

MOXCENT

1. Generic Name

Moxonidine Tablets B.P.

2. Qualitative and quantitative composition

MOXCENT 0.2

Each film coated tablet contains:

Moxonidine B.P.....0.2 mg

Colours: Ferric Oxide U.S.P.-NF Red & Titanium Dioxide I.P.

MOXCENT 0.3

Each film coated tablet contains:

Moxonidine B.P.....0.3 mg

Colours: Ferric Oxide U.S.P.-NF Red & Titanium Dioxide I.P.

3. Dosage form and strength

Dosage form: Film coated Tablets

Strength:

MOXCENT 0.2

Moxonidine 0.2 mg tablet

MOXCENT 0.3

Moxonidine 0.3 mg tablet

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for hypertension.

4.2 Posology and method of administration

Adults (including the elderly):

Treatment should be started with 200 micrograms of MOXCENT in the morning. The dose may be titrated after three weeks to 400 micrograms, given as one dose or as divided doses (morning and evening) until a satisfactory response has been achieved. If the response is still unsatisfactory after a further three weeks' treatment, the dosage can be increased up to a maximum of 600 micrograms in divided doses (morning and evening).

A single dose of 400 micrograms of MOXCENT and a daily dose of 600 micrograms in divided doses (morning and evening) should not be exceeded.

In patients with moderate renal dysfunction (GFR above 30 ml/min, but below 60 ml/min), the single dose should not exceed 200 micrograms and the daily dose should not exceed 400 micrograms of moxonidine.

The tablets should be taken with sufficient liquid. As the intake of food has no influence on the pharmacokinetic properties of moxonidine, the tablets may be taken before, during or after the meal.

Paediatric population

MOXCENT is not recommended for use in children and adolescents below 18 years due to lack of data on safety and efficacy.

4.3 Contraindications

MOXCENT should not be used in cases of:

- Hypersensitivity to the active substance or to any of the excipients
- Sick sinus syndrome or sino-atrial block
- 2nd or 3rd degree atrioventricular block
- Bradycardia (below 50 beats/minute at rest)
- Severe heart failure (see Section 4.4)
- Severe renal dysfunction (GFR <30 ml/min, serum creatinine concentration >160 µmol/l).

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 kidneys. In these patients careful titration of the dose is recommended, especially at the start of therapy. Dosing should be initiated with 200 micrograms daily and can be increased to a maximum of 400 micrograms daily for patients with moderate renal impairment (GFR above 30 ml/min, but below 60 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.

Due to a lack of clinical data supporting the safety in patients with co-existing moderate heart failure, MOXCENT must be used with caution in such patients.

The elderly population may be more susceptible to the cardiovascular 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, the rare Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Due to a lack of data on safety and efficacy, MOXCENT should not be used in children and adolescents below 18 years of age.

4.5 Drugs interactions

Concurrent administration of other antihypertensive agents enhances the hypotensive effect of MOXCENT.

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. Interaction with other agents that are excreted through tubular excretion cannot be excluded.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy:

There are no adequate data from use of moxonidine in pregnant woman. Studies in animals have shown embryotoxicological 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, breast-feeding should 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, <1/10	Uncommon ≥1/1,000, <1/100
Cardiac disorders			Bradycardia
Ear and labyrinth disorders			Tinnitus
Nervous system disorders		Headache*, Dizziness/Vertigo, Somnolence	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 reactions		Asthenia	Oedema
Musculoskeletal and connective tissue disorders		Back pain	Neck pain
Psychiatric disorders		Insomnia	Nervousness

* There was no increase in frequency compared to placebo

Reporting of side effects

- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

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.

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.

5 Pharmacological properties

5.1 Mechanism of Action

MOXCENT differs from other available centrally acting antihypertensives by exhibiting only low affinity to central α_2 -adrenoceptors as compared to I1-imidazoline receptors; α_2 -adrenoceptors are considered the molecular target via which sedation and dry mouth, the most common undesired side effects of centrally acting antihypertensives, are mediated.

In humans, MOXCENT leads to a reduction of systemic vascular resistance and consequently in arterial blood pressure.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Imidazoline receptor agonists, moxonidine, ATC code: C02AC05.

In different reported animal models, MOXCENT has been shown to be a potent antihypertensive agent. Available reported experimental data convincingly suggest that the site of the antihypertensive action of MOXCENT is the central nervous system (CNS). Within the brainstem, MOXCENT has been shown to selectively interact with I1-imidazoline receptors. These imidazoline-sensitive receptors are concentrated in the rostral ventrolateral medulla, an area critical to the central control of the peripheral sympathetic nervous system. The net effect of this interaction with the I1-imidazoline receptor appears to result in a reduced activity of sympathetic nerves (demonstrated for cardiac, splanchnic and renal sympathetic nerves).

