SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Moxonur 0,2 mg, filmomhulde tabletten
Moxonur 0,3 mg, filmomhulde tabletten
Moxonur 0,4 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.2 mg moxonidine.
Each tablet contains 0.3 mg moxonidine.
Each tablet contains 0.4 mg moxonidine.

Excipient with known effect: 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 0.2 mg tablet is light pink, the 0.3 mg tablet is pink and the 0.4 mg 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 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.

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.

The treatment should not be stopped abruptly, but withdrawn over a period of two weeks (see also section 4.4).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

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- sick sinus syndrome or sino-atrial block
- bradycardia (resting HR < 50 beats/minute)
- AV-block 2nd or 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 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 beta-blocker and both treatments have to be discontinued, the beta-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.

Patients with rare hereditary problems of galactose intolerance, 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 antihypertensives 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 are 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 agents 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.

Lactation
Moxonidine is secreted in breast milk and should therefore not be used during breastfeeding. If therapy with moxonidine is considered absolutely necessary, the breastfeeding 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

Summary of the safety profile
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.

List of adverse reactions
Undesirable Effects by System Organ Class (observed during placebo-controlled clinical trials with n=886 patients exposed to moxonidine resulted in frequencies below):

	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Endocrine disorders			Gynaecomasty, impotence and loss of libido
Psychiatric disorders		Insomnia, altered thought processes	Nervousness
Nervous system disorders		Headache*, dizziness, vertigo, somnolence	Syncope*, paraesthesia of extremities
Ear and labyrinth disorders			Tinnitus
Cardiac disorders			Bradycardia
Vascular disorders			Hypotension (including orthostatic)
Gastrointestinal disorders	Dry mouth	Diarrhoea, constipation, nausea, vomiting, dyspepsia	
Skin and subcutaneous tissue disorders		Allergic skin reactions including rash, pruritus	Angioedema
Musculoskeletal and connective tissue disorders		Back pain	Neck pain
General disorders and administration site reactions		Asthenia	Oedema

*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 national reporting system listed in Appendix V.

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.

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.

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

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
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.

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.

In patients with moderately impaired renal function (GFR 30-60 ml/min), the AUC increased by 85% and the clearance reduced by 52%. 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) 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.

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.
Reproductive toxicity studies revealed no effects on fertility and no teratogenic potential .
Embryotoxic effects were seen in rats at dosages above 3 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 1 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.
Store in the original container in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC/Al blister pack with 10, 20, 28, 30, 50, 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 <and other handling>

No special requirements

7. MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Str. 3
89079 Ulm
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 27261 - Moxonur 0,2 mg, filmomhulde tabletten
RVG 27262 - Moxonur 0,3 mg, filmomhulde tabletten
RVG 27263 - Moxonur 0,4 mg, filmomhulde tabletten

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 20 december 2002
Datum van laatste verlenging: 5 augustus 2008

10. DATE OF REVISION OF THE TEXT

Laatst volledige herziening: 19 april 2011
Laatste gedeeltelijke herziening: 13 september 2013, betreft rubriek: 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9 en 5.2.