To be sold by retail on the prescription of a Pulmonologists/Cardiologists/Internal Medicines Specialists/Pediatricians only

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Riociguat 0.5mg, 1mg, 1.5mg, 2mg and 2.5mg

Rioci **0.5, 1, 1.5, 2, & 2.5**

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COMPOSITION

Each film coated tablet contains:

Riociguat 0.5mg

Riociguat 1mg

Riociguat 1.5mg

Riociguat 2mg

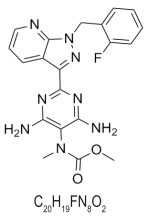
Riociguat 2.5mg

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer Riociguat to a pregnant female because it may cause fetal harm.**
- **Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception.**

DRUG DESCRIPTION

Riociguat is a tablet for oral administration. Riociguat is methyl 4, 6-diamino-2-[1-(2-fluorobenzyl)-1Hpyrazolo [3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl) carbamate with the following structural formula:



$C_{20}H_{19}FN_8O_2$

Riociguat is a white to yellowish, crystalline, non-hygroscopic substance with a molecular weight of 422.42 g/mol. In solid form it is stable to temperature, light, and humidity.

DOSAGE FORM AND STRENGTHS

Film coated Tablets; 0.5mg, 1mg, 1.5mg, 2mg and 2.5mg

INDICATIONS

Chronic-Thromboembolic Pulmonary Hypertension

Riociguat is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.

Pulmonary Arterial Hypertension

Riociguat is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

DOSE AND METHOD OF ADMINISTRATION

Recommended Dosage in Adult Patients

The recommended starting dosage is 1 mg taken 3 times a day. For patients who may not tolerate the hypotensive effect of Riociguat, consider a starting dose of 0.5 mg taken three times a day. If systolic blood pressure remains greater than 95 mmHg and the patient has no signs or symptoms of hypotension, up-titrate the dose by 0.5 mg taken three times a day. Dose increases should be no sooner than 2 weeks apart. The dose can be increased to the highest tolerated dosage, up to a maximum of 2.5 mg taken three times a day. If at any time, the patient has symptoms of hypotension, decrease the dosage by 0.5 mg taken three times a day.

Dosage Interruption

If a dose is missed, advise patients to continue with the next regularly scheduled dose. In case Riociguat is interrupted for 3 days or more, re-titrate Riociguat.

Pregnancy Testing in Females of Reproductive Potential

Obtain pregnancy tests prior to initiation and monthly during treatment.

Use in Patients who Smoke

Consider titrating to dosages higher than 2.5 mg three times a day, if tolerated, in patients who smoke. A dose decrease may be required in patients who stop smoking.

Strong CYP and P-gp/BCRP Inhibitors

Consider a starting dose of 0.5 mg, three times a day when initiating Riociguat in patients receiving strong cytochrome P450 (CYP) and P-glycoprotein/breast cancer resistance protein (P-gp/BCRP) inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (for example, ritonavir). Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors.

Transitioning to and from Riociguat

Discontinue sildenafil at least 24 hours prior to administering Riociguat.

- Discontinue tadalafil at least 48 hours prior to administering Riociguat. Consider initiating Riociguat at a starting dose of 0.5 mg in patients at risk of hypotension. It is recommended to monitor for signs and symptoms of hypotension on initiation.
- Discontinue Riociguat at least 24 hours prior to administering a PDE5-inhibitor. It is recommended to monitor for signs and symptoms of hypotension on initiation.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X

Riociguat may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Riociguat was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, Riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 times the human exposure. If Riociguat is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.

Nursing Mothers

It is not known if Riociguat is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from Riociguat, discontinue nursing or Riociguat.

Paediatric population

The safety and efficacy of Riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone. Until more is known about the implications of these findings the use of Riociguat in children and in growing adolescents should be avoided.

Elderly population

In elderly patients (65 years or older) there is a higher risk of hypotension and therefore particular care should be exercised during individual dose titration

Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Riociguat, monthly during treatment, and one month after discontinuation of treatment with Riociguat. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus.

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Riociguat and for 1 month after treatment with Riociguat. Patients may choose one highly effective form of contraception (intrauterine devices [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling.

Renal Impairment

Data in patients with severe renal impairment (creatinine clearance <30 mL/min) are limited and there are no data for patients on dialysis. Therefore use of Riociguat is not recommended in these patients. Patients with moderate renal impairment (creatinine clearance <50 - 30 mL/min) showed a higher exposure to this medicine. There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration.

Hepatic Impairment

Patients with severe hepatic impairment (Child Pugh C) have not been studied and therefore use of Riociguat is contraindicated in these patients. Patients with moderate hepatic impairment (Child Pugh B) showed a higher exposure to this medicine. Particular care should be exercised during individual dose titration.

CONTRAINDICATIONS

Pregnancy

Riociguat may cause fetal harm when administered to a pregnant woman. Riociguat is contraindicated in females who are pregnant. Riociguat was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nitrates and Nitric Oxide Donors

Co-administration of Riociguat with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated.

