For use in India only
To be sold by retail on the prescription of a Cardiologist /Pulmonologist only.
PRESCRIBING INFORMATION

1. GENERIC NAME

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Selexipag for Injection 1800 mcg/vial

Selepeg IV

सेलिपेग आई. वी.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Selexipag for Injection 1800 mcg/vial
Each Vial contains
Selexipag……1800 mcg

3. DOSAGE FORM AND STRENGTH
Injection; 1800 mcg/vial

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications
Selexipag is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

4.2. Posology and Method of Administration
Posology
Selexipag for Injection
Use Selexipag for injection in patients who are already under treatment with Selexipag tablets, but temporarily unable to take oral therapy due to any serious condition or stage of hospitalization.
Administer Selexipag for injection twice daily by intravenous infusion at a dose that corresponds to the patient's current dose of Selexipag tablets. Administer Selexipag for injection as an 80-minute intravenous infusion.

Preparation Instructions
Reconstitute and further dilute Selexipag for injection prior to intravenous infusion following aseptic procedures.
Determine the dose and total volume of reconstituted Selexipag solution required.

Reconstitution
- Remove the carton of Selexipag for injection from the refrigerator and allow to stand for approximately 30 to 60 minutes to reach room temperature (20°C to 25°C [68°F to 77°F]).
- The vial needs to be protected from light at all times. Ensure the protective wrap around label is covering the entire vial.
- Peel back light protective wrap on vial to inspect the contents in the vial. It should appear white to almost white broken cake or powdered material. Immediately close the light protective wrap on the vial.
- Reconstitute Selexipag for injection using a polypropylene syringe with 8.6 mL of 0.9% Sodium Chloride Injection, USP and slowly inject into the Selexipag vial with the stream directed toward the inside wall of the vial to obtain a concentration of 225 mcg/mL of selexipag.
- Document date and time of first puncture. Complete infusion within 4 hours of first puncture.
- Gently invert the vial and repeat until powder is completely dissolved. *Do not shake.*
- Inspect the vial by peeling back the light protective wrap around label for discoloration. The reconstituted solution should appear clear, colorless and free from foreign material. Do not use if the reconstituted solution is discolored, cloudy, or contains visible particles.

Dilution
- Selexipag for injection must be diluted in glass containers only.
- Withdraw 100 mL of 0.9% Sodium Chloride Injection, USP and transfer into an empty sterile glass container.
- Withdraw the required volume of reconstituted solution (see Table 1 for reconstituted transfer volume) from the Selexipag vial using a single, appropriately sized polypropylene syringe and dilute into the glass container containing 100 mL 0.9% Sodium Chloride Injection, USP to obtain the desired final dose.
- Mix the diluted Selexipag infusion solution by gentle inversion of the glass container 5times. *Do not shake.*
- Protect diluted Selexipag infusion solution from light at all times. Assign a 4-hour expiry from the time of first vial puncture and wrap the glass container completely with light protective cover.
- The Selexipag infusion solution should be kept at room temperature (20°C-25°C [68°F 77°F]) and must be infused within 4 hours from the first puncture of the vial stopper (including infusion time).
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. The diluted Selexipag infusion solution should be clear and colorless. Discard if particulate matter is observed.
- Selexipag for injection vials are single-dose, for single administration. All remaining reconstituted product must be discarded.

Table 1 Dosing Table for TRADENAME intravenous based on current Selexipag tablets dose

Selexipag tablets dose (mcg) for twice daily dosing	Corresponding IV Selexipag Dose (mcg) for twice daily dosing	Reconstituted transfer volume (mL) for dilution
200	225	1.0
400	450	2.0
600	675	3.0
800	900	4.0
1000	1125	5.0
1200	1350	6.0
1400	1575	7.0
1600	1800	8.0

Administration Instructions
Administer by intravenous infusion over 80 minutes using an infusion set made of DEHP-free polyvinyl chloride (PVC), natural latex rubber-free microbore tubing protected from light.
Do not use a filter for administration.
Once the solution for infusion glass container is empty, continue the infusion at the same rate with 0.9% saline to empty the remaining solution for infusion in the IV line, to ensure that the entire solution for infusion has been administered.

