combination preparation could not be determined. Small decreases in haemoglobin and haematocrit values are frequently reported in patients with hypertension, but were rarely of clinical significance unless other anaemia causes existed. Increases in liver enzymes and/or serum bilirubin have been noted rarely, but a causal link to lisinopril/hydrochlorothiazide has not been determined.
Haemolytic anaemia has been reported rarely.

Undesirable effects reported of the individual components:

Hydrochlorothiazide (frequencies not known unless otherwise specified):
Infections and infestations
sialoadenitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Blood and lymphatic system disorders
leucopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression.

Metabolism and nutrition disorders
anorexia, hyperglyceamia, glucosuria, hyperuricemia, electrolyte imbalance (including hyponatraemia hypokalaemia, hypochloremic alkalosis and hypomagnesaemia), increases in cholesterol and triglycerides, gout.

Psychiatric disorders
restlessness, depression, sleep disturbance

Nervous system disorders
loss of appetite, paraesthesia, light-headedness

Eye disorders
xanthopsia, transient blurred vision, choroidal effusion, acute myopia, acute angle-closure glaucoma

Ear and labyrinth disorders
vertigo

Cardiac disorders
postural hypotension, cardiac arrhythmias

Vascular disorders
necrotising angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders
acute respiratory distress syndrome (ARDS) (see section 4.4) (frequency: very rare)

Gastrointestinal disorders
gastric irritation, diarrhoea, constipation, pancreatitis

Hepato-biliary disorders
jaundice (intrahepatic cholstatic jaundice)

Skin and subcutaneous disorders
photosensivity reactions, rash, cutaneous lupus erythematosus, systemic lupus erythematosus, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders
muscle spasm, muscle weakness

Renal and urinary disorders
renal dysfunction, interstitial nephritis

General disorders
fever, weakness

Lisinopril and other ACE inhibitors:
Blood and the lymphatic system disorders

rare:	decreases in haemoglobin, decreases in haematocrit.
very rare:	bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease

Metabolism and nutrition disorders

very rare:	hypoglycaemia

Nervous system and psychiatric disorders

common:	dizziness, headache, syncope
uncommon:	mood alterations, depressive symptoms, hallucinations, paraesthesia, vertigo, taste disturbance, sleep disturbances.
rare:	mental confusion, olfactory disorder.

Cardiac and vascular disorders

common:	orthostatic effects (including orthostatic hypotension)
uncommon:	myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia. Raynaud's phenomenon
not known:	flushing

Respiratory, thoracic and mediastinal disorders

common:	cough (see section 4.4)
uncommon:	rhinitis
very rare:	bronchospasm, sinusitis, allergic alveolitis /eosinophilic pneumonia

Gastrointestinal disorders

common:	diarrhoea, vomiting
uncommon:	nausea, abdominal pain and indigestion
rare:	dry mouth
very rare:	pancreatitis, intestinal angioedema,

Hepatobiliary disorders

uncommon:	elevated liver enzymes and bilirubin
very rare.	hepatitis- either hepatocellular or cholestatic, jaundice and hepatic failure (see section 4.4)*

Skin and subcutaneous tissue disorders

uncommon: rash, pruritus, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4)
rare: urticaria, alopecia, psoriasis
very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme cutaneous pseudolymphoma**.

Renal and urinary disorders
common: renal dysfunction
rare: uraemia, acute renal failure
very rare: oliguria/anuria

Reproductive system and breast disorders
uncommon: impotence
rare: gynaecomastia

Endocrine disorders
rare: Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

General disorders and administration site conditions
uncommon: fatigue, asthenia

Investigations
uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
rare: hyponatraemia.

