Core Safety Profile

Active substance: Moexipril + Hydrochlorothiazide
Pharmaceutical form(s)/strength: film-coated tablet 15 mg/25 mg
P-RMS: IT/H/PSUR/0027/001
Date of FAR: 02.07.2013
4.2 Posology and Method of Administration

Patients whose blood pressure has been stabilised with the free combination consisting of 7.5 mg moexipril hydrochloride and 12.5 mg hydrochlorothiazide, 15 mg moexipril hydrochloride and 12.5 mg hydrochlorothiazide or 15 mg moexipril hydrochloride and 25 mg hydrochlorothiazide, must take one film coated tablet of moexipril hydrochloride / HCTZ 5 mg/12.5 mg, moexipril hydrochloride / HCTZ 15 mg/12.5 mg or moexipril hydrochloride / HCTZ 15 mg/25 mg daily in the morning.

Fixed dose combinations are not recommended for initial therapy. Therefore, a patient whose blood pressure is not adequately controlled with either moexipril or hydrochlorothiazide may be given the fixed combination of moexipril hydrochloride and hydrochlorothiazide, if his/her blood pressure has been stabilised with the free combination of these components given in the same proportions.

Patients with impaired renal function
Moexipril hydrochloride / HCTZ must not be given to patients with severely impaired renal function (creatinine clearance < 40 ml/min; see section 4.3).

In patients with mild to moderate impaired renal function (creatinine clearance of > 40 ml/min but < 60 ml/min) this fixed combination must be administered very carefully and moexipril hydrochloride / HCTZ 7.5 mg/12.5 mg must be used preferably. Additionally, in patients with impaired renal function close monitoring of kidney function by the treating physician is imperative.

Use in the elderly
No dose adjustment is required in elderly patients

Use in children
Moexipril hydrochloride / HCTZ must not be given to children.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients

- History of angioneurotic edema associated with previous ACE inhibitor therapy
- Hereditary/idiopathic angioneurotic oedema
- Renal artery stenosis (bilateral or an anatomic or functional solitary kidney)
- Patients treated with aliskiren and suffering from diabetes mellitus or moderate to severe renal impairment (creatinine clearance < 60 ml/min)
- Recent kidney transplantation
- Severely impaired renal function (creatinine clearance < 40 ml/min)
- Severe hepatic impairment
- Anuria
- Hemodynamic important aortic or mitral valve stenosis
- Hypertrophic cardiomyopathy
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia
- Second and third trimester of pregnancy (see also section 4.6 Use during pregnancy and lactation)
To avoid the risk of life-threatening anaphylactic reactions ACE inhibitors must not be used

- During dialysis or hemofiltration with poly-(acrylonitrile, natrium-2-
methylallylsulfonat)-high-flux-membranes
- During low density lipoprotein (LDL) apheresis with dextrane sulphate
- During desensitization therapy versus insect poisons (e.g. bee or wasp stings)

4.4 Special Warnings and Precautions for Use

Moexipril hydrochloride/ HCTZ must only be used with caution in patients with:

- Clinical important serum electrolyte imbalances
- Decreased immune response
- Collagenous vascular diseases (e.g. lupus erythematosus, scleroderma)
- Concomitant systemic drug therapy suppressing the immune response (e.g. corticosteroids, cytostatic agents, antimetabolites) and allopurinol, procainamide, or lithium

Especially at the beginning of the ACE inhibitor therapy the blood pressure and the respective laboratory values must be monitored carefully in patients with:

- Impaired renal function (creatinine clearance 40 – 60 ml/min)
- Severe hypertension, renal hypertension
- Cardiac failure
- Salt and/or fluid volume depletion
- Age of more than 65 years

4.4.1 Hypotension

Moexipril hydrochloride / HCTZ may cause a profound fall of blood pressure especially at the beginning of the therapy with symptoms of dizziness, feeling of weakness and disturbances of vision. Rarely syncope may occur. Symptomatic hypotension was observed in 8 % of patients given a combination of moexipril hydrochloride and HCTZ and led to discontinuation of therapy in about 1 % of patients. It is rare in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume and/or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. Volume and/or salt depletion must be corrected before initiating therapy with moexipril hydrochloride / HCTZ.

Excessive hypotension caused by ACE inhibitor therapy in patients with congestive heart failure with or without concomitant renal insufficiency, may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. Those patients must be followed closely at the beginning of the therapy and whenever the moexipril hydrochloride / HCTZ dose is increased.