Interruptions and Discontinuations
If a dose of Selexipag is missed, patients should take a missed dose as soon as possible unless the next dose is within the next 6 hours.
If treatment is missed for 3 days or more, restart Selexipag at a lower dose and then retitrate.

Dosage Adjustment in Patients with Hepatic Impairment
No dose adjustment of Selexipag is necessary for patients with mild hepatic impairment (Child-Pugh class A).
For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of Selexipag tablets is 200 mcg once daily. Increase in increments of 200 mcg once daily at weekly intervals, as tolerated.
Avoid use of Selexipag in patients with severe hepatic impairment (Child-Pugh class C).

Dosage Adjustment with Co-administration of Moderate CYP2C8 Inhibitors
When co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox and teriflunomide), reduce the dosing of Selexipag to once daily.

Method of administration
Intravenous use.

4.3. Contraindications
- Hypersensitivity to the active substance or to any of the excipients used in the formulation.
- Severe coronary heart disease or unstable angina.
- Myocardial infarction within the last 6 months.
- Decompensated cardiac failure if not under close medical supervision.
- Severe arrhythmias.
- Cerebrovascular events (e.g., transient ischaemic attack, stroke) within the last 3 months.
- Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension.
- Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil).

4.4. Special Warnings and Precautions for Use
Hypotension
Selexipag has vasodilatory properties that may result in lowering of blood pressure. Before prescribing Selexipag, 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).

Hyperthyroidism
Hyperthyroidism has been observed with Selexipag. Thyroid function tests are recommended as clinically indicated in the presence of signs or symptoms of hyperthyroidism.

Pulmonary veno-occlusive disease
Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when Selexipag is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered. If confirmed, treatment with Selexipag should be discontinued.

Elderly (≥ 65 years)
There is limited clinical experience with Selexipag in patients over the age of 75 years, therefore Selexipag should be used with caution in this population.

Hepatic impairment
There is no clinical experience with Selexipag in patients with severe liver impairment (Child-Pugh class C), therefore Selexipag should not be administered in these patients. The exposure to selexipag and its active metabolite is increased in subjects with moderate hepatic impairment (Child-Pugh class B). In patients with moderate hepatic impairment, Selexipag should be dosed once daily.

Renal impairment
In patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), caution should be exercised during dose titration. There is no experience with Selexipag in patients undergoing dialysis, therefore Selexipag should not be used in these patients.

Women of childbearing potential
Women of childbearing potential should practice effective contraception while taking selexipag.

"Use Selexipag for injection only in cases who are already on this drug in tablets form"

4.5. Drug Interactions
Effect of other medicinal products on Selexipag
Selexipag is hydrolysed to its active metabolite by carboxylesterases. Selexipag and its active metabolite both undergo oxidative metabolism mainly by CYP2C8 and to a smaller extent by CYP3A4. The glucuronidation of the active metabolite is catalysed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates of OATP1B1 and OATP1B3. Selexipag is a weak substrate of the P-gp efflux pump. The active metabolite is a weak substrate of the breast cancer resistance protein (BCRP).
The pharmacokinetics of selexipag and its active metabolite are not affected by warfarin.

Inhibitors of CYP2C8
In the presence of 600 mg gemfibrozil, twice a day, a strong inhibitor of CYP2C8, exposure to selexipag increased approximately 2-fold, whereas exposure to the active metabolite, the major contributor to efficacy, increased approximately 11-fold. Concomitant administration of Selexipag with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated.
Concomitant administration of Selexipag with clopidogrel (loading dose of 300 mg or maintenance dose of 75 mg once a day), a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to Selexipag but increased the exposure to the active metabolite approximately 2.2 and 2.7-fold following loading dose and maintenance dose, respectively. Dosing frequency of Selexipag should be reduced to once daily when co-administered with moderate CYP2C8 inhibitors (e.g., clopidogrel, deferasirox, teriflunomide). Dosing frequency of Selexipag should be reverted to twice daily when co-administration of moderate CYP2C8 inhibitor is stopped.