Phosphodiesterase Inhibitors

Concomitant administration of Riociguat with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil.

Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias (PH-IIP)

Riociguat is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP).

Severe hepatic impairment (Child Pugh C)

Riociguat is contraindicated in patient with severe hepatic impairment (Child Pugh C).

Hypersensitivity

Riociguat is contraindicated in patient with hypersensitivity to the active substance or to any of the excipients.

Nitrates or nitric oxide donors

Co-administration of Riociguat with nitrates or nitric oxide donors (such as amyl nitrite) in any form including recreational drugs called 'poppers' is contraindicated.

Systolic blood pressure

Riociguat is contraindicated in patient with systolic blood pressure < 95 mm Hg at treatment initiation.

WARNINGS AND PRECAUTIONS

In pulmonary arterial hypertension, studies with riociguat have been mainly performed in forms related to idiopathic or heritable PAH and PAH associated with connective tissue disease. The use of riociguat in other forms of PAH not studied is not recommended.

In chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy is the treatment of choice as it is a potentially curative option. According to standard medical practice, expert assessment of operability should be done prior to treatment with riociguat.

Pulmonary veno-occlusive disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of riociguat to such patients is not recommended. Should signs of pulmonary oedema occur, the possibility of associated PVOD should be considered and treatment with riociguat should be discontinued.

Respiratory tract bleeding

In pulmonary hypertension patients there is increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy. A careful monitoring of patients taking anticoagulants according to common medical practice is recommended.

The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with riociguat, especially in the presence of risk factors, such as recent episodes of serious haemoptysis including those managed by bronchial arterial embolisation. Riociguat should be avoided in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolisation. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit-risk of treatment continuation.

Hypotension

Riociguat has vasodilatory properties which may result in lowering of blood pressure. Before prescribing riociguat, physicians should carefully consider whether patients with certain underlying conditions, could be adversely affected by vasodilatory effects (e.g. patients on antihypertensive therapy or with resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction).

Riociguat must not be used in patients with a systolic blood pressure below 95 mmHg. Patients older than 65 years are at increased risk of hypotension. Therefore, caution should be exercised when administering riociguat in these patients.

Renal impairment

Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis, therefore riociguat is not recommended in these patients. Patients with mild and moderate renal impairment were included in the pivotal studies. There is increased riociguat exposure in these patients. There is a higher risk of hypotension in these patients; particular care should be exercised during individual dose titration.

Hepatic impairment

There is no experience in patients with severe hepatic impairment (Child Pugh C); riociguat is contraindicated in these patients. PK data show that higher riociguat exposure was observed in patients with moderate hepatic impairment (Child Pugh B). Particular care should be exercised during individual dose titration.

There is no clinical experience with riociguat in patients with elevated liver aminotransferases (> 3 x Upper Limit of Normal (ULN)) or with elevated direct bilirubin (> 2 x ULN) prior to initiation of treatment; riociguat is not recommended in these patients.

Pregnancy/contraception

Riociguat is contraindicated during pregnancy. Therefore, female patients at potential risk of pregnancy must use an effective method of contraception. Monthly pregnancy tests are recommended.

Smokers

Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. Dose adjustment may be necessary in patients who start or stop smoking during treatment with riociguat.

Concomitant use with other medicinal products

- The concomitant use of riociguat with strong multi pathway cytochrome P450 (CYP) and P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) is not recommended, due to the pronounced increase in riociguat exposure.
- The concomitant use of riociguat with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase riociguat exposure. These medicinal products should be used with caution. Blood pressure should be monitored and dose reduction of riociguat be considered.

Paediatric population

The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone. Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided.

DRUG INTERACTIONS

Pharmacodynamic interactions

Nitrates: Co-administration of Riociguat with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension.

PDE Inhibitors: Co-administration of Riociguat with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil. Clinical experience with co-administration of Riociguat, and other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

Pharmacokinetic Interactions with Riociguat

Smoking: Plasma concentrations in smokers are reduced by 50% to 60% compared to non-smokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Riociguat doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking.

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of Riociguat with strong cytochrome CYP inhibitors and Pgp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Riociguat in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat.

Strong CYP3A inducers: Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered.

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Riociguat.

UNDESIRABLE EFFECTS

Summary of the safety profile

The safety of riociguat has been evaluated in phase III studies of 681 patients with CTEPH and PAH receiving at least one dose of riociguat.

Most of the adverse reactions are caused by relaxation of smooth muscle cells in vasculature or the gastrointestinal tract.

The most commonly reported adverse reactions, occurring in ≥10% of patients under riociguat treatment (up to 2.5 mg three times daily), were headache, dizziness, dyspepsia, peripheral oedema, nausea, diarrhoea and vomiting.

Serious haemoptysis and pulmonary haemorrhage, including cases with fatal outcome have been observed in patients with CTEPH or PAH treated with riociguat.

