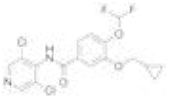
# ROMILAST™ Tablets 500 mcg روملاسٹ

(RofIumilast)

**DESCRIPTION**
The active ingredient in ROMILAST tablets is roflumilast. Roflumilast and its active metabolite (roflumilast N-oxide) are selective phosphodiesterase 4 (PDE4) inhibitors. The chemical name of roflumilast is N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and the molecular weight is 403.22

The chemical structure is:



**QUALITATIVE & QUANTITATIVE COMPOSITION**
**ROMILAST** (Roflumilast) is available for oral administration as:
Romilast Tablets 500mcg
Each tablet contains
Roflumilast……500 mcg

**CLINICAL PHARMACOLOGY**
**Mechanism of Action**
Roflumilast and its active metabolite (roflumilast N-oxide) are selective inhibitors of phosphodiesterase 4 (PDE4). Roflumilast and roflumilast N-oxide inhibition of PDE4 (a major cyclic-3',5'-adenosine monophosphate (cyclic AMP)-metabolizing enzyme in lung tissue) activity leads to accumulation of intracellular cyclic AMP. While the specific mechanism(s) by which ROMILAST exerts its therapeutic action in COPD patients is not well defined, it is thought to be related to the effects of increased intracellular cyclic AMP in lung cells.

**Pharmacodynamics**
In COPD patients, 4 week treatment with ROMILAST 500 mcg oral once daily reduced sputum neutrophils and eosinophils by 31%, and 42%, respectively. In a pharmacodynamic study in healthy volunteers, ROMILAST 500 mcg once daily reduced the number of total cells, neutrophils and eosinophils found in bronchoalveolar lavage fluid following segmental pulmonary lipopolysaccharide (LPS) challenge by 35%, 38% and 73%, respectively. The clinical significance of these findings is unknown.

**Pharmacokinetics**
**Absorption**
The absolute bioavailability of roflumilast following a 500 mcg oral dose is approximately 80%. Maximum plasma concentrations ($C_{max}$) of roflumilast typically occur approximately one hour after dosing (ranging from 0.5 to 2 hours) in the fasted state while plateau-like maximum concentrations of the N-oxide metabolite are reached in approximately eight hours (ranging from 4 to 13 hours). Food has no effect on total drug absorption, but delays time to maximum concentration ($T_{max}$) of roflumilast by one hour and reduces $C_{max}$ by approximately 40%, however, $C_{max}$ and $T_{max}$ of roflumilast N-oxide are unaffected. An in vitro study showed that roflumilast and roflumilast N-oxide did not inhibit P-gp transporter.

**Distribution**
Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively. Volume of distribution for single dose 500 mcg roflumilast is about 2.9 L/kg. Studies in rats with radiolabeled roflumilast indicate low penetration across the blood-brain barrier.

**Metabolism**
Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The N-oxide metabolite is the only major metabolite observed in the plasma of humans. Together, roflumilast and roflumilast N-oxide account for the majority (87.5%) of total dose administered in plasma. In urine, roflumilast was not detectable while roflumilast N-oxide was only a trace metabolite (less than 1%). Other conjugated metabolites such as roflumilast N-oxide glucuronide and 4-amino-3,5-dichloropyridine N-oxide were detected in urine.
While roflumilast is three times more potent than roflumilast N-oxide at inhibition of the PDE4 enzyme in vitro, the plasma AUC of roflumilast N-oxide on average is about 10-fold greater than the plasma AUC of roflumilast.

In vitro studies and clinical drug-drug interaction studies suggest that the biotransformation of roflumilast to its N-oxide metabolite is mediated by CYP 1A2 and 3A4. Based on further in vitro results in human liver microsomes, therapeutic plasma concentrations of roflumilast and roflumilast N-oxide do not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, or 4A9/11. Therefore, there is a low probability of relevant interactions with substances metabolized by these P450 enzymes. In addition, in vitro studies demonstrated no induction of the CYP 1A2, 2A6, 2C9, 2C19, or 3A4/5 and only a weak induction of CYP 2B6 by roflumilast.