Inducers of CYP2C8
In the presence of 600 mg rifampicin, once a day, an inducer of CYP2C8 (and UGT enzymes), the exposure to selexipag did not change, whereas exposure to the active metabolite was reduced by half. Dose adjustment of selexipag may be required with concomitant administration of inducers of CYP2C8 (e.g., rifampicin, carbamazepine, phenytoin).

Inhibitors of UGT1A3 and UGT2B7
The effect of strong inhibitors of UGT1A3 and UGT2B7 (valproic acid, probenecid, and fluconazole) on the exposure to Selexipag and its active metabolite has not been studied. Caution is required when administering these medicinal products concomitantly with Selexipag. A potential pharmacokinetic interaction with strong inhibitors of UGT1A3 and UGT2B7 cannot be excluded.

Inhibitors and inducers of CYP3A4
In the presence of 400/100 mg lopinavir/ritonavir twice daily, a strong CYP3A4 inhibitor, exposure to Selexipag increased approximately 2-fold, whereas the exposure to the active metabolite of selexipag did not change. Given the 37-fold higher potency of the active metabolite, this effect is not clinically relevant. Since a strong inhibitor of CYP3A4 did not affect the pharmacokinetics of the active metabolite, indicating that the CYP3A4 pathway is not important in the elimination of the active metabolite, no effect of inducers of CYP3A4 on the pharmacokinetics of the active metabolite is expected.

PAH-specific therapies
In the Phase 3 placebo-controlled trial in patients with PAH, the use of selexipag in combination with both an ERA and a PDE-5 inhibitor resulted in a 30% lower exposure to the active metabolite.

Transporter inhibitors (lopinavir/ritonavir)
In the presence of 400/100 mg lopinavir/ritonavir twice daily, a strong OATP (OATP1B1 and OATP1B3) and P-gp inhibitor, exposure to selexipag increased approximately 2-fold, whereas the exposure to the active metabolite of selexipag did not change. Given that the majority of the pharmacological effect is driven by the active metabolite, this effect is not clinically relevant.

Effect of Selexipag on other medicinal products
Selexipag and its active metabolite do not inhibit or induce cytochrome P450 enzymes and transport proteins at clinically relevant concentrations.

Anticoagulants or inhibitors of platelet aggregation
Selexipag is an inhibitor of platelet aggregation *in vitro*. Selexipag did not influence the pharmacodynamic effect of warfarin on the international normalised ratio.

Midazolam
At steady state after up-titration to 1,600 µg selexipag twice a day, no clinically relevant change in exposure to midazolam, a sensitive intestinal and hepatic CYP3A4 substrate, or its metabolite, 1-hydroxymidazolam, was observed. Concomitant administration of selexipag with CYP3A4 substrates does not require dose adjustment.

Hormonal contraceptives
Specific drug-drug interaction studies with hormonal contraceptives have not been conducted. Since selexipag did not affect the exposure to the CYP3A4 substrates midazolam and R-warfarin or to the CYP2C9 substrate S-warfarin, reduced efficacy of hormonal contraceptives is not expected.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
Women of childbearing potential
Women of childbearing potential should practise effective contraception while taking selexipag.

Pregnancy
There are no data from the use of selexipag in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Selexipag and its main metabolite showed 20- to 80-times lower prostacyclin (IP) receptor potency *in vitro* for animal species used in reproductive toxicity testing compared to humans. Therefore, safety margins for potential IP receptor-mediated effects on reproduction are accordingly lower than for non-IP-related effects.
Selexipag is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether selexipag or its metabolites are excreted in human milk. In rats, Selexipag or its metabolites are excreted in milk. A risk to the suckling child cannot be excluded. Selexipag should not be used during breast-feeding.

Fertility
There are no clinical data available. In rat studies, selexipag at high doses caused transient disturbances in oestrus cycles that did not affect fertility (see section 5.3). The relevance for humans is not known.

Elderly (≥ 65 years)
No adjustment to the dose regimen is needed in elderly people. There is limited clinical experience in patients over the age of 75 years, therefore Selexipag should be used with caution in this population.

