SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Moxonidine 400 microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400mcg moxonidine.

Excipients with known effect:
Each tablet contains 94.3 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Appearance: All tablets are round, approximately 6 mm in diameter.
The 400 microgram tablet is dark pink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate essential hypertension.

4.2 Posology and method of administration

Posology

Adults
Treatment must be instituted with the lowest dosage of Moxonidine. This means a daily dose of 200 mcg moxonidine in the morning. If the therapeutic effect is insufficient, the dose can be increased after three weeks to 400 mcg. This dose can be given as a single dose (to be taken in the morning) or as a divided daily dose (morning and evening). If the results are still insufficient after a further three weeks, the dosage can be increased further to a maximum of 600 mcg given divided in the morning and evening. A single dose of 400 mcg moxonidine and a daily dose of 600 mcg moxonidine should not be exceeded.

Paediatric population
The safety and efficacy of Moxonidine in children and adolescents under 16 years of age has not yet been established

Elderly Provided that renal function is not impaired, dosage recommendation is the same as for adults.

Renal impairment

Patients with moderately impaired renal function (GFR > 30 ml/min but < 60 ml/min), should start the treatment with a dose of 0.2 mg daily and the daily dose could be increased to a maximum of 0.4 mg. Patients with severely impaired renal function (GFR < 30 ml/min) may also start the treatment with 0.2 mg daily but they may increase the daily dose to a maximum of 0.3 mg, if clinically indicated and well tolerated (see section 4.4).

Method of administration

As concomitant ingestion of food does not affect the pharmacokinetics of moxonidine, moxonidine can be taken before, during or after meals. The tablets should be taken with sufficient fluid.

4.3 Contraindications

Moxonidine is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Sick sinus syndrome
- Bradycardia (resting HR< 50 beats/minute)
- AV-block 2nd and 3rd degree
- Cardiac insufficiency (see section 4.4)

4.4 Special warnings and precautions for use

Cases of varying degrees of AV block have been reported in the post-marketing setting in patients undergoing moxonidine treatment. Based on these case reports, the causative role of moxonidine in delaying atrioventricular conduction cannot be completely ruled out.
Therefore, caution is recommended when treating patients with a possible predisposition to developing an AV block.

When moxonidine is used in patients with 1st degree AV block special care should be exercised to avoid bradycardia. Moxonidine must not be used in higher degree AV blocks (see section 4.3).

When moxonidine is used in patients with severe coronary artery disease or unstable angina pectoris special care should be exercised due to the fact that there is limited experience in this patient population.

Due to lack of clinical evidence supporting safe use in patients with moderate cardiac insufficiency, moxonidine should be administered with caution in these patients

Caution is advised in the administration of moxonidine to patients with renal impairment as moxonidine is excreted primarily via kidney. In these patients

careful titration of the dose is recommended, especially at the start of therapy. Dosing should be initiated with 0.2 mg daily and can be increased to a maximum of 0.4 mg daily for patients with moderate renal impairment (GFR > 30 ml/min but < 60 ml/min) and to a maximum of 0.3 mg daily for patients with severe renal impairment (GFR < 30 ml/min), if clinically indicated and well tolerated.

If moxonidine is used in combination with a β-blocker and both treatments have to be discontinued the β-blocker should be discontinued first and then moxonidine after a few days. So far, no rebound-effect has been observed on the blood pressure after discontinuing the treatment with moxonidine. However, an abrupt discontinuance of the moxonidine treatment is not advisable; instead the dose should be reduced gradually over a period of two weeks.

The elderly population may be more susceptible to the CV effects of blood pressure lowering drugs. Therefore therapy should be started with the lowest dose and dose increments should be introduced with caution to prevent the serious consequences these reactions may lead to.

Excipient(s)

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration moxonidine and other antihypertensive agents result in an additive effect.

Since tricyclic antidepressants may reduce the effectiveness of centrally acting antihypertensive agents, it is not recommended that tricyclic antidepressants be co-administered with moxonidine.

Moxonidine can potentiate the sedative effect of tricyclic anti-depressants (avoid co-prescribing), tranquillisers, alcohol, sedatives and hypnotics.

Moxonidine moderately augmented the impaired performance in cognitive functions in subjects receiving lorazepam. Moxonidine may enhance the sedative effect of benzodiazepines when administered concomitantly.

