MSN LABORATORIES LTD-FORMULATIONS DIVISION

ROFLUMILAST TABLETS 0. 5 mg

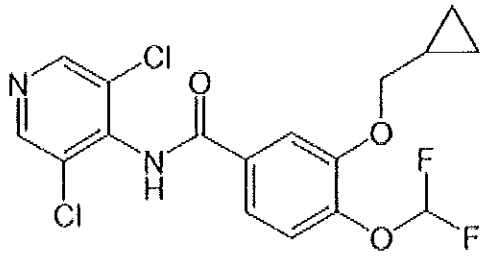
Each film coated tablets contains
Roflumilast ----------500 mcg
Colors: Titanium dioxide & Iron oxide yellow

Chemical Name : 3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy) benzamide N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide

Empirical Formula: $C_{17}H_{14}Cl_2F_2N_2O_3$

Molecular weight : 403.22 g/mol

Structural Formula:



Roflumilast is a white to off-white powder. It is practically insoluble in water (0.52 – 0.56 mg/l at 22°C) and hexane, sparingly soluble in ethanol and freely soluble in acetone

INDICATIONS AND USAGE: Roflumilast is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with 81 chronic bronchitis and a history of exacerbations.

Limitations of Use Roflumilast is not a bronchodilator and is not indicated for the relief of acute bronchospasm

DOSAGE AND ADMINISTRATION : The recommended dose of Roflumilast is one 500 microgram (mcg) tablet per day, with or without food.

DOSAGE FORMS AND STRENGTHS: Roflumilast Tablets are supplied as Light yellow colored round shaped film coated tablet with plain surface on both sides. Each tablet contains 500 mcg of roflumilast.

use of Roflumilast is contraindicated in the following conditions: Moderate to severe liver impairment (Child-Pugh B or C)

WARNINGS AND PRECAUTIONS

Treatment of Acute Bronchospasm.

Roflumilast is not a bronchodilator and should not be used for the relief of acute bronchospasm

Psychiatric Events including Suicidality

Treatment with Roflumilast is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with Roflumilast 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo.The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with Roflumilast 500 mcg daily (2.4%, 1.4%, and 1.2% for Roflumilast versus 1.0%, 0.9%, and 0.9% for placebo,respectively). Instances of suicidal ideation and behavior, including completed suicide, have been 108 observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving Roflumilast compared to one patient (suicidal ideation) who received placebo

Weight Decrease

Before using Roflumilast in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with Roflumilast 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 Roflumilast if such events occur.

Drug Interactions

loss was a common adverse reaction in Roflumilast clinical trials and was reported in 7.5% (331) of patients treated with Roflumilast 500 mcg once daily compared to 2.1% (89) treated with placebo. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving Roflumilast. Patients treated with Roflumilast should have their weight

monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of Roflumilast should be considered

major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease in the therapeutic effectiveness of Roflumilast. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with Roflumilast is not recommended.

ADVERSE REACTIONS:

The following adverse reactions are described in greater detail in other sections:

- Psychiatric Events Including Suicidality
- Weight Decrease

Adverse Reactions in Clinical Studies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure of 4438 patients to Roflumilast 500 mcg once daily in four 1-year placebo-controlled 145 trials, two 6-month placebo-controlled trials, and two 6-month drug add-on trials.. In these trials, 3136 and 1232 COPD patients were exposed to Roflumilast 500 mcg once daily for 6 months and 1-year, respectively.

The population had a median age of 64 years (range 40-91), 73% were male, 92.9% were Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV1) of 8.9 to 89.1% predicted. In these trials, 68.5% of the patients treated with Roflumilast reported an adverse reaction compared with 65.3% treated with placebo

The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for Roflumilast-treated patients and 9.9%for placebo-treated patients. The most common adverse reactions that led to discontinuation of Roflumilast were diarrhea (2.4%) and 154 nausea (1.6%).

Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in Roflumilast treated patients include diarrhea, atrial fibrillation, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure.