Hepatic impairment
Selexipag should not be administered in patients with severe liver impairment (Child-Pugh class C). For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose of Selexipag should be 200 micrograms once daily, and increased at weekly intervals by increments of 200 micrograms given once daily until adverse reactions, reflecting the mode of action of selexipag, that cannot be tolerated or medically managed are experienced. No adjustment to the dose regimen is needed in patients with mild hepatic impairment (Child-Pugh class A).

Renal impairment
No adjustment to the dose regimen is needed in patients with mild or moderate renal impairment. No change in starting dose is required in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2); dose titration should be done with caution in these patients.

Paediatric population (< 18 years)
The safety and efficacy of Selexipag in children aged 0 to less than 18 years have not yet been established. No data are available. Administration of Selexipag in the paediatric population is not recommended. Animal studies indicated an increased risk of intussusception, but the clinical relevance of these findings is unknown.

4.7. Effects on ability to drive and use machines
Selexipag has minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of Selexipag (such as headache or hypotension) should be kept in mind when considering the patient's ability to drive and use machines.

4.8. Undesirable Effects
The most commonly reported adverse reactions are headache, diarrhoea, nausea and vomiting, jaw pain, myalgia, pain in extremity, arthralgia, and flushing. These reactions are more frequent during the up-titration phase. The majority of these reactions are of mild to moderate intensity.

System organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Blood and lymphatic disorders		Anaemia Haemoglobin decreased	
Endocrine disorders		Hyperthyroidism Thyroid-stimulating Hormone decreased	
Metabolism and nutrition disorders		Decreased appetite Weight decrease	
Nervous system disorders	Headache		
Cardiac disorders			Sinus tachycardia
Vascular disorders	Flushing	Hypotension	
Respiratory, thoracic and mediastinal disorders	Nasopharyngitis (of non-infectious origin)	Nasal congestion	
Gastro-intestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain	
Skin and subcutaneous tissue disorders		Rash Urticaria Erythema	
Musculoskeletal and connective tissue disorders	Jaw pain Myalgia Arthralgia Pain in extremity		
General disorders and administration site conditions		Pain	

Infusion-site reactions (infusion site erythema/redness, pain and swelling) were reported with selexipag for Injection

Laboratory Test Abnormalities
Hemoglobin
In a Phase 3 placebo-controlled study in patients with PAH, mean absolute changes in hemoglobin at regular visits compared to baseline ranged from −0.34 to −0.02 g/dL in the selexipag group compared to −0.05 to 0.25 g/dL in the placebo group. A decrease in hemoglobin concentration to below 10 g/dL was reported in 8.6% of patients treated with selexipag tablets and 5.0% of placebo-treated patients.

Thyroid Function Tests
In a Phase 3 placebo-controlled study in patients with PAH, a reduction (up to −0.3 MU/L from a baseline median of 2.5 MU/L) in median thyroid-stimulating hormone (TSH) was observed at most visits in the selexipag group. In the placebo group, little change in median values was apparent. There were no mean changes in triiodothyronine or thyroxine in either group.

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. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on 1800 180 3024 or you can report to MSN Labs on +91- 40 38265227 (Direct line); +91 7331134745 (WhatApp). By reporting side effects, you can help provide more information on the safety of this product.

4.9. Overdose
Isolated cases of overdose up to 3200 mcg were reported. Mild, transient nausea was the only reported consequence. In the event of overdose, supportive measures must be taken as required. Dialysis is unlikely to be effective because selexipag and its active metabolite are highly protein-bound.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action
Selexipag is an oral prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin. Selexipag is hydrolyzed by carboxylesterase 1 to yield its active metabolite, which is approximately 37-fold as potent as selexipag. Selexipag and the active metabolite are selective for the IP receptor versus other prostanoid receptors (EP1-4, DP, FP, and TP).

5.2 Pharmacodynamic Properties
Pharmacotherapeutic group: Platelet aggregation inhibitors excl. heparin

Cardiac electrophysiology:
At the maximum tolerated dose of 1600 mcg twice daily, selexipag does not prolong the QT interval to any clinically relevant extent.