If hypotension occurs, the patient must be placed in a supine position and, if necessary, intravenously sodium chloride solution infusion must be given. Moexipril hydrochloride / HCTZ treatment usually can be continued following reconstitution of an adequate blood pressure and substitution of the fluid volume.

For patients who experience an excessive reduction in blood pressure with moexipril hydrochlorothiazide 7.5 mg /12.5 mg, the physician in charge may consider prescribing 3.75 mg moexipril / 6.25 mg hydrochlorothiazide.
4.4.2 Renal vascular hypertension

Before ACE inhibitor therapy is started, renal function has to be controlled. There is an increased risk of severe hypotension and renal insufficiency when patients with renal vascular hypertension are treated with moexipril hydrochloride / HCTZ. Loss of renal function may occur with only mild changes in serum creatinine. In case of renal artery stenosis (bilateral or stenosis of an anatomic or functional solitary kidney) ACE inhibitors are contraindicated (see also section 4.3 contraindications).

4.4.3 Impaired renal function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including moexipril, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

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

Dosage recommendation for patients with moderately impaired renal function (creatinine clearance 40 – 60 ml/min or serum creatinine >1.2 mg/dl and <1.8 mg/dl): According to the available results of moexipril hydrochloride / HCTZ, normally no dose adaption will be necessary. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, and moexipril hydrochlorothiazide is not recommended.

(See also section 4.3 Contraindications)

4.4.4 Proteinuria

Clinically relevant proteinuria (> 1 g/dl) may occur, particularly in patients with existing renal function impairment or on relatively high doses of moexipril hydrochloride / HCTZ.

4.4.5 Angioneurotic edema

Angioneurotic edema of the face, lips, mucous membranes, tongue, glottis and/or larynx and of the extremities has been reported in patients treated with ACE inhibitors, especially during the first weeks of treatment. However, in rare cases, severe angioneurotic edema may develop even after long-term treatment with an ACE inhibitor. Treatment must promptly be discontinued and replaced by an agent belonging to another class of antihypertensive medicinal products. Symptoms suggestive of angioedema or facial oedema occurred in < 0.5% of moexipril hydrochloride / HCTZ treated patients in placebo controlled trials. None of the cases was considered to be life-threatening.

Angioneurotic edema involving the tongue, glottis or larynx may be fatal due to airway obstruction. Emergency therapy must include intravenous administration of corticosteroids, H1-receptor antagonists and H2-receptor antagonists. If the condition of the patient does not ameliorate with the above mentioned therapy, epinephrine must be administered slowly intravenously monitored by ECG control.
In case of hereditary angioneurotic edema due to C1-inactivator deficiency associated with ACE inhibitor therapy, additionally a C1-inactivator must be administered. Furthermore, intubation or tracheotomy are to be considered.
(See also section 4.8 Undesirable effects)

### 4.4.6 Intestinal angioneurotic edema

Intestinal Angioneurotic edema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea and vomiting). In some cases there was no prior history of facial angioneurotic edema and C1-esterase levels were normal. Intestinal Angioneurotic edema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery. Symptoms resolved after stopping the ACE inhibitor. Intestinal Angioneurotic edema must be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

### 4.4.7 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).

### 4.4.8 Cough

During treatment with an ACE inhibitor a dry and non-productive cough may occur which disappears after discontinuation. In controlled trials with a combination of moexipril hydrochloride and HCTZ cough was present in 5 % of patients treated with this combination and in 2 % given placebo.

### 4.4.9 Elderly

In elderly male subjects (> 65 years of age) with clinically normal renal and hepatic function, the AUC and Cmax of moexiprilat are greater than those of younger subjects. According to the available results of moexipril hydrochloride / HCTZ, normally no dose adaptation will be necessary.

Control of renal function before start and during moexipril hydrochloride / HCTZ therapy is recommended.