Adverse reactions that occurred in the Roflumilast group at a frequency of 1 to 2% where rates exceeded that in the placebo group include:

Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting Infections and infestations - rhinitis, sinusitis, urinary tract infection, 1Musculoskeletal and connective tissue disorders - muscle spasms Nervous system disorders - tremor Psychiatric disorders - anxiety, depression

DRUG INTERACTIONS

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2.

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

Drugs That Inhibit Cytochrome P450 (CYP) Enzymes The co-administration of Roflumilast (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 Roflumilast (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.

OVERDOSE

Human Experience

No case of overdose has been reported in clinical studies with Roflumilast. During the Phase I studies of Roflumilast, 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.

CONTRAINDICATIONS

The use of Roflumilast is contraindicated in the following conditions:

- Moderate to severe liver impairment (Child-Pugh B or C)

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 Roflumilast 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 Roflumilast 500 mcg oral once daily reduced sputum neutrophils and eosinophils by 31%, and 42%, respectively. In a pharmacodynamic study in healthy volunteers, Roflumilast 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 (Cmax) 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 affect on total drug absorption, but delays time to maximum concentration (Tmax) of roflumilast by one hour and reduces Cmax by approximately 40%, however, Cmax and Tmax 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 penetrati 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 Populations

Hepatic Impairment

Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUC of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The Cmax of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. Roflumilast 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering Roflumilast to patients who have mild liver impairment (Child-Pugh A). Roflumilast is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C).

Renal Impairment

In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, roflumilast and roflumilast N-oxide AUCs were decreased by 21% and 7%, respectively and Cmax were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment.

Age

Roflumilast 500 mcg once daily for 15 days was studied in young, middle aged, and elderly healthy subjects. The exposure in elderly (> 65 years of age) were 27% higher in AUC and 16% higher in Cmax for roflumilast and 19% higher in AUC and 13% higher in Cmax for roflumilast-N-oxide than that in young volunteers (18-45 years old). No dosage adjustment is necessary for elderly patients .

Gender

In a Phase I study evaluating the effect of age and gender on the pharmacokinetics of roflumilast and roflumilast N-oxide, a 39% and 33% increase in roflumilast and roflumilast N-oxide AUC were noted in healthy female subjects as compared to healthy male subjects. No dosage adjustment is necessary

based on gender.

Smoking

The pharmacokinetics of roflumilast and roflumilast N-oxide were comparable in smokers as compared to non-smokers. There was no difference in Cmax 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 non-smokers.

Race

As compared to Caucasians, African Americans, Hispanics, and Japanese showed 16%, 41%, and 15% higher AUC, respectively, for roflumilast and 43%, 27%, and 16% higher AUC, respectively, for roflumilast N-oxide. As compared to Caucasians, African Americans, Hispanics, and Japanese showed 8%, 21%, and 5% higher Cmax, respectively, for roflumilast and 43%, 27%, and 17% higher Cmax, respectively, for roflumilast N-oxide. No dosage adjustment is necessary for race.

Drug Interactions

Drug interaction studies were performed with roflumilast and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction

No significant drug interactions were observed when 500 mcg oral roflumilast was administered with inhaled salbutamol, formoterol, budesonide and oral montelukast, digoxin, theophylline, warfarin, sildenafil, midazolam, or antacids.

The effect of concomitant drugs on the exposure of roflumilast and roflumilast N-oxide is shown in the Figure 1 below.

