SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Moxonidine 400 Microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.4 mg of moxonidine.

Excipient with known effect
Each film-coated tablet contains 89.3 mg of lactose (as monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Dark pink, round, approximately 6 mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential or primary hypertension.

4.2 Posology and method of administration

Posology
Adults

Treatment must be instituted with the lowest dose 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 treatment, the dose 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.

Paediatric population
Moxonidine should not be given to children and adolescents under 16 years of age as insufficient therapeutic data are available for this.

Elderly

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

Renal impairment:

In patients with moderately impaired renal function (GFR > 30 ml/min but < 60 ml/min), the single dose should be not more than 0.2 mg and the daily dose not more than 0.4 mg moxonidine.

Hepatic impairment:

No studies are available in patients with impaired hepatic function. However, as moxonidine lacks extensive hepatic metabolism no major influence on the pharmacokinetics may be expected and dosage recommendation is the same for patients with mild to moderate hepatic impairment as for adults.

The treatment should not be stopped abruptly, but withdrawn over a period of two weeks (see also section 4.4).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 heart rate <50 beats/minute)
- AV-block 2nd and 3rd degree
- 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.

Caution is advised in the administration of moxonidine to patients with renal impairment as moxonidine is excreted primarily via the 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 cardiovascular effects of blood pressure lowering medicinal products. 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, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of moxonidine and other antihypertensive medicinal products result in an additive effect.

Since tricyclic antidepressants may reduce the effectiveness of centrally acting antihypertensive medicinal products, 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. Interaction with other medicinal products that are excreted through tubular excretion cannot be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from use of moxonidine in pregnant women. Studies in animals have shown embryo-toxicological effects (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 in 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 adverse reactions 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

MedDRA System Organ Class	**Very common (≥1/10)**	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1,000, <1/100)**
Cardiac disorders			Bradycardia
Ear and labyrinth disorders			Tinnitus
Nervous system disorders		Headache*, dizziness, somnolence, vertigo	Syncope*
Vascular disorders			Hypotension (including orthostatic)
Gastrointestinal disorders	Dry mouth	Diarrhoea, nausea, vomiting, dyspepsia	
Skin and subcutaneous tissue disorders		Rash, pruritus	Angioedema
General disorders and administration site conditions		Asthenia	Oedema
Musculoskeletal and connective tissue disorders		Back pain	Neck pain
Psychiatric disorders		Insomnia	Nervousness

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

4.9 Overdose

Symptoms

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.

Treatment

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihypertensives, antiadrenergic agents, centrally acting, imidazoline receptor agonists

ATC code: C02A C05

In various animal models moxonidine has been shown to be a potent antihypertensive. Available experimental data indicate that the site of action of the antihypertensive effect of moxonidine is the central nervous system (CNS).

Moxonidine has been shown to bind selectively to the I_1-imidazoline receptors in the brain stem. These imidazoline-sensitive receptors are concentrated in the rostral ventrolateral medulla, an area which is of crucial importance for central control of the peripheral sympathetic nervous system. The result of this effect on the I_1-imidazoline receptors has been apparent in reduced activity in the sympathetic nerves. (demonstrated for cardiac, splanchnic and renal sympathetic nerves).

Moxonidine differs from other available centrally acting antihypertensives by having only a weak affinity for central alpha 2-adrenoceptors compared to I_1-imidazoline receptors alpha-2-adrenoceptors are considered to be the molecular target though which most common adverse reactions of centrally acting antihypertensives such as drowsiness and dry mouth - are mediated. In humans, moxonidine results in a reduction of systemic vascular resistance and consequently of arterial blood pressure.

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

5.2 Pharmacokinetic properties

Absorption

In humans, about 90% of an oral dose of moxonidine is absorbed; there is no first-pass effect and the bioavailability is 88 %. Food intake does not affect moxonidine.

Distribution

The peak plasma concentration of moxonidine is reached in the course of 30-180 minutes after administration of a film-coated tablet.

Only about 7 % of moxonidine is plasma protein bound (VD_{ss} = 1.8 ± 0.4 l/kg).

Biotransformation

10-20% of moxonidine is metabolised, principally to 4,5-dehydromoxonidine and a guanidine derivative on opening of the imidazoline ring. The hypotensive effect of 4,5-dehydromoxonidine is only 1/10 that of moxonidine and for the guanidine derivative it is less than 1/100.

Elimination

Moxonidine and its metabolites are excreted almost exclusively via the kidneys. More than 90% of the dose is eliminated via the kidneys in the

course of the first 24 hours after administration, but only about 1% is eliminated in the faeces. The cumulative elimination of unchanged moxonidine via the kidneys is about 50-75%. The mean plasma elimination half life is 2.2-2.3 hours and the renal elimination half-life is 2.6-2.8 hours.

Pharmacokinetics in the elderly
Small variations in the pharmacokinetic properties of moxonidine in healthy elderly patients and young adults have not proved to be clinically significant. As there is no accumulation of moxonidine, a dose adjustment is not necessary, provided that renal function is normal.

Pharmacokinetics in children

No pharmacokinetic studies in children have been performed.

Pharmacokinetics in impaired renal function
In patients with moderately impaired renal function (GFR 30-60 ml/min), the AUC is increased by 85 % and the clearance reduced by 52 %. In these patients, the hypotensive effect of moxonidine should be monitored carefully, particularly at the beginning of treatment. In addition, the individual dose should not exceed 0.2 mg and the daily dose 0.4 mg.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Chronic oral treatment for 52 weeks of rats (with doses of 0.12-4 mg/kg) and dogs (with doses of 0.04-0.4 mg/kg) revealed significant effects of moxonidine only at the highest doses. Slight disturbances of electrolyte balance (decrease of blood sodium and increase of potassium, urea and creatinine) were found in the high dose rats and emesis and salivation only for the high dose dogs. In addition slight increases of liver weight were obvious for both high dose species.

Reproductive toxicity studies showed no effect on fertility and no teratogenic potential. Embryo-foetal toxicity was seen at doses associated with maternal toxicity.

Increased embryo-foetal loss and delayed foetal development were seen in rats with doses above 2 mg/kg/day and in rabbits with doses above 0.7 mg /kg/day.

In a peri- and post natal study in rats reduced pup weight, viability and delayed development was noted with doses above 1 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Crospovidone
Lactose monohydrate
Magnesium stearate
Povidone K25

Coating
Hypromellose
Macrogol 400
Titanium dioxide (E 171)
Red iron oxide (E 172)

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

The film-coated tablets are packed in PVC/PVDC/Aluminium blisters and inserted in a carton.

Pack sizes:
10, 20, 28, 30, 50, 60, 98, 100, 400 (20x20, 10x40 only as hospital pack) film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1289

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/08/2008

10 DATE OF REVISION OF THE TEXT

16/12/2020