Platelet aggregation:
Both selexipag and its active metabolite caused concentration-dependent inhibition of platelet aggregation *in vitro* with an IC50 of 5.5 µM and 0.21 µM, respectively. However, at clinically relevant concentrations, there was no effect on platelet aggregation test parameters as seen following multiple-dose administrations of selexipag in healthy subjects from 400 mcg up to 1800 mcg twice daily.

Drug interaction:
Selexipag (400 mcg twice a day) did not influence the pharmacodynamic effect of warfarin on the international normalized ratio.

Pulmonary hemodynamics:
A Phase 2 clinical study assessed hemodynamic variables after 17 weeks of treatment in patients with PAH WHO Functional Class II–III and concomitantly receiving endothelin receptor antagonists (ERAs) and/or phosphodiesterase type 5 (PDE-5) inhibitors. Patients titrating selexipag to an individually tolerated dose (200 mcg twice daily increments up to 800 mcg twice daily) (N=33) achieved a statistically-significant mean reduction in pulmonary vascular resistance of 30.2% (95% confidence interval [CI] −44.7%, −12.2%) and an increase in cardiac index (median treatment effect) of 0.41 L/min/m^2 (95% CI 0.10, 0.71) compared to placebo (N=10).

5.3 Pharmacokinetic Properties
The pharmacokinetics of Selexipag and its active metabolite have been studied primarily in healthy subjects. The pharmacokinetics of Selexipag and the active metabolite, both after single- and multiple-dose administration, were dose-proportional up to a single dose of 800 micrograms and multiple doses of up to 1,800 micrograms twice daily. After multiple-dose administration, steady state conditions of selexipag and the active metabolite were reached within 3 days. No accumulation in plasma, either of parent compound or active metabolite, occurred after multiple-dose administration.
In healthy subjects, inter-subject variability in exposure (area under the curve over a dosing interval) at steady state was 43% and 39% for selexipag and the active metabolite, respectively. Intra-subject variability in exposure was 24% and 19% for selexipag and the active metabolite, respectively.
Exposure to selexipag and the active metabolite at steady state in PAH patients and healthy subjects was similar. The pharmacokinetics of selexipag and the active metabolite in PAH patients were not influenced by the severity of the disease and did not change with time.

Absorption
Selexipag is rapidly absorbed and is hydrolysed by carboxylesterases to its active metabolite.
The absolute bioavailability of Selexipag is approximately 49%. Upon oral administration, maximum observed plasma concentrations of Selexipag and its active metabolite are reached within about 1–3 hours and 3–4 hours, respectively.
In the presence of food, the absorption of Selexipag was prolonged resulting in a delayed time to peak concentration (T_{max}) and ~30% lower peak plasma concentration (C_{max}). The exposure to selexipag and the active metabolite (AUC) did not significantly change in the presence of food.

Distribution
The volume of distribution of Selexipag at steady state is 11.7 L.
Selexipag and its active metabolite are highly bound to plasma proteins (approximately 99% in total and to the same extent to albumin and alpha1-acid glycoprotein).

Metabolism
Selexipag is hydrolyzed to its active metabolite, (free carboxylic acid) in the liver and intestine by carboxylesterases. Oxidative metabolism, catalyzed mainly by CYP2C8 and to a smaller extent by CYP3A4, leads to the formation of hydroxylated and dealkylated products. UGT1A3 and UGT2B7 are involved in the glucuronidation of the active metabolite. Except for the active metabolite, none of the circulating metabolites in human plasma exceeds 3% of the total drug-related material.

Elimination
Elimination of selexipag is predominately via metabolism with a mean terminal half-life of 0.8-2.5 hours. The terminal half-life of the active metabolite is 6.2-13.5 hours. There is minimal accumulation of the active metabolite upon twice daily repeat administration suggesting that the effective half-life is in the range of 3-4 hours. The total body clearance of selexipag is 17.9 L/hour.

Excretion
In a study in healthy subjects with radiolabeled selexipag, approximately 93% of radioactive drug material was eliminated in feces and only 12% in urine. Neither selexipag nor its active metabolites were found in urine.

Specific Populations:
No clinically relevant effects of sex, race, age or body weight on the pharmacokinetics of selexipag and its active metabolite have been observed in healthy subjects or PAH patients.