Moxonidine is excreted through tubular excretion. Interactions with other agents that are excreted through tubular excretion cannot be excluded. Tolazoline can reduce the effect of moxonidine dose-dependently.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Moxonidine in pregnant women. Studies in animals have shown embryo-toxicological effects at high dosages (see section 5.3). The potential risk for humans is unknown.

Moxonidine should not be used during pregnancy unless clearly necessary.

Breast-feeding

Moxonidine is secreted into breast milk and should therefore not be used during breast-feeding. If therapy with moxonidine is considered absolutely necessary, the breast-feeding shall be stopped.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Somnolence and dizziness have been reported. This should be borne in mind when performing these tasks.

4.8 Undesirable effects

Most frequent side effects reported by those taking moxonidine include dry mouth, dizziness, asthenia and somnolence. These symptoms often decrease after the first few weeks of treatment. Undesirable Effects by System Organ Class (observed during placebo-controlled clinical trials with n=886 patients exposed to moxonidine resulted in frequencies below):

MedDRA system organ class	**Very common ≥ 1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**
Cardiac disorders			Bradycardia
Ear and labyrinth disorders			Tinnitus
Nervous system disorders	Drowsiness	Headache*, Dizziness/ Vertigo, Somnolence	Syncope *
Vascular disorders		Vasodilatation	Hypotension* (including orthostatic), paraesthesia of extremities, peripheral circulation disorders
Gastrointestinal disorders	Dry mouth	Diarrhoea, Nausea/ Vomiting/Dyspepsia*	
Skin and subcutaneous tissue disorders		Rash/Pruritus	Angioedema
General disorders and administration site		Asthenia	Oedema, leg weakness,

MedDRA system organ class	Very common ≥ 1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
reactions			fluid retention, anorexia, parotid pain
Eye disorders			Dry itching or burning sensation of the eye
Musculoskeletal and connective tissue disorders		Back pain	Neck pain
Psychiatric disorders		Insomnia, altered thought processes	Nervousness, anxiety
Endocrine disorders			Gynaecomasty, impotence and loss of libido

*there was no increase in frequency compared to placebo

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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose
In the few cases of overdose that have been reported, a dose of 19.6 mg was ingested acutely without fatality. Signs and symptoms reported included: headache, sedation, somnolence, hypotension, dizziness, asthenia, bradycardia, dry mouth, vomiting, fatigue and upper abdominal pain. In case of a severe overdose close monitoring of especially consciousness disturbances and respiratory depression is recommended.

In addition, based on a few high dose studies in animals, transient hypertension, tachycardia, and hyperglycaemia may also occur.

The following case of inadvertent overdose in a 2-year old child has been described:

The child ingested an unknown quantity of moxonidine. The maximum dose that could have been taken was 14 mg. The child exhibited the following symptoms:

Sedation, coma hypotension, miosis and dyspnoea. Gastric lavage, glucose infusions, mechanical ventilation and rest resulted in the symptoms completely disappearing over the course of 11 hours.

Based on the pharmacodynamic properties of Moxonidine, the following reactions may be expected in adults: sedation, hypotension, orthostatic dysregulation, bradycardia, dry mouth. In rare cases, emesis and a paradoxical increase in blood pressure can occur.

Treatment of overdose
No specific antidote is known. In case of hypotension, circulatory support such as fluids and dopamine administration may be considered. Bradycardia may be treated with atropine.

α-Receptor antagonists may diminish or abolish the paradoxal hypertensive effects of a moxonidine overdose.

Treatment consists of absorption-reducing measures such as gastric lavage (if shortly after ingestion), administration of activated charcoal and laxatives, and otherwise is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives, antiadrenergic agents, centrally acting

ATC code: C02AC05

In various animal models it has been shown that moxonidine has a strongly hypotensive effect. Available experimental data indicate that the site of action of moxonidine is located in the central nervous system (CNS).

In the brain stem, moxonidine binds selectively to I_1-imidazoline receptors. These imidazoline-sensitive receptors are predominantly found in the rostral ventrolateral medulla, an area which plays an important role in central control of the sympathetic nervous system. The effect of this interaction with these I_1-imidazoline receptors appears to be a reduction in the activity of the sympathetic nerves. This has been demonstrated for cardiac, splanchnic and renal sympathetic nerves.

