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ROFLAIR Tablets (Roflumilast)

Composition

ROFLAIR Tablets
Each uncoated tablet contains:
Roflumilast IP.....500 mcg

Dosage Form

Oral tablet

Pharmacology

Pharmacodynamics

Mechanism of Action
Roflumilast is a phosphodiesterase 4 (PDE4) inhibitor and a non-steroid, anti-inflammatory agent designed to target both the systemic and pulmonary inflammation associated with chronic obstructive pulmonary disease (COPD). The mechanism of action is the inhibition of PDE4, a major cyclic adenosine monophosphate (cAMP)-metabolizing enzyme found in structural and inflammatory cells important to the pathogenesis of COPD. Roflumilast targets the PDE4A, 4B and 4D splicing variants with similar potency in the nanomolar range. The affinity to the PDE4C splicing variants is 5- to 10-fold lower. This mechanism of action and the selectivity also apply to roflumilast N-oxide, which is the major active metabolite of roflumilast.
Pharmacodynamic Effects
Inhibition of PDE4 leads to elevated intracellular cAMP levels and mitigates COPD-related malfunctions of leucocytes, airway and pulmonary vascular smooth muscle cells, endothelial and airway epithelial cells and fibroblasts in experimental models. Upon *in vitro* stimulation of human neutrophils, monocytes, macrophages or lymphocytes, roflumilast and roflumilast N-oxide suppress the release of inflammatory mediators, e.g. leukotriene B4, reactive oxygen species, tumour necrosis factor-alpha, interferon-gammaand granzyme B.
In patients with COPD, roflumilast reduced sputum neutrophils. Furthermore, roflumilast attenuated influx of neutrophils and eosinophils into the airways of endotoxin-challenged healthy volunteers.

Pharmacokinetics

Roflumilast is extensively metabolized in humans, with the formation of a major pharmacodynamically active metabolite, roflumilast N-oxide. Since both roflumilast and roflumilast N-oxide contribute to PDE4 inhibitory activity *in vivo*, pharmacokinetic considerations are based on total PDE4 inhibitory activity (i.e. total exposure to roflumilast and roflumilast N-oxide).
Absorption

The absolute bioavailability of roflumilast following a 500 mcg oral dose is approximately 80%. Maximum plasma concentration (C_{max}) of roflumilast typically occurs approximately 1hour after dosing (ranging from 0.5 to 2 hours) in the fasted state. Maximum concentrations of the N-oxide metabolite are reached after about 8hours (ranging from 4 to 13 hours). Food intake does not affect the total PDE4 inhibitory activity, but delays time to maximum concentration (t_{max}) of roflumilast by 1hour and reduces the $C_{max}$by approximately 40%. However, the C_{max} and t_{max} of roflumilast N-oxide are unaffected.

Distribution

Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively. Volume of distribution for a single dose of 500 mcgroflumilast is about 2.9 L/kg. Due to the physico-chemical properties, roflumilast is readily distributed to organs and tissues, including fatty tissue of mice, hamster and rat. An early distribution phase with marked penetration into tissues is followed by a marked elimination phase out of fatty tissue, most probably due to pronounced break-down of the parent compound to roflumilast N-oxide. These studies in rats with radio labelled Roflumilast also indicate low penetration across the blood-brain barrier. There is no evidence for a specific accumulation or retention of roflumilast or its metabolites in organs and fattytissue.

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 the 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 *invitro* 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 radio labelled roflumilast, about 70% of the radioactivity was recovered in the urine.

Indications

ROFLAIR Tablets are indicated for the maintenance treatment of severe COPD (FEV_1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment to reduce the risk of COPD exacerbations.

Dosage And Administration

The recommended dose of ROFLAIR Tablets is one 500 mcg tablet per day, with or without food. The tablet should be swallowed with water and taken at the same time every day.

Contraindications

The use of ROFLAIR Tablets is contraindicated in case of hypersensitivity to the active substance or to any of the excipients, and also in moderate or severe hepatic impairment (Child-Pugh B or C).