### 4.4.10 Serum Electrolyte Imbalances

#### 4.4.10.1 Moexipril

In clinical trials with moexipril hydrochloride, persistent hyperkalemia (serum potassium > 5.4 mEq/l) occurred in approximately 2.6 % of hypertensive patients. In clinical trials, 0.1 % of patients (two patients) were discontinued from therapy due to elevated serum potassium. Risk factors for the development of hyperkalemia with ACE inhibitors include renal insufficiency and/or heart failure, diabetes mellitus, hypoaldosteronism and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium containing salt substitutes which have to be used cautiously if at all with moexipril hydrochloride / HCTZ.
4.4.10.2 Hydrochlorothiazide/thiazide diuretics

Treatment with thiazide diuretics has been associated with hypokalemia, hyponatremia and hypochloremic alkalosis. The risk to develop hypokalemia is greatest in patients with liver cirrhosis, in patients experiencing a brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH.

In clinical studies with moexipril hydrochloride / HCTZ, moexipril hydrochloride and HCTZ have been shown to have a counterbalancing effect on serum potassium, so that little net effect upon serum potassium will be seen with this combination. However, patients must be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician.

Chloride deficits generally are mild and require specific treatment under extraordinary circumstances only (e.g. in liver disease or renal disease). Dilutional hyponatremia may occur in oedematous patients. Appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Calcium excretion is reduced by thiazides. In a few patients on prolonged thiazide therapy pathological changes in the parathyroid gland have been observed with hypercalcemia and hypophosphatemia. More serious complications of hyperparathyroidism (nephrolithiasis, bone resorption and peptic ulceration) have not been observed.

Thiazides enhance urinary excretion of magnesium and may result in hypomagnesemia.

Patients receiving thiazide diuretics must be observed for clinical signs of fluid or electrolyte imbalance. Warning signs of fluid or electrolyte imbalance are dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances as nausea or vomiting.

4.4.11 Other metabolic disturbances

Thiazide diuretics may reduce glucose tolerance and may raise serum levels of cholesterol and triglycerides. These effects are usually minor. Thiazide diuretics have been associated with the development of hyperuricemia and/or gout in some patients. This effect appears to be dose related.

4.4.12 Surgery and anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, moexipril hydrochloride / HCTZ will block the effect of compensatory renin release. Hypotension occurring as a result of this mechanism can be corrected by volume expansion (see also section 4.8 Undesirable effects).

4.4.13 Neutropenia/Agranulocytosis

Other ACE inhibitors have been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagenosis such as systemic lupus erythematosus or dermatosclerosis. Available data from clinical trials of moexipril are insufficient to show that moexipril does not cause agranulocytosis at rates similar as captopril. Although, there were no cases of severe neutropenia (absolute neutrophil count <500/mm3) among patients given moexipril hydrochloride, as with other ACE inhibitors. Monitoring of white blood cell counts must be considered for patients suffering from collagenosis, especially if the disease is associated with impaired renal function.
4.4.14 **Lupus**

Thiazide diuretics have been reported to exacerbate or activate systemic lupus erythematosus.

4.4.15 **Lactose**

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption must not take this moexipril hydrochloride.

4.4.16 **Acute Myopia and Secondary Angle-Closure Glaucoma**

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

4.4.17 **Primary Hyperaldosteronism**

The combination moexipril + hydrochlorothiazide does not represent a treatment of choice for primary hyperaldosteronism. If moexipril + hydrochlorothiazide are used in a patient with primary hyperaldosteronism, then careful monitoring of plasma potassium level is required.

4.4.18 **Dual blockade of the renin-angiotensin-aldosterone system**

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

4.4.19 **Ethnicity**

ACE inhibitors are less effective as antihypertensives in patients with a black skin colour. These patients also have a higher risk of angioedema.

4.5 **Interaction with other medicinal products and other forms of interaction**

4.5.1 **Potassium sparing diuretics or potassium supplements**

Moexipril hydrochloride / HCTZ can increase serum potassium because it decreases aldosterone secretion. As noted above, moexipril and hydrochlorothiazide have counterbalancing effects on serum potassium, so that little net effect on serum potassium will be seen. Potassium-sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements can increase the risk of hyperkalaemia. Therefore, if concomitant use of such agents is indicated, they must be given with caution and the patient’s serum potassium must be monitored.
4.5.2 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 risk of lithium toxicity with ACE inhibitors. Use of Moexipril Hydrochloride / HCTZ with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.

4.5.3 Anaesthetic medicinal products

Moexipril hydrochloride / HCTZ may enhance the hypotensive effects of certain anaesthetic medicinal products.

4.5.4 Narcotic medicinal products/Antipsychotics

Potentiation of orthostatic hypotension may occur in.

