

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022522Orig1s000

LABELING

1 **HIGHLIGHTS OF PRESCRIBING INFORMATION**
2 **These highlights do not include all the information needed**
3 **to use DALIRESP safely and effectively. See full**
4 **prescribing information for DALIRESP.**

5
6 **DALIRESP® (roflumilast) tablets**
7 **Initial U.S. Approval: 20XX**

8
9 -----**INDICATIONS AND USAGE**-----

10 DALIRESP is indicated as a treatment to reduce the risk of
11 COPD exacerbations in patients with severe COPD associated
12 with chronic bronchitis and a history of exacerbations. (1, 14)

13
14 *Limitations of Use:* DALIRESP is not a bronchodilator and is not
15 indicated for the relief of acute bronchospasm. (1, 14)

16
17 -----**DOSAGE AND ADMINISTRATION**-----

18 The recommended dosage for patients with COPD is one 500
19 mcg tablet per day, with or without food. (2)

20
21 -----**DOSAGE FORMS AND STRENGTHS**-----

22 Tablets: 500 mcg (3)

23
24 -----**CONTRAINDICATIONS**-----

- 25 • Moderate to severe liver impairment (Child-Pugh B or C)
26 (4)

27
28 -----**WARNINGS AND PRECAUTIONS**-----

- 29 • Acute bronchospasm: Do not use for the relief of acute
30 bronchospasm. (5.1)
31 • Psychiatric Events including Suicidality: Advise patients ,
32 their caregivers, and families to be alert for the emergence
33 or worsening of insomnia, anxiety, depression, suicidal
34 thoughts or other mood changes, and if such changes
35 occur to contact their healthcare provider. Carefully weigh
36 the risks and benefits of treatment with DALIRESP in
37 patients with a history of depression and/or suicidal
38 thoughts or behavior. (5.2)
39 • Weight Decrease: Monitor weight regularly. If unexplained
40 or clinically significant weight loss occurs, evaluate weight
41 loss and consider discontinuation of DALIRESP. (5.3)

75

- 42 • Drug Interactions: Use with strong cytochrome P450
43 enzyme inducers (e.g. rifampicin, phenobarbital,
44 carbamazepine, phenytoin) is not recommended. (5.4)

45
46 -----**ADVERSE REACTIONS**-----

47 Most common adverse reactions (≥ 2%) are diarrhea, weight
48 decrease, nausea, headache, back pain, influenza, insomnia,
49 dizziness and decreased appetite. (6.1)

50
51 **To report SUSPECTED ADVERSE REACTIONS, Contact**
52 **Forest Laboratories, Inc. at 1-800-678-1605 or FDA at 1-800-**
53 **FDA-1088 or www.fda.gov/medwatch.**

54
55 -----**DRUG INTERACTIONS**-----

- 56 • Use with inhibitors of CYP3A4 or dual inhibitors of
57 CYP3A4 and CYP1A2 (e.g. erythromycin, ketoconazole,
58 fluvoxamine, enoxacin, cimetidine) will increase roflumilast
59 systemic exposure and may result in increased adverse
60 reactions. The risk of such concurrent use should be
61 weighed carefully against benefit. (7.2)

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63 -----**USE IN SPECIFIC POPULATIONS**-----

- 64 • Nursing Mothers: DALIRESP should not be used by
65 women who are nursing as excretion of roflumilast and/or
66 its metabolites into human milk is probable and there are
67 no human studies that have investigated effects of
68 DALIRESP on breast-fed infants. (8.3)

