SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Moxonidine 0.3 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Moxonidine 0.3 mg Film-coated Tablets

Each tablet contains 0.3 mg moxonidine
Excipient with known effect
Each tablet contains 94.4 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Each tablet is round, approximately 6 mm in diameter.

The 0.3 mg film-coated tablet is pink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Moxonidine is indicated in adults for treatment of 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 0.2 mg moxonidine in the morning. If the therapeutic effect is

insufficient, the dose can be increased after three weeks to 0.4 mg. 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 0.6 mg given divided in the morning and evening. A single dose of 0.4 mg moxonidine and a daily dose of 0.6 mg moxonidine should not be exceeded.

The treatment should not be stopped abruptly, but withdrawn over a period of two weeks (see also section 4.4).

Special populations

Elderly
Provided that renal function is not impaired, dosage recommendation is the same as for adults (see section 4.4).

Paediatric population

Moxonidine should not be given to children and adolescents under 18 years of age as insufficient safety and therapeutic data are available for this.

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)
- 2nd or 3rd degree atrioventricular block
- cardiac insufficiency

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 co-existing 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 the kidneys. 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 on blood pressure has been observed after the discontinuation of treatment with moxonidine. However, it is advisable not to stop taking moxonidine abruptly, but to reduce it 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.

Moxonidine contains 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 of 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 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 breastfeeding. If therapy with moxonidine is considered absolutely necessary, the breastfeeding shall be stopped.

Fertility

There are no adequate data from the use of moxonidine in women of childbearing potential.

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. However, somnolence and dizziness have been reported. This should be taken into account 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):
*there was no increase in frequency compared to placebo

	Very common (>1/10)	**Common (>1/100, <1/10)**	**Uncommon (>1/1,000, <1/100)**	**Very rare (<1/10,000)**
Endocrine disorders			Gynaecomastia, impotence and	

	Very common (>1/10)	**Common (>1/100, <1/10)**	**Uncommon (>1/1,000, <1/100)**	**Very rare (<1/10,000)**
			loss of libido	
Psychiatric disorders		Altered thought processes, insomnia	Anxiety, nervousness, anorexia	
Nervous system disorders		Sleep disturbances, headache*, dizziness, vertigo, somnolence	Sedation, syncope*	
Eye disorders			Dry, itching or burning sensation of the eye	
Ear and labyrinth disorders			Tinnitus	
Cardiac disorders			Bradycardia	
Vascular disorders		Vasodilatation	Hypotension (including orthostatic), paraesthesia of extremities, peripheral circulation disorders	
Gastrointestinal disorders	Dry mouth	Diarrhoea, nausea / vomiting / dyspepsia*, constipation and other gastrointestinal disorders		
Hepatobiliary disorders				Hepatic reactions
Skin and subcutaneous tissue disorders		Rash / Pruritus,	Angioedema	
Musculosketal and connective tissue disorders		Back pain	Neck pain	
General disorders and administration site conditions		Asthenia	Oedema of different location, leg weakness, fluid retention,	

	Very common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Very rare (<1/10,000)
			parotid pain	

**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 at: www.mhra.gov.uk/yellowcard.

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. Based on the pharmacodynamic properties of moxonidine, the following reactions may be expected in adults: headache, sedation, somnolence, hypotension, orthostatic dysregulation, dizziness, asthenia, bradycardia, dry mouth, fatigue and upper abdominal pain. In rare cases, emesis and a transient paradoxical increase in blood pressure can occur. 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.

Treatment of overdose
In the case of a severe overdose, in particular the observation of disorders of consciousness and respiratory depression is advisable. Treatment consists of absorption-reducing measures such as gastric lavage (if shortly after ingestion), administration of activated charcoal and laxatives, and otherwise is symptomatic.

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. Alpha-receptor antagonists may diminish or abolish the paradoxical hypertensive effects of a moxonidine overdose.

Paediatric population
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.

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 antihypertensives 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 leads to a reduction of systemic vascular resistance and consequently in arterial blood pressure.

5.2 Pharmacokinetic properties

Absorption
Moxonidine is rapidly absorbed after oral administration. 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). Peak plasma levels of moxonidine are reached 30-180 minutes after administration of a film-coated tablet.

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.

Characteristics in patients with renal impairment
In patients with moderately impaired renal function (GFR 30 – 60 ml/min), the AUC increased by 85% and the clearance decreased by 52%. In such patients the hypotensive effect of moxonidine should be closely monitored, especially at the start of treatment. The dose must be adapted in these patients so that the maximum daily dose is not more than 0.4 mg and the maximum single dose is 0.2 mg.

In patients with severely impaired renal function (GFR < 30 ml/min) the clearance is reduced by 68 % and the elimination half live is prolonged up to 7 hours. In these patients moxonidine dosing should be initiated with 0.2 mg daily and can be increased to a maximum of 0.3 mg daily, if clinically indicated and well tolerated. In such patients the hypotensive effect of moxonidine should be closely monitored, especially at the start of treatment.

Paediatric population
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.

Reproductive toxicity studies revealed no effects on fertility and no teratogenic potential. Embryotic effects were seen in rats and in rabbits. In a perinatal and postnatal study in rats the development as well as the viability of the offspring was affected. All effects were seen at maternal toxic dosages above the human exposure.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Crospovidone (Type A)
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.

6.5 Nature and contents of container

PVC/PVDC/Al blister pack with 10, 28, 28 x 1, 30, 50, 98 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd t/a Mylan
Station Close
Potters Bar
Herts
EN6 1TL

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0621

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/09/2012

10 DATE OF REVISION OF THE TEXT

13/04/2017