**Elimination**
The plasma clearance after short-term intravenous infusion of roflumilast is on average about 9.6 L/h. Following an oral dose, the median plasma effective half-life of roflumilast and its N-oxide metabolite are approximately 17 and 30 hours, respectively. Steady state plasma concentrations of roflumilast and its N-oxide metabolite are reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing. Following intravenous or oral administration of radiolabeled roflumilast, about 70% of the radioactivity was recovered in the urine.

**SPECIAL POPULATION**
**Pregnancy**
Teratogenic effects: Pregnancy Category C:
**ROMILAST** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery**
**ROMILAST** should not be used during labor and delivery.

**Nursing Mothers**
Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of **ROMILAST** on breast-fed infants **ROMILAST** should not be used by women who are nursing.

**Pediatric Use**
COPD does not normally occur in children. The safety and effectiveness of **ROMILAST** in pediatric patients have not been established

**Age**
No dosage adjustment is necessary for elderly patients

**Gender**
No dosage adjustment is necessary based on gender.

**Renal Impairment**
No dosage adjustment is necessary for patients with renal impairment.

**Hepatic Impairment**
**ROMILAST** is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C).

**Smoking**
The pharmacokinetics of roflumilast and roflumilast N-oxide were comparable in smokers as compared to nonsmokers. There was no difference in $C_{max}$ between smokers and non-smokers when roflumilast 500 mcg was administered as a single dose to 12 smokers and 12 non-smokers. The AUC of roflumilast in smokers was 13% less than that in non-smokers while the AUC of roflumilast N-oxide in smokers was 17% more than that in nonsmokers.
**Race**
No dosage adjustment is necessary for race.

**THERAPEUTIC INDICATIONS**
**ROMILAST** (Roflumilast) is indicated for the treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

**Limitations of Use**
**ROMILAST** is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

**DOSAGE & ADMINISTRATION**
The recommended dose of **ROMILAST** is one 500 microgram (mcg) tablet per day, with or without food.
**ADVERSE EFFECTS**
The following adverse reactions are described in greater detail in other sections:
• Psychiatric Events Including Suicidality
• Weight Decrease

**CONTRAINDICATIONS**
The use of **ROMILAST** is contraindicated in the following condition;
• Hypersensitivity to the active substance or to any of the excipients
• Moderate to severe liver impairment (Child-Pugh B or C).

**OVERDOSAGE**
The following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

**Management of overdose**
In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

**WARNINGS AND PRECAUTIONS**
**Treatment of Acute Bronchospasm**
**ROMILAST** is not a bronchodilator and should not be used for the relief of acute bronchospasm.

**Psychiatric Events including Suicidality**
Before using ROMILAST in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with ROMILAST in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with ROMILAST if such events occur.
**Weight Decrease**
Patients treated with ROMILAST should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of ROMILAST should be considered.

**DRUG INTERACTIONS**
**Drugs That Induce Cytochrome P450 (CYP)**
Enzymes Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of ROMILAST. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with ROMILAST is not recommended.

**Drugs That Inhibit Cytochrome P450 (CYP) Enzymes**
The co-administration of ROMILAST (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit.

**Oral Contraceptives Containing Gestodene and Ethinyl Estradiol**
The co-administration of ROMILAST (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit.

**STORAGE**
Store at 25°C. (Excursions permitted between 15°C to 30°C).
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

**HOW SUPPLIED**
**ROMILAST** (Roflumilast) 500mcg tablets are available in blister pack of 10's.

***Keep out of reach of children.***

***To be sold on prescription of a registered medical practitioner only.***

**Please read the contents carefully before use.**
**This package insert is continually updated from time to time.**

ہدایات:
دوا کو ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔
(درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے)۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

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SCILIFE

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