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In humans, MOXCENT leads to a reduction of systemic vascular resistance and consequently in arterial blood pressure

5.3 Pharmacokinetic properties

Oral moxonidine treatment of rats and dogs resulted in rapid and almost complete absorption and peak plasma levels within <0.5 hours. Average plasma concentrations were comparable in both species after p.o. and i.v. administration. The elimination half-lives of radioactivity and unchanged compound were estimated to be 1-3 hours. Moxonidine and its two main metabolites (4,5-dehydromoxonidine and a guanidine derivative) was predominantly excreted in the urine. No indication of moxonidine cumulation was observed in either species in reported chronic toxicity studies after 52 weeks.

In humans, about 90% of an oral dose of moxonidine is absorbed; it is not subject to first-pass metabolism and its bio-availability is 88%. Food intake does not interfere with moxonidine pharmacokinetics. Moxonidine is 10-20% metabolised, mainly to 4,5-dehydromoxonidine and to a guanidine derivative by opening of the imidazoline ring. The hypotensive effect of 4,5-dehydromoxonidine is only 1/10, and that of the guanidine

derivative is less than 1/100 of that of moxonidine. The maximum plasma levels of moxonidine are reached 30-180 minutes after the intake of a film-coated tablet.

Only about 7% of moxonidine is bound to plasma protein ($V_{dss}=1.8 \pm 0.4$ l/kg). Moxonidine and its metabolites are eliminated almost entirely via the kidneys. More than 90% of the dose is eliminated via the kidneys in the first 24 hours after administration, while only about 1% is eliminated via the faeces. The cumulative renal excretion of unchanged moxonidine is about 50-75%.

The mean plasma elimination half-life of moxonidine is 2.2-2.3 hours, and the renal elimination half-life is 2.6-2.8 hours.

Pharmacokinetics in the elderly

Small differences between the pharmacokinetic properties of moxonidine in the healthy elderly and younger adults are unlikely to be clinically significant. As there is no accumulation of moxonidine, dosage adjustment is unnecessary provided renal function is normal.

Pharmacokinetics in children

No pharmacokinetic studies have been performed in children.

Pharmacokinetics in renal impairment

In moderately impaired renal function (GFR 30-60 ml/min), AUC increased by 85% and clearance decreased to 52% is reported. In such patients the hypotensive effect of MOXCENT should be closely monitored, especially at the start of treatment; additionally, single doses should not exceed 200 micrograms and the daily dose should not exceed 400 micrograms.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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

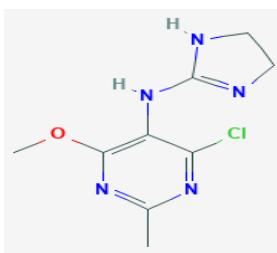
Chronic oral treatment for 52 weeks of rats (with dosages of 0.12-4 mg/kg) and dogs (with dosages of 0.04-0.4 mg/kg) revealed significant effects of moxonidine only at the highest doses. Slight disturbances of electrolyte balance (decrease of blood sodium and increase of potassium, urea and creatinine) 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-fetal toxicity was seen at doses associated with maternal toxicity.

Increased embryo-fetal loss and delayed fetal 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.

7 Description

Moxonidine is 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methylpyrimidin-5-amine with the following structural formula:



The molecular formula for moxonidine is C₉H₁₂ClN₅O and the molecular weight is 241.68 g/mol.

MOXCENT 0.2 & 0.3

Moxonidine Tablets are pink coloured, circular film coated tablets.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

MOXCENT is available in blister strips of 10 tablets.

8.4 Storage and handing instructions

Store below 30°C. Protect from light & moisture. Keep all medicines out of reach of children.

9 Patient Counselling Information MOXCENT

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any questions, or if there is anything you do not understand, ask your doctor or pharmacist.
- **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1.What MOXCENT is and what it is used for

9.2.What you need to know before you take MOXCENT

9.3.How to take MOXCENT

9.4.Possible side effects

9.5.How to store MOXCENT

9.6.Contents of the pack and other information

9.1. What MOXCENT is and what it is used for

MOXCENT contains a medicine called moxonidine. This medicine belongs to a group of medicines called "anti-hypertensives".

MOXCENT is used to treat high blood pressure (hypertension). It works by making your blood vessels relax and widen. This helps to lower your blood pressure.

9.2. What you need to know before you take MOXCENT

Do not take MOXCENT if:

- you are allergic (hypersensitive) to moxonidine or any of the other ingredients of MOXCENT (listed in Section 6)
- you have a slow heart rate caused by a heart problem called "sick sinus syndrome" or "2nd or 3rd degree AV-block"
- you have heart failure.
- you have serious kidney problems

Do not take MOXCENT if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking MOXCENT.

Warnings and precautions

Talk to your doctor or pharmacist before taking MOXCENT if:

- you have a heart problem called "1st degree AV-block"
- you have a severe heart problem such as angina or chest pain at rest
- you have kidney problems. Your doctor may need to adjust your dose.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking MOXCENT.