4.5.5 Antihypertensive agents

Increase of the hypotensive effect of moexipril hydrochloride / HCTZ may occur. Concomitant use of thiazide diuretics with betablockers may increase the risk of hyperglycaemia. Thiazide diuretics may enhance the hyperglycaemic effect of diazoxide.

4.5.6 Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide

Concomitant administration with moexipril hydrochloride / HCTZ may lead to an increased risk for leucopenia and may intensify electrolyte depletion, particularly hypokalaemia. Administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.

4.5.7 Non-Steroidal anti-inflammatory medicinal products

The administration of non-steroidal anti-inflammatory agents may reduce the diuretic, natriuretic and antihypertensive effect of moexipril hydrochloride / HCTZ. Furthermore, it has been described that NSAIDs and ACE-inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are in principle reversible, and occur especially in patients with compromised renal function.

4.5.8 Antacids

Decreased bioavailability of ACE-inhibitors may be induced.

4.5.9 Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of moexipril hydrochloride / HCTZ; patients must be carefully monitored to confirm that the desired effect is being obtained.

4.5.10 Alcohol

Alcohol enhances the hypotensive effect.
4.5.11  **Food**

Food may reduce the bioavailability of ACE-inhibitors.

4.5.12  **Antidiabetic agents**

Use of thiazide diuretics and ACE-inhibitors concomitantly with antidiabetic agents (oral agents and insulin) may require an adjustment of the posology of the antidiabetic agents. HCTZ may increase the risk for lactic acidosis under treatment with metformin due to a possible functional renal insufficiency.

4.5.13  **Vitamin D or calcium salts**

Administration of thiazide diuretics with vitamin D or with calcium salts may potentiate the rise in serum calcium.

4.5.14  **Common salt**

Common salt may attenuate the antihypertensive effect of moexipril hydrochloride / HCTZ.

4.5.15  **High doses of salicylates**

High doses of salicylates may potentiate the toxic effect of salicylates on the central nervous system caused by hydrochlorothiazide.

4.5.16  **Kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, carbenoxolone, amphotericin B, penicillin G, salicylates or abuses of laxatives**

Use of thiazide diuretics concomitantly with these agents may intensify electrolyte depletion, particularly hypokalaemia.

4.5.17  **Skeletal muscle relaxants, nondepolarizing**

Use of HCTZ concomitantly with muscle relaxants may potentiate and prolong the muscle relaxing effect of e. g. tubocurarine (the anaesthetist must be informed about the therapy with moexipril hydrochloride / HCTZ).

4.5.18  **Anticholinergic agents**

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (eg atropine, biperidon), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.

4.5.19  **Catecholamines (eg epinephrine)**

Hydrochlorothiazide administered concomitantly may reduce the efficacy of catecholamines.

4.5.20  **Cytostatic agents (eg cyclophosphamide, fluorouracil, methotrexate)**

Use of cytostatic agents may increase toxicity of hydrochlorothiazide on the bone marrow, especially granulocytopenia.
4.5.21 Non-antiarrhythmic medicinal products inducing torsades de pointes (eg astemizole, bepridil, erythromycin i.v., halofantrine, sultopride, terfenadine, vincamine) and antiarrhythmic medicinal products inducing torsades de pointes

HCTZ may increase the risk for torsades de pointes induced by hypokalaemia.

4.5.22 Digitalis glycosides

Efficacy and adverse reactions of digitalis glycosides could be potentiated by simultaneous deficiency in potassium and/or magnesium.

4.5.23 Methyldopa

Concomitant use of hydrochlorothiazide and methyldopa may cause haemolytic anaemia.

4.5.24 Cholestipol/cholestyramine

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or cholestipol resins bind hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

4.5.25 Amantadine

Administration of thiazide diuretics may increase the risk of adverse reactions caused by amantadine.

4.5.26 Iodinated contrast media

HCTZ may increase the risk of acute renal insufficiency, especially with high doses of iodinated contrast media.

4.5.27 Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension leading to collapse) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor.

4.5.28 Vildagliptin:

An increased incidence of angioedema incidence was found in patients taking ACE-Inhibitors and vildagliptin. The majority of the events was mild in severity and resolved with ongoing vildagliptin treatment.