The safety profile of riociguat in patients with CTEPH and PAH appeared to be similar, therefore adverse reactions identified from placebo controlled 12 and 16 weeks clinical studies are presented as pooled frequency in the table listed below (see table 1).

Tabulated list of adverse reactions

The adverse reactions reported with riociguat are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 1: Adverse reactions reported with riociguat in the phase III studies

MedDRA System Organ Class	Very common	Common	Uncommon
Infections and infestations		Gastroenteritis	
Blood and the lymphatic system disorders		Anaemia (incl. respective laboratory parameters)	
Nervous system disorders	Dizziness, Headache		
Cardiac disorders		Palpitations	
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Haemoptysis, Epistaxis, Nasal congestion	Pulmonary haemorrhage*
Gastrointestinal disorders	Dyspepsia, Diarrhoea, Nausea, Vomiting	Gastritis, Gastro-oesophageal reflux disease, Dysphagia, Gastrointestinal and abdominal pains, Constipation, Abdominal distension	
General disorders and administration site conditions	Oedema peripheral		

* fatal pulmonary haemorrhage was reported in uncontrolled long term extension studies

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. To report SUSPECTED ADVERSE REACTIONS, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/To report a side effect.

OVERDOSE

Inadvertent overdosing with total daily doses of 9 to 25 mg riociguat between 2 to 32 days was reported. Adverse reactions were similar to those seen at lower doses.

In case of overdose, standard supportive measures should be adopted as required. In case of pronounced hypotension, active cardiovascular support may be required. Based on the high plasma protein binding riociguat is not expected to be dialysable.

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antihypertensives for pulmonary arterial hypertension,

ATC code: C02KX05

Mechanism of action

Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). When NO binds to sGC, the enzyme catalyses synthesis of the signaling molecule cyclic guanosine monophosphate (cGMP). Intra-cellular cGMP plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis, and inflammation.

Pulmonary hypertension is associated with endothelial dysfunction, impaired synthesis of NO and insufficient stimulation of the NO-sGC-cGMP pathway.

Riociguat has a dual mode of action. It sensitises sGC to endogenous NO by stabilising the NO-sGC binding. Riociguat also directly stimulates sGC independently of NO.

Riociguat restores the NO-sGC-cGMP pathway and leads to increased generation of cGMP.

Pharmacodynamic effects

Riociguat restores the NO-sGC-cGMP pathway resulting in a significant improvement of pulmonary vascular haemodynamics and an increase in exercise ability.

There is a direct relationship between riociguat plasma concentration and haemodynamic parameters such as systemic and pulmonary vascular resistance, systolic blood pressure and cardiac output.

PHARMACOKINETIC PROPERTIES

Absorption

The absolute bioavailability of riociguat is high (94%). Riociguat is rapidly absorbed with maximum concentrations (C_{max}) appearing 1-1.5 hours after tablet intake. Intake with food reduced riociguat AUC slightly; C_{max} was reduced by 35%.

Bioavailability (AUC and Cmax) is comparable for riociguat administered orally as a crushed tablet suspended in applesauce or in water compared to a whole tablet.

Distribution

Plasma protein binding in humans is high at approximately 95%, with serum albumin and alpha 1-acidic glycoprotein being the main binding components. The volume of distribution is moderate with volume of distribution at steady state being approximately 30 L.

Biotransformation

N-demethylation, catalysed by CYP1A1, CYP3A4, CYP3A5 and CYP2J2 is the major biotransformation pathway of riociguat leading to its major circulating active metabolite M-1 (pharmacological activity: 1/10th to 1/3rd of riociguat) which is further metabolised to the pharmacologically inactive N-glucuronide.

CYP1A1 catalyses the formation of riociguat's main metabolite in liver and lungs and is known to be inducible by polycyclic aromatic hydrocarbons, which, for example, are present in cigarette smoke.

Elimination

Total riociguat (parent compound and metabolites) is excreted via both renal (33-45%) and biliary/faecal routes (48-59%). Approximately 4-19% of the administered dose was excreted as unchanged riociguat via the kidneys. Approximately 9-44% of the administered dose was found as unchanged riociguat in faeces.

Based on *in vitro* data riociguat and its main metabolite are substrates of the transporter proteins P-gp (P-glycoprotein) and BCRP (breast cancer resistance protein). With a systemic clearance of about 3-6 L/h, riociguat can be classified as a low-clearance drug. Elimination half-life is about 7 hours in healthy subjects and about 12 hours in patients.

Linearity

Riociguat pharmacokinetics are linear from 0.5 to 2.5 mg. Inter-individual variability (CV) of riociguat exposure (AUC) across all doses is approximately 60%.

INCOMPATIBILITIES

Not applicable.

PACKING INFORMATION

Pack: 10's PVC/PVdC blister

STORAGE

Do not Store above 30ºC.

KEEP AWAY FROM INFANTS AND SMALL CHILDREN

Manufactured by:
MSN Laboratories Private Limited,
Formulation Division,
Unit-II, Sy.No. 1277, 1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy (District),
Telangana - 509 228, India.

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