Other medicines and MOXCENT

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because MOXCENT can affect the way some other medicines work. Also some other medicines can affect the way MOXCENT works.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:

- other medicines to lower your blood pressure. MOXCENT may increase the effect of these medicines
- medicines for depression such as imipramine or amitriptyline
- tranquillisers, sedatives or sleeping tablets such as benzodiazepines
- beta-blockers (see "If you stop taking MOXCENT" in Section 3)
- MOXCENT is removed from your body by your kidneys through a process called "tubular excretion". Other medicines removed from the kidneys in the same way could affect how MOXCENT works.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking MOXCENT.

MOXCENT with food, drink and alcohol

- You can take the tablets with or without food.
- Do not drink alcohol while you are taking MOXCENT. This is because MOXCENT may increase the effects of alcohol.

Pregnancy and breast-feeding

- Tell your doctor if you are pregnant or might become pregnant. Your doctor will normally advise you to stop taking MOXCENT. Your doctor will advise you to take another medicine instead of MOXCENT.
- Tell your doctor if you are breast-feeding or about to start breast-feeding. MOXCENT is not recommended for mothers who are breast-feeding. Your doctor may advise you to take another medicine if you want to breast-feed, or may ask you to stop breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines

You may feel sleepy or dizzy while taking MOXCENT. If this happens, talk to your doctor before driving or using any tools or machines.

MOXCENT contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

9.3.How to take MOXCENT

Always take MOXCENT exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Taking this medicine

- Swallow the tablets whole with a glass of water.
- Try to take your tablets around the same time each day. This will help you remember to take them.

How much to take

The usual starting dose is 200 micrograms a day.

- Your doctor may increase this dose to up to 600 micrograms a day. You should not take more than 400 micrograms as a single dose or more than 600 micrograms in any one day.
- If your doctor has told you to take 600 micrograms a day, this should be split in two (300 micrograms in the morning and 300 micrograms in the evening).
- Your doctor may tell you to take a lower dose if you have kidney problems.

Use in children and adolescents

MOXCENT should not be given to children and adolescents under 18 years.

If you take more MOXCENT than you should

If you take more MOXCENT than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you. The following effects may happen: headache, feeling sleepy (somnolence, sedation), fall in blood pressure (hypotension), slow heart rate (bradycardia), feeling dizzy (vertigo), dry mouth, being sick (vomiting), feeling tired (fatigue), weakness and pain in your stomach (abdominal pain).

If you forget to take MOXCENT

- If you forget to take a dose, take it as soon as you remember it. However, if it is nearly time for the next dose, skip the missed dose.

- Do not take a double dose to make up for a forgotten dose.

If you stop taking MOXCENT

- Keep taking your tablets until your doctor decides that you should stop.
- If you need to stop, your doctor will lower your dose slowly over a few weeks. If you are taking more than one medicine for high blood pressure (such as beta-blockers), your doctor will tell you which medicine to stop first. This is so that your body can adjust slowly to the change.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

9.4.Possible side effects

Like all medicines, MOXCENT can cause side effects, although not everybody gets them. The following **side** effects may happen with this medicine:

Stop taking MOXCENT and see a doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:

- swelling of the face, lips or mouth (angioedema). This is uncommon, affecting less than 1 in 100 people.

Other side effects include:

Very Common (affects more than 1 in 10 people)

- dry mouth

Common (affects less than 1 in 10 people)

- back pain
- headache
- weakness (asthenia)
- feeling dizzy (vertigo)
- rash or itching (pruritus)
- difficulty sleeping (insomnia), feeling sleepy (somnolence)
- feeling sick (nausea), diarrhoea, being sick (vomiting), indigestion (dyspepsia).

Uncommon (affects less than 1 in 100 people)

- neck pain
- feeling nervous
- fainting (syncope)
- swelling (oedema)
- ringing or noise in the ears (tinnitus)
- unusually slow heartbeat (bradycardia)
- low blood pressure, including low blood pressure when standing up.

Like all medicines, MOXCENT can cause side effects, although not everybody gets them.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store MOXCENT

Store below 30°C. Protect from light & moisture

9.6 Contents of the pack and other information

What **MOXCENT** contains:

The active substances of **MOXCENT** is Moxonidine.

MOXCENT 0.2

Moxonidine 0.2 mg

MOXCENT 0.3

Moxonidine 0.3 mg

10 Details of manufacturer

Manufactured in India by:

Hetero Labs Limited (Unit-II)

Village Kalyanpur, Chakkan Road, Baddi (Tehsil), Solan (Distt.), Himachal Pradesh - 173205.

11 Details of permission or licence number with date

Mfg Lic No. MNB/09/780 issued on 28.11.2019

12 Date of revision

Not Applicable

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

IN/MOXCENT 0.2 mg,0.3mg/AUG-20/01/PI