69
70 **See 17 for PATIENT COUNSELING INFORMATION AND**
71 **MEDICATION GUIDE**

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75
REVISED XX/20XX

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1. INDICATIONS AND USAGE**
- 2. DOSAGE AND ADMINISTRATION**
- 3. DOSAGE FORMS AND STRENGTHS**
- 4. CONTRAINDICATIONS**
- 5. WARNINGS AND PRECAUTIONS**
 - 5.1 Treatment of Acute Bronchospasm
 - 5.2 Psychiatric Events including Suicidality
 - 5.3 Weight Decrease
 - 5.4 Drug Interactions
- 6. ADVERSE REACTIONS**
 - 6.1 Adverse Reactions in Clinical Trials
- 7. DRUG INTERACTIONS**
 - 7.1 Drugs that induce Cytochrome P450 (CYP) Enzymes
 - 7.2 Drugs that inhibit Cytochrome P450 (CYP) Enzymes
 - 7.3 Oral combination contraceptives containing gestodene and ethinyl estradiol
- 8. USE IN SPECIFIC PATIENT POPULATIONS**
 - 8.1 Pregnancy
 - 8.2 Labor and Delivery
 - 8.3 Nursing Mothers
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
 - 8.6 Hepatic Impairment
 - 8.7 Renal Impairment
- 10. OVERDOSAGE**
 - 10.1 Human Experience
 - 10.2 Management of Overdose
- 11. DESCRIPTION**
- 12. CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13. NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14. CLINICAL STUDIES**
 - 14.1 Chronic Obstructive Pulmonary Disease
- 16. HOW SUPPLIED/STORAGE AND HANDLING**
 - 16.1 How Supplied
 - 16.2 Storage and Handling
- 17. PATIENT COUNSELING INFORMATION**
 - 17.1 Bronchospasm
 - 17.2 Psychiatric Events including Suicidality
 - 17.3 Weight Decrease
 - 17.4 Drug Interactions

*Sections or subsections omitted from the full prescribing information are not listed

77 **FULL PRESCRIBING INFORMATION**

78
79 **1 INDICATIONS AND USAGE**

80 DALIRESP® 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.

82
83 *Limitations of Use*

84 DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

85
86 **2 DOSAGE AND ADMINISTRATION**

87 The recommended dose of DALIRESP is one 500 microgram (mcg) tablet per day, with or without food.

88
89 **3 DOSAGE FORMS AND STRENGTHS**

90 DALIRESP is supplied as white to off-white, round tablets, embossed with "D" on one side and "500" on the other side. Each tablet
91 contains 500 mcg of roflumilast.

92
93 **4 CONTRAINDICATIONS**

94 The use of DALIRESP is contraindicated in the following conditions:

- 95 • Moderate to severe liver impairment (Child-Pugh B or C) [see *Clinical Pharmacology (12.3) and Use in Special Populations (8.6)*].

96
97 **5 WARNINGS AND PRECAUTIONS**

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99 **5.1 Treatment of Acute Bronchospasm**

100 DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

101
102 **5.2 Psychiatric Events including Suicidality**

103 Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of
104 patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo.
105 The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher
106 rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo,
107 respectively) [see *Adverse Reactions (6.1)*]. 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
109 attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who received placebo.

110
111 Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully
112 weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of
113 the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if
114 such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing
115 treatment with DALIRESP if such events occur.

116
117 **5.3 Weight Decrease**

118 Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with
119 DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [see *Adverse Reactions (6.1)*]. In addition to being
120 reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In
121 these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight)
122 compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients
123 receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of
124 patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP
125 should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be
126 evaluated, and discontinuation of DALIRESP should be considered.

127
128 **5.4 Drug Interactions**

129 A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The
130 administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease
131 in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin,
132 phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended. [see *Drugs That Induce Cytochrome P450 (CYP)*
133 *Enzymes (7.1) and Clinical Pharmacology (12.3)*].

134
135 **6 ADVERSE REACTIONS**

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

- 137 • Psychiatric Events Including Suicidality [see *Warnings and Precautions (5.2)*]
- 138 • Weight Decrease [see *Warnings and Precautions (5.3)*]

139
140 **6.1 Adverse Reactions in Clinical Studies**

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

143
144 The safety data described below reflect exposure of 4438 patients to DALIRESP 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 [see *Clinical Studies (14.1)*]. In these trials, 3136 and
146 1232 COPD patients were exposed to DALIRESP 500 mcg once daily for 6 months and 1-year, respectively.