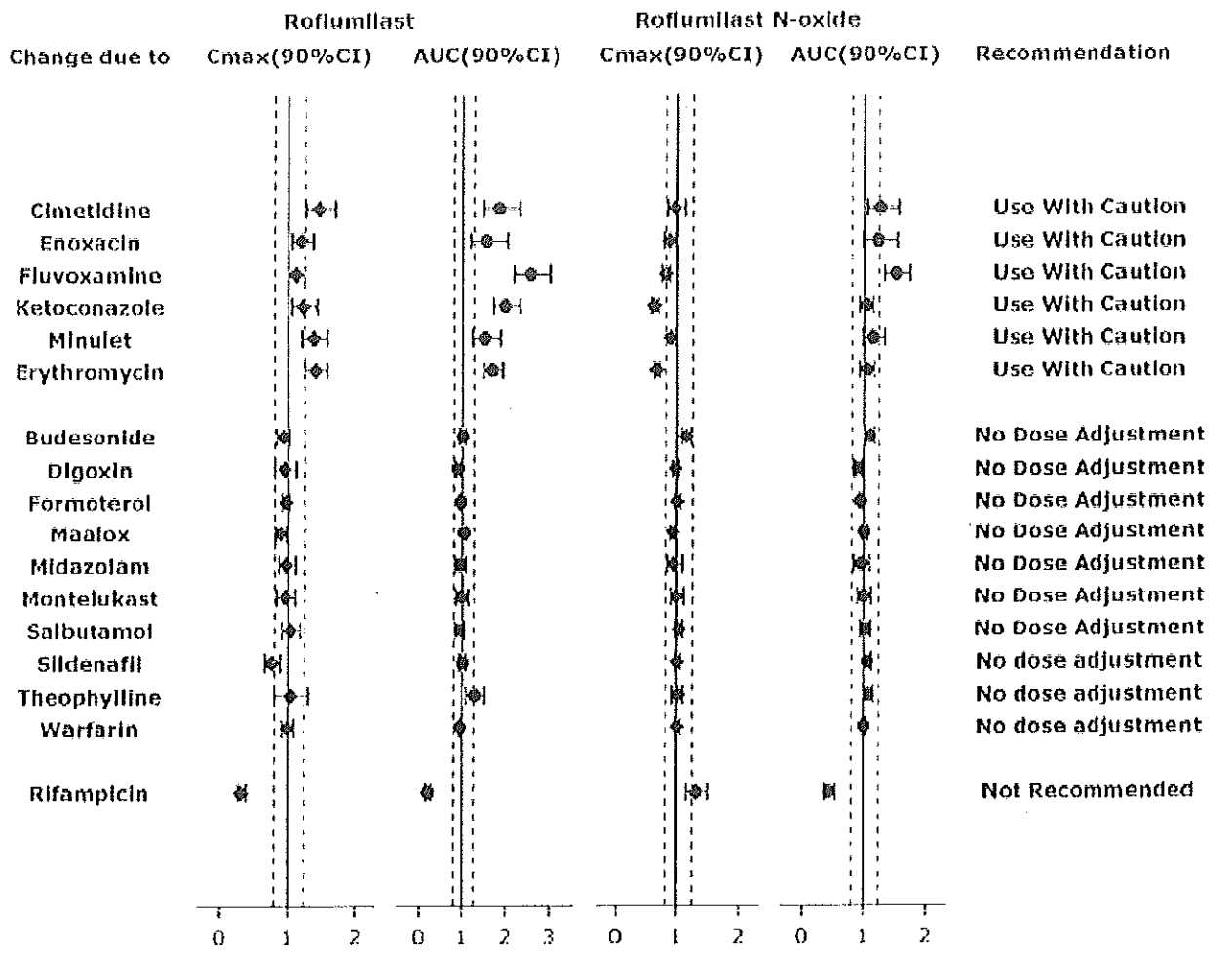


Figure 1. Effect of concomitant drugs on the exposure of roflumilast and roflumilast N-oxide. Note that the dashed lines indicate the lower and higher bounds (0.8-1.25) of the 90% confidence interval of the geometric mean ratio of Cmax or AUC for roflumilast or roflumilast N-oxide for Treatment (Roflumilast+Coadministered Drug) vs. Reference (Roflumilast). The dosing regimens of coadministered drugs was: Midazolam: 2mg po SD; Erythromycin: 500mg po TID; Ketoconazole: 200mg po BID; Rifampicin:600mg po QD; Fluvoxamine:50mg po QD; Digoxin: 250ug po SD; Maalox:30mL po SD; Salbutamol: 0.2mg pi TID; Cimetidine:400mg po BID; Formoterol: 40ug po BID; Budesonide:400ug po BID; Theophylline:375 mg po BID; Warfarin:250 mg po SD; Enoxacin:400mg po BID; Sildenafil:100mg SD; Minulet (combination oral contraceptive):0.075mg gestodene/0.03mg ethinylestradiol po QD; Montelukast:10mg po QD390

Drug interactions considered to be significant are described in more detail below.