Moxonidine differs from other centrally acting hypertensives in the fact that it has only a weak affinity for the central α_2-adrenergic receptors compared to the affinity for I_1-imidazoline receptors. Alpha$_2$-adrenergic receptors are considered to be the intermediate pathway that causes sedation and dry mouth, the most commonly observed undesirable effects of centrally acting antihypertensives.

Mean systolic and diastolic blood pressure is reduced both at rest and during exercise.

The effects of moxonidine on mortality and cardiovascular morbidity are currently unknown.

In humans, moxonidine induces a reduction in systemic vascular resistance and consequently blood pressure. The antihypertensive effect of moxonidine has been demonstrated in randomised, placebo-controlled, double-blind studies. Published data show that in hypertensive patients with ventricular hypertrophy (LVH), for the same blood pressure reduction, the combined use of an angiotensin II receptor antagonist with moxonidine resulted in better regression of LVH than with a free combination of a thiazide and a calcium antagonist. In a two-month therapeutic trial, moxonidine improved the insulin sensitivity index by 21% compared to placebo in obese, insulin-resistant patients with moderate hypertension.

5.2 Pharmacokinetic properties

Absorption
Moxonidine is rapidly absorbed after oral administration (t_{max} about 1 h) and almost totally absorbed from the upper gastrointestinal tract. In humans, approximately 90% of an oral dose is absorbed. Ingestion of food has no effect on the pharmacokinetics of moxonidine.

There is no first-pass metabolism and bioavailability is 88 %.

Distribution
Only about 7% of moxonidine is bound to human plasma proteins (Vd_{ss} = 1.8 ± 0.4 l/kg).
Biotransformation
Moxonidine is 10-20% metabolised, predominantly to 4,5-dehydromoxonidine and to an aminomethanamidine derivative by opening of the imidazoline ring. The hypotensive effect of 4,5-dehydromoxonidine is only 1/10, and that of the aminomethanamidine derivative less than 1/100, of that of moxonidine.

Elimination
Moxonidine and its metabolites are almost entirely eliminated via the kidney. More than 90% of the dose is eliminated in the first 24 hours via the kidney, while approximately 1% is eliminated in the faeces. The cumulative excretion of unchanged moxonidine is approximately 50-75%. The mean plasma elimination half life is 2.2-2.3 hours and the renal half-life 2.6-2.8 hours.

Pharmacokinetics in renal impairment
Elimination of moxonidine is significantly related to creatinine clearance. In patients with moderate renal impairment (GFR 30-60 ml/min), steady-state plasma concentrations and terminal half-life are approximately 2-fold and 1.5-fold higher, respectively, than in hypertensive patients with normal renal function (GFR > 90 ml/min).

In patients with severe renal impairment (GFR < 30 ml/min), steady-state plasma concentrations and terminal half-life are approximately 3-fold higher. No unexpected accumulation of the drug was observed after repeated administration in these patients. In patients with end-stage renal disease (GFR< 10 ml/min) undergoing haemodialysis, the AUC and terminal half-life are 6-fold and 4-fold higher, respectively, than in hypertensive patients with normal renal function.
In patients with moderate renal impairment, peak plasma concentrations of moxonidine are only 1.5 to 2 times higher.
In patients with impaired renal function, the dose should therefore be titrated according to individual needs.
Moxonidine is poorly eliminated by haemodialysis.

Pharmacokinetics in children
No pharmacokinetic studies in children have been performed.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of repeated toxicity, genotoxicity and carcinogenic potential.
Animal studies have shown embryonic toxicity at maternally toxic doses. Reproductive toxicity studies revealed no effects on fertility and no teratogenic potential. Embryotoxic effects were seen in rats at dosages above 9 mg/kg/d and in rabbits at dosages above 0.7 mg/kg/d. In a perinatal and postnatal study in rats the development as well as the viability of the offspring was affected in dosages above 3 mg/kg/d.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
lactose monohydrate
crospovidone
povidone K25
magnesium stearate
Film-coating:
Hypromellose
titanium dioxide (E171)
macrogol 400
red iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C. Keep blister in the outer carton in order to protect from light

6.5 Nature and contents of container

PVC/PVDC/Al blister pack with 10, 20, 28, 30, 50, 56, 98, 100, 400 (20 x 20, 10 x 40, as hospital pack sizes only) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0598

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10/03/2004
Date of latest renewal: 05/08/2008

10 DATE OF REVISION OF THE TEXT

12/10/2022