* Very rarely, it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving lisinopril-hydrochlorothiazide combination who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril-hydrochlorothiazide combination and receive appropriate medical follow up.
**A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Description of selected adverse reactions
Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).
Cases of choroidal effusion with visual field defect have been reported after use of thiazides and thiazide-like diuretics.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no specific information available on the treatment of a lisinopril/hydrochlorothiazide overdose. The treatment is symptomatic and supportive. Use of the medicinal product must immediately be discontinued and the patient should be observed closely. Therapeutic measures depend on the nature and severity of the symptoms. Measures should be taken to prevent absorption and accelerate elimination. The recommended measures include inducing vomiting and/or pumping the stomach if the drug was ingested recently, whereas dehydration, disturbances of the electrolyte balance and hypotension should be treated in the usual manner.

Lisinopril
Limited data are available for overdose in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating lisinopril (e.g., emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

Hydrochlorothiazide
The most common objective and subjective signs and symptoms are the result of electrolyte depletion (hypokalaemia, hypochloremia, hyponatraemia) and dehydration due to excessive diuresis. Additional symptoms of hydrochlorothiazide overdose are increased diuresis, depression of consciousness (incl. coma), convulsions, paresis, cardiac arrhythmias and renal failure.
Bradycardia or extensive vagal reactions should be treated by administering atropine.

If digitalis has also been given, hypokalaemia may accentuate arrhythmia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitor (ACE: angiotensin converting enzyme) and thiazide diuretic, ATC-code: C09B A03

Mechanism of action
Both components, the ACE inhibitor and diuretic, have complementary modes of action and exert an additive antihypertensive effect. ACE catalyses the conversion of angiotension I to angiotension II, which has a strong vasoconstrictor effect and stimulates aldosterone secretion. The antihypertensive effect of lisinopril is mainly due to the suppression of the renin angiotensin-aldosterone system with reduction of plasma concentration of angiotension II and aldosterone. Lisinopril exerts an antihypertensive effect even in patients with low-renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. It remains unclear whether increased levels of bradykinin (a potent vasodilator) plays a role in the therapeutic effect of lisinopril.

Hydrochlorothiazide is a thiazide diuretic and an antihypertensive that increases the plasma-renin activity. It suppresses the renal reabsorption of electrolytes in the renal distal tubule and increases the excretion of sodium, chloride, potassium, magnesium, bicarbonates and water. The excretion of calcium may be reduced. Concomitant administration of lisinopril and hydrochlorothiazide gives a greater reduction in blood pressure than monotherapy. Lisinopril normally attenuates the potassium loss associated with hydrochlorothiazide.
The effects of the fixed dose combination of lisinopril and hydrochlorothiazide on mortality and cardiovascular morbidity are currently unknown.

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

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

5.2 Pharmacokinetic properties

The combined tablet is bioequivalent to monotherapy with each of the active ingredients.

Absorption
Lisinopril: Approx 25%, with an interindividual variability of 6-60% on all the tested dosages (5-80 mg). The absorption of lisinopril is not affected by food. Peak serum concentrations are reached within 6-8 hours. Effect on blood pressure was observed after 1-2 hours. The peak effect is obtained after 6 hours and lasts for at least 24 hours.
Hydrochlorothiazide: The diuretic effect is observed within 2 hours. The maximum effect is attained after 4 hours. Clinically noticeable effect will last 6-12 hours.

Distribution
Protein binding: Lisinopril is not bound to plasma proteins except to ACE. A reduced distribution volume may result in higher plasma concentrations in older patients than in younger patients.

Half-life
Lisinopril: after multiple dosing 12 hours. *Hydrochlorothiazide:* 5½ - 15 hours.

Biotransformation /elimination
Both active components are excreted unchanged via the kidneys. Approx. 60% of the orally administered hydrochlorothiazide is eliminated within 24 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and carcinogenic potential. In animal tests ACE inhibitors induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Fetotoxity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to the direct action of ACE inhibitors on the foetal renin-angiotensin system and partly due to the ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus (see 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate
Magnesium stearate
Pregelatinised starch
Mannitol
Maize starch.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PVdC-aluminium blisters, packs of 14, 28, 30, 50, 98 and 100 tablets.
Hospital packs 50 (perforated unit dose blisters), 100.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point
Whistler Drive
Castleford
WF10 5HX
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0455

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 July 2003

10 DATE OF REVISION OF THE TEXT

09/01/2023