***Inhibitors of CYP3A4 and CYP1A2*:** Erythromycin: In an open-label crossover study in 16 healthy volunteers, the coadministration of CYP 3A4 inhibitor erythromycin (500 mg three times daily for 13

days) with a single oral dose of 500 mcg Roflumilast resulted in 40% and 70% increase in Cmax and AUC for roflumilast, respectively, and a 34% decrease and a 4% increase in Cmax and AUC for roflumilast N-oxide, respectively.

Ketoconazole: In an open-label crossover study in 16 healthy volunteers, the coadministration of a strong CYP 3A4 inhibitor ketoconazole (200 mg twice daily for 13 days) with a single oral dose of 500 mcg Roflumilast resulted in 23% and 99% increase in Cmax and AUC for roflumilast, respectively, and a 38% reduction and 3% increase in Cmax and AUC for roflumilast N-oxide, respectively.

Fluvoxamine: In an open-label crossover study in 16 healthy volunteers, the coadministration of dual CYP 3A4/1A2 inhibitor fluvoxamine (50 mg daily for 14 days) with a single oral dose of 500 mcg Roflumilast showed a 12% and 156% increase in roflumilast Cmax and AUC along with a 210% decrease and 52% increase in roflumilast N-oxide Cmax and AUC, respectively.

Enoxacin: In an open-label crossover study in 16 healthy volunteers, the coadministration of dual CYP 3A4/1A2 inhibitor enoxacin (400 mg twice daily for 12 days) with a single oral dose of 500 mcg Roflumilast resulted in an increased Cmax and AUC of roflumilast by 20% and 56%, respectively. Roflumilast N-oxide Cmax was decreased by 14% while roflumilast N-oxide AUC was increased by 23%.

Cimetidine: In an open-label crossover study in 16 healthy volunteers, the coadministration of a dual CYP 3A4/1A2 inhibitor cimetidine (400 mg twice daily for 7 days) with a single dose of 500 mcg oral Roflumilast resulted in a 46% and 85% increase in roflumilast Cmax and AUC; and a 4% decrease in Cmax and 27% increase in AUC for roflumilast N-oxide, respectively.

Oral Contraceptives containing Gestodene and Ethinyl Estradiol: In an open-label crossover study in 20 healthy adult volunteers, coadministration of a single oral dose of 500 mcg Roflumilast with repeated doses of a fixed combination oral contraceptive containing 0.075 mg gestodene and 0.03 mg ethinyl estradiol to steady state caused a 38% increase and 12 % decrease in Cmax of roflumilast and roflumilast N-oxide, respectively. Roflumilast and roflumilast N-oxide AUCs were increased by 51% and 14%, respectively.

Inducers of CYP enzymes: Rifampicin: In an open-label, three-period, fixed-sequence study in 15 healthy volunteers, coadministration of the strong CYP3A4 inducer rifampicin (600 mg once daily for 11 days) with a single oral dose of 500 mcg Roflumilast resulted in reduction of roflumilast Cmax and AUC by 68% and 79%, respectively; and an increase of roflumilast N-oxide Cmax by 30% and reduced roflumilast N-oxide AUC by 56%.

STORAGE AND HANDLING

Store Roflumilast 500 mcg tablets at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F).

SHELF LIFE

3 years

PACKING INFORMATION:

Roflumilast 0.5 mcg available as PVC/PVDC aluminium blisters in packs of 10 film-coated tablets.

Manufactured by
MSN Laboratories Limited
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