4.5.29 Dual blockade of the renin-angiotensin-aldosterone system

Dual blockade of the renin-angiotensin-aldosterone system with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on moexipril hydrochloride and other agents that affect the renin-angiotensin-aldosterone system.
Co-administration of aliskiren and moexipril hydrochloride in patients with diabetes and in patients with renal impairment (GFR < 60 ml/min) is contraindicated. Co-administration of aliskiren and moexipril hydrochloride should be avoided in other patients.

4.6 Pregnancy and lactation

4.6.1 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). 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).

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.

4.6.2 Lactation
ACE-inhibitors:
Because no information is available regarding the use of [Product] during breastfeeding, [Product] 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 [product name] during breast feeding is not recommended. If [product name] is used during breast feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

There are no studies on the effect of this medicinal product on the ability to drive. When driving vehicles or operating machines it must be taken into account that occasionally dizziness or weariness may occur.
4.8 Undesirable Effects

The frequencies of undesirable effects are defined as:

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, including isolated cases (< 1/10,000)
not known ((cannot be estimated from the available data).

a. The most commonly reported undesirable effects considered to be possibly or probably related to moexipril hydrochloride / HCTZ, occurring in more than 1% of the patients treated in controlled trials, were cough (3%), dizziness (3%), headache (2%), fatigue (2%) and hyperuricemia (2%).

b. In general, the following undesirable effects have been observed associated with moexipril hydrochloride / HCTZ and are specified in the following table:

<table>
<thead>
<tr>
<th>MedRA System Organ Class</th>
<th>Very common (≥ 1/10)</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
<th>Rare (≥ 1/10,000 to &lt; 1/1,000)</th>
<th>Very rare including isolated cases (&lt; )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders *see also section d 1)</td>
<td>anemia, neutropenia, eosinophilia, thrombocytopenia (especially in patients with impaired renal function or collagenosis or in patients, who simultaneously receive treatment with allopurinol, procainamide or medicinal suppressing the immune system)products</td>
<td>hemoconcentration (caused by HCTZ)</td>
<td>pancytopenia, agranulocytosis</td>
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<tr>
<td>MedRA System Organ Class</td>
<td>Very common (≥)</td>
<td>Common (≥ 1/100 to 1/1,000)</td>
<td>Uncommon (≥ 1/10,000 to &lt; 1/1,000)</td>
<td>Rare (≥ 1/10,000 to &lt; 1/1,000)</td>
<td>Very rare including</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>appetite loss, weight loss</td>
<td>confusion, depression, anxiety, nervousness</td>
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<tr>
<td>Psychiatric disorders</td>
<td>headache, dizziness,</td>
<td>convulsion, numbness, paraesthesia, balance disturbance, drowsiness, sleep disturbance, tingling sensations, alteration or loss of taste, paresis (caused by HCTZ)</td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td>transient ischemic attack (TIA), ischemic stroke</td>
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<td>Eye disorders</td>
<td>vision disturbances (e.g. blurred vision) decreased production of tear fluid (caused by HCTZ)</td>
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<tr>
<td>Ear and labyrinth</td>
<td>tinnitus</td>
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<tr>
<td>Cardiac disorders</td>
<td>myocardial infarction, angina pectoris</td>
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<tr>
<td>Vascular</td>
<td>Hypertension, syncope, embolism</td>
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<tr>
<td>MedRA System Organ Class</td>
<td>Very common (≥ 1/10)</td>
<td>Common (≥ 1/100 to &lt; 1/10)</td>
<td>Uncommon (≥ 1/1,000 to &lt; 1/100)</td>
<td>Rare (≥ 1/10,000 to &lt; 1/1,000)</td>
<td>Very rare including isolated cases (&lt;)</td>
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<tr>
<td><strong>disorders</strong>&lt;br&gt; *see also section c²&lt;sup&gt;2&lt;/sup&gt;</td>
<td>sion</td>
<td>high doses of HCTZ inducing hemoconcentration, especially in older patients suffering from venous insufficiency), thrombosis, vascular collapse</td>
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<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong>&lt;br&gt; *see also section c³&lt;sup&gt;3&lt;/sup&gt;</td>
<td>cough</td>
<td>*airway obstruction due to angioneurotic edema involving the tongue, glottis or larynx may be fatal: for treatment see also section c³&lt;sup&gt;3&lt;/sup&gt; bronchitis</td>
<td>respiratory disorders like sinusitis, pharyngitis, common cold (rhinitis)</td>
<td>pulmonary infiltrates, asthma, bronchospasm</td>
<td>pulmonary edema (possibly caused by an allergic reaction to HCTZ)</td>
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<tr>
<td><strong>Gastrointestinal disorders</strong>&lt;br&gt; <em>see also section d&lt;sup&gt;4&lt;/sup&gt;</em></td>
<td>digestive disorders, upper abdominal discomfort, dyspepsia, diarrhoea, constipation, meteorism, vomiting, nausea</td>
<td>elevation of liver enzymes and/or serum bilirubin</td>
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<td>pancreatitis, ileus, stomatitis, glossitis, dryness of the mouth</td>
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<td><strong>Hepatobiliary disorders</strong>&lt;br&gt; <em>see also section c&lt;sup&gt;4&lt;/sup&gt;</em></td>
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<tr>
<td>MedRA System Organ Class</td>
<td>Very common (≥ 1/10)</td>
<td>Common (≥ 1/100 to &lt; 1/10)</td>
<td>Uncommon (≥ 1/1,000 to &lt; 1/100)</td>
<td>Rare (≥ 1/10,000 to &lt; 1/1,000)</td>
<td>Very rare including isolated cases (&lt;)</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>*see also section c^3) c^5)</td>
<td>*angioneurotic edema (involving the lips, face and/or extremities), urticaria, pruritus *see also section c^3)</td>
<td>Respiratory, thoracic and mediastinal disorders: recommendation for treatment of airway obstruction caused by angioneurotic edema; allergic skin reactions e.g. exanthema</td>
<td>Stevens-Johnson syndrome, dermatitis exfoliativa, cutaneous lupus erythematosus (with HCTZ), toxic epidermal necrolysis, pemphigus, erythema multiforme, skin reddening</td>
<td></td>
</tr>
</tbody>
</table>