Warnings And Precautions

General

Treatment of Acute Bronchospasm

ROFLAIR Tablets do not act as 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 eight 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 behaviour, including completed suicide, have been observed in clinical trials. Cases of suicidal ideation and behaviour, including completed suicide, have been observed in the post-marketing setting in patients with or without a history of depression.

Before using roflumilast in patients with a history of depression and/or suicidal thoughts or behaviour, prescribers should carefully weigh the risks and benefits of treatment with roflumilast in such patients. Patients, their carers 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.

Weight Decrease

Weight 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 an adverse reaction, weight was prospectively assessed in two placebo-controlled clinical trials of 1-year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5 and 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.

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 CYP450 Enzymes

Strong CYP450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of roflumilast. Therefore, the use of strong CYP450 inducers (e.g. rifampicin, phenobarbital, carbamazepine and phenytoin) with roflumilast is not recommended.

Drugs That Inhibit CYP450 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 EthinylOestradiol

The co-administration of roflumilast (500 mcg) with oral contraceptives containing gestodene and ethinyloestradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against the benefits.

▶ Renal Impairment

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

▶ 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. The AUCs and C_{max} of roflumilast and roflumilast N-oxide were increased in both groups. Clinicians should consider the risk–benefit ratio 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). Roflumilast 500 mcg has not been studied in hepatically impaired patients.

▶ Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of roflumilast in pregnant women. Roflumilast was not teratogenic in mice, rats or rabbits. ROFLAIR Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

ROFLAIR Tablets should not be used during labour and delivery. There are no human studies that have investigated the effects of roflumilast on preterm labour or labour at term; however, animal studies showed that roflumilast disrupted the labour and delivery process in mice.

▶ Lactation

ROFLAIR Tablets 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 the effects of roflumilast on breastfed infants. Roflumilast should not be used by women who are nursing.

▶ Paediatric Use

COPD does not normally occur in children. The safety and effectiveness of ROFLAIR Tablets in paediatric patients has not been established.

▶ Geriatric Use

No overall differences in safety or effectiveness were observed between the elderly and younger subjects in the clinical trials. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but the greater sensitivity of some older individuals cannot be ruled out. Based on available data for Roflumilast, no adjustment of dosage in geriatric patients is warranted.

Undesirable Effects

Roflumilast has been evaluated for safety in 4,438 patients in four 1-year placebo-controlled trials, two 6-month placebo-controlled trials and two 6-month drug add-on trials. In these trials, 3,136 and 1,232 COPD patients were exposed to roflumilast 500 mcg once daily for 6 months and 1year, respectively.

The proportion of patients who discontinued treatment due to adverse reactions 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 diarrhoea (2.4%) and nausea (1.6%).

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

The most common adverse reactions (incidence ≥2% and greater than placebo; listed in descending order of frequency) reported in controlled clinical trials were diarrhoea, weight-decrease, nausea, headache, back pain, influenza, insomnia, dizziness, and decreased appetite.

Adverse reactions that occurred in the roflumilast group at a frequency of 1 to 2%, where rates exceeded that in the placebo group, included the following:

Gastrointestinal Disorders: abdominal pain, dyspepsia, gastritis, vomiting.

Infections and Infestations: rhinitis, sinusitis, urinary tract infection,

Musculoskeletal and Connective Tissue Disorders: muscle spasms

Nervous System Disorders: tremor

Psychiatric Disorders: anxiety, depression

In the post-marketing experience, the following adverse reactions have been identified from spontaneous reports of roflumilast received worldwide: hypersensitivity reactions, including angio-oedema, urticaria and rash. These adverse reactions were chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to roflumilast. Because these adverse reactions were reported voluntarily from a population of uncertain size, it was not possible to estimate their frequency or establish a causal relationship to roflumilast exposure.

Overdosage

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 2,500 mcg and a single dose of 5,000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

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

Incompatibility

Not applicable.

Storage And Handling Instructions

Store ROFLAIR Tablets below 30°C.Protect from light and moisture. Keep ROFLAIR Tablets out of the reach of children.

Packaging Information

ROFLAIR Tablets..... Blister pack of 10 tablets

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