Age:
The pharmacokinetic variables (C_{max} and AUC) were similar in adult and elderly subjects up to 75 years of age. There was no effect of age on the pharmacokinetics of selexipag and the active metabolite in PAH patients.

Hepatic Impairment:
In subjects with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, exposure to selexipag was 2-and 4-fold that seen in healthy subjects. Exposure to the active metabolite of selexipag remained almost unchanged in subjects with mild hepatic impairment and was doubled in subjects with moderate hepatic impairment.

Renal Impairment:
A 40-70% increase in exposure (maximum plasma concentration and area under the plasma concentration-time curve) to selexipag and its active metabolite was observed in subjects with severe renal impairment (estimated glomerular filtration rate ≥ 15 mL/min/1.73 m2 and < 30 mL/min/1.73 m^2).

Drug Interaction Studies:
In vitro studies
Selexipag is hydrolyzed to its active metabolite by carboxylesterases. Selexipag and its active metabolite both undergo oxidative metabolism mainly by CYP2C8 and to a smaller extent by CYP3A4. The glucuronidation of the active metabolite is catalyzed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates of OATP1B1 and OATP1B3. Selexipag is a substrate of P-gp, and the active metabolite is a substrate of the transporter of breast cancer resistance protein (BCRP). Selexipag and its active metabolite do not inhibit or induce cytochrome P450 enzymes and transport proteins at clinically relevant concentrations.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology
In the repeated-dose toxicity studies in rodents, strong blood pressure decrease as a result of exaggerated pharmacology induced transient clinical signs and reduced food consumption and body-weight gain. In adult and juvenile dogs, intestine and bone / bone marrow were identified as the main target organs after treatment with selexipag. A delay in the closure of the femoral and/or tibial epiphyseal growth plate was observed in juvenile dogs. A no-observed-adverse-effect level was not established. In juvenile dogs, intussusception due to prostacyclin-related effects on intestinal motility was observed sporadically. Safety margins adapted for IP receptor potency for the active metabolite were 2-fold (based on total exposure) in relation to human therapeutic exposure. The finding did not occur in mouse or rat toxicity studies. Because of the species-specific sensitivity of dogs to develop intussusception, this finding is considered not relevant for adult humans.
Increased bone ossification and related changes in the bone marrow in dog studies are considered to be due to the activation of EP4 receptors in dogs. As human EP4 receptors are not activated by selexipag or its active metabolite, this effect is species-specific and, therefore, not relevant to humans. Selexipag and the active metabolite are not genotoxic.
Selexipag was not teratogenic in rats and rabbits (exposure margins above therapeutic exposure of 13-fold for selexipag and 43-fold for the active metabolite, based on total exposure). Safety margins for potential IP receptor-related effects on reproduction were 20 for fertility and 5 and 1 (based on free exposure) for embryo-foetal development in rats and rabbits, respectively, when adapted for differences in receptor potency. In the rat pre-/post-natal development study, selexipag induced no effects on maternal and pup reproductive function.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Selexipag revealed no evidence of carcinogenic potential.
Mutagenesis: Selexipag and the active metabolite are not genotoxic on the basis of the overall evidence of conducted genotoxicity studies.
Fertility: The no effect dose for effects on fertility.

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities
None

7.2. Packing Information
Clear tubular10ml/20mm European blow back Lyo vial with 20mm Bromobutyl Igloo rubber stopper and 20 mm Aluminum flip-off seals.

7.3. Shelf life
18 months

7.4. Storage and Handling Instructions
Store in a refrigerator at (-2°C – 8°C) (36°F to 46°F) until use in order to protect from light.

8. PATIENT COUNSELLING INFORMATION
Inform patients:
- what to do if they miss a dose
- not to split, crush, or chew tablets.

9. DETAILS OF MANUFACTURER
MSN Laboratories Private Limited,
Formulation Division,
Unit II, Survey No. 1277 & 1319 to 1324,
Nandigama (Village and Mandal),
Rangareddy District, Pin Code: 509228,
Telangana, India.

10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
Not Applicable

11. DATE OF REVISION
Apr 2024

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