**Musculoskeletal and connective tissue disorders**

| Renal and urinary system disorders | polyuria, oliguria, azotemia, acute renal failure, deterioration of renal function, proteinuria | muscle cramps (caused by HCTZ induced hypokalemia), myalgia | acute renal failure has been reported in patients treated with ACE inhibitors including moexipril (see also section 4.4 Special warnings and special precautions for interstitial nephritis (abacterial) |

**Stevens-Johnson syndrome, dermatitis exfoliativa, cutaneous lupus erythematosus (with HCTZ), toxic epidermal necrolysis, pemphigus, erythema multiforme, skin reddening**
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<tbody>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Impotence</td>
<td></td>
<td></td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Tiredness</td>
<td>Feeling of weakness</td>
<td>Thirst</td>
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<tr>
<td>Investigations *see also section c 6)</td>
<td>Decrease of haemoglobin, haematocrit, white blood cell count, and platelet count (especially in patients with impaired renal function)</td>
<td>Increase of serum urea (blood urea nitrogen) and serum creatinine, hyperkalemia, hypokalemia (especially in patients with impaired renal function), increased proteinuria, increased bilirubin, increased liver enzymes</td>
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</tbody>
</table>

**c.** This section includes information characterising individual serious and/or frequent adverse reactions, or those where there have been reports of particularly severe cases.

Additionally, measures to be taken to avoid specific adverse reactions or actions to be taken, if specific adverse reactions occur, are mentioned below.

Supplementary to table b. statements are provided, which particular adverse reaction is usually attributable to which component of the combination product moexipril hydrochloride / HCTZ:

**c 1) Cardiac disorder**

ECG changes and cardiac rhythm disorders may be a consequence of hydrochlorothiazide induced hypokalemia.

**c 2) Vascular disorders**

Hypotension caused by moexipril hydrochloride / HCTZ is experienced particularly by certain risk groups (see section 4.4 special warnings and special precautions for use). Symptomatic hypotension caused by moexipril hydrochloride / HCTZ may be
associated with dizziness, feeling of weakness, perspiration, vision disturbances, and rarely with loss of consciousness (syncope).

Careful monitoring of blood pressure is also recommended in patients with ischemic heart disease, aortic stenosis (see also section 4.3. Contraindications) and cerebrovascular disease, where an excessive hypotension could result in myocardial infarction or cerebrovascular accident.

In case of excessive hypotension, the patient must be placed in a supine position and if necessary, fluid must be administered intravenously. Moexipril hydrochloride / HCTZ treatment usually can be continued following reconstitution of an adequate blood pressure and substitution of the fluid volume.

3) Respiratory, thoracic, and mediastinal disorders

Angioneurotic edema has been reported in patients treated with ACE inhibitors including moexipril hydrochloride / HCTZ. Angioneurotic edema involving the tongue, glottis or larynx may be fatal due to airway obstruction. Emergency therapy must include intravenous administration of corticosteroids, H1-receptor antagonists and H2-receptor antagonists. If the condition of the patient does not ameliorate with the above mentioned therapy, epinephrine must be administered slowly intravenously monitored by ECG control.

In case of hereditary angioneurotic edema due to C1-inactivator deficiency associated with ACE inhibitor therapy, additionally a C1-inactivator must be administered. Furthermore, intubation or tracheotomy must be considered. (See also section 4.4 Special warnings and special precautions for use)

4) Hepato-biliary disorders

In case of significant increase of liver enzymes and in case of icterus, the ACE inhibitor therapy must be stopped and the patients must be monitored carefully.

5) Skin and subcutaneous tissue disorders

Cutaneous alterations caused by ACE inhibitors may be associated with fever, myalgia, arthralgia, vasculitis, serositis and changes in laboratory values (e.g. eosinophilia, leukocytosis, and/or elevation of ESR and/or ANA titres). In case of severe skin reactions a physician must be consulted and, if necessary, moexipril hydrochloride / HCTZ must be discontinued.

6) Investigations

An increase in serum potassium has been observed in patients with manifest diabetes mellitus.
Potassium supplements and potassium-sparing diuretics must be given with caution in patients with ACE inhibitors and the patient’s serum potassium must be monitored frequently.

Hydrochlorothiazide:
uncommon: hypokalemia, hyponatremia, hypochloremia, hypercalcemia (further diagnostics regarding hyperparathyroidism are considered as necessary) rare: hyperglycemia, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, increased amylase levels, hypomagnesemia, metabolic alkalosis, hypermagnesiuria, glucosuria

Important note: The above mentioned laboratory values must be monitored before and at regular intervals during the treatment with moexipril hydrochloride / HCTZ. Monitoring of the serum electrolytes, serum creatinine and blood values is indicated for a short period particularly at the start of treatment and in high risk patients (patients with impaired renal function, collagen diseases or patients treated with allopurinol, procainamide, digitalis glycosides, corticosteroids, laxatives or with medicinal products suppressing the immune system).

d. In this section, class-adverse reactions of ACE inhibitors are mentioned, which have not yet been observed in relation to moexipril hydrochloride / HCTZ:

d1) Blood and lymphatic system disorders

For haemolysis/haemolytic anaemia during treatment with ACE inhibitors – rarely associated with G-6-PDH deficiency – no causal relationship to ACE inhibitor therapy could be established.

d2) Vascular disorders

Very rare increased vasospasm in Raynaud’s disease has been observed with ACE inhibitor therapy.

d3) Respiratory, thoracic and mediastinal disorders

Very rare eosinophilic pneumonitis has been reported with the use of other ACE inhibitors.

d4) Gastrointestinal disorders

Intestinal Angioedema has been reported in patients treated with ACE inhibitors. For moexipril hydrochloride so far no “Intestinal Angioedema” has been reported (see also section 4.4 Special warnings and precautions for use).

d5) Skin and subcutaneous tissue disorders

Very rare psoriasiform cutaneous alterations, photosensitivity, alopecia and onycholysis have been observed with ACE inhibitor therapy.
4.9 Overdose

To date, no case of overdose has been reported.

Symptoms of overdose would be severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure. No specific information is available on the treatment of overdose with moexipril hydrochloride / HCTZ. Treatment must be symptomatic and supportive.

After ingestion of an overdose the patient must be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine must be monitored frequently. Therapeutic measures depend on the nature and severity of symptoms. Measurements to prevent absorption and to hasten elimination such as administration of absorbents and sodium sulphate or gastric lavage must be applied if ingestion is recent, within 1 hour after intake. If hypotension occurs, the patient must be placed in a supine position and salt and volume supplementation must be given rapidly. Treatment with angiotensin II and/or intravenous catecholamines must be considered. Bradycardia or extensive vagal reactions must be treated by administering atropine intravenously. The use of a pacemaker may be considered. It is not yet known whether moexiprilat may be removed by haemodialysis.