147
148 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
149 pre-bronchodilator forced expiratory volume in one second (FEV₁) of 8.9 to 89.1% predicted. In these trials, 68.5% of the patients
150 treated with DALIRESP reported an adverse reaction compared with 65.3% treated with placebo.
151

152 The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.9%
153 for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and
154 nausea (1.6%).
155

156 Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in DALIRESP-
157 treated patients include diarrhea, atrial fibrillation, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure.
158

159 Table 1 summarizes the adverse reactions reported by ≥ 2% of patients in the DALIRESP group 8 controlled COPD clinical trials.
160
161

**Table 1: Adverse Reactions Reported by ≥ 2% of Patients
Treated with DALIRESP 500 mcg daily and Greater Than Placebo**

Adverse Reactions (Preferred Term)	Treatment	
	DALIRESP (N=4438)	Placebo (N=4192)
	n (%)	n (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

163 Adverse reactions that occurred in the DALIRESP group at a frequency of 1 to 2% where rates exceeded that in the placebo group
164 include:
165
166

- 167 Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting
- 168 Infections and infestations - rhinitis, sinusitis, urinary tract infection,
- 169 Musculoskeletal and connective tissue disorders - muscle spasms
- 170 Nervous system disorders - tremor
- 171 Psychiatric disorders - anxiety, depression
- 172

173 **7 DRUG INTERACTIONS**

174 A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2 [see *Clinical*
175 *Pharmacology* (12.3)].
176

177 **7.1 Drugs That Induce Cytochrome P450 (CYP) Enzymes**

178 Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of
179 DALIRESP. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin)
180 with DALIRESP is not recommended [see *Drug Interactions* (5.4) and *Clinical Pharmacology* (12.3)].
181

182 **7.2 Drugs That Inhibit Cytochrome P450 (CYP) Enzymes**

183 The co-administration of DALIRESP (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2
184 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and
185 may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. [see *Clinical*
186 *Pharmacology* (12.3)].
187

188 **7.3 Oral Contraceptives Containing Gestodene and Ethinyl Estradiol**

189 The co-administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase
190 roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully
191 against benefit [see *Clinical Pharmacology* (12.3)].
192

193 **8 USE IN SPECIFIC POPULATIONS**

194 **8.1 Pregnancy**

195 Teratogenic effects: Pregnancy Category C: There are no adequate and well controlled studies of DALIRESP in pregnant women.
196 DALIRESP was not teratogenic in mice, rats, or rabbits. DALIRESP should be used during pregnancy only if the potential benefit
197 justifies the potential risk to the fetus.
198

199 DALIRESP induced stillbirth and decreased pup viability in mice at doses corresponding to approximately 16 and 49 times,
200 respectively, the maximum recommended human dose (MRHD) (on a mg/m² basis at maternal doses > 2 mg/kg/day and 6 mg/kg/day,
201 respectively). DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD
202 (on a mg/m² basis at maternal doses ≥ 0.6 mg/kg/day). No treatment-related effects on embryo-fetal development were observed in
203

204 mice, rats, and rabbits at approximately 12, 3, and 26 times the MRHD, respectively (on a mg/m² basis at maternal doses of 1.5, 0.2,
205 and 0.8 mg/kg/day, respectively).
206

207 Nonteratogenic effects: DALIRESP has been shown to adversely affect pup post-natal development when dams were treated with the
208 drug during pregnancy and lactation periods in mice. These studies found that DALIRESP decreased pup rearing frequencies at
209 approximately 49 times the MRHD (on a mg/mg² basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP
210 also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at approximately 97 times the MRHD
211 (on a mg/m² basis at a maternal dose of 12 mg/kg/day) during pregnancy and lactation.
212

213 **8.2 Labor and Delivery**

214 DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on
215 preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice.
216 DALIRESP induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a
217 mg/m² basis at a maternal dose of > 2 mg/kg/day).
218

219 **8.3 Nursing Mothers**

220 Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human
221 milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not
222 be used by women who are nursing.
223

224 **8.4 Pediatric Use**

225 COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.
226

227 **8.5 Geriatric Use**

228 Of the 4438 COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were > 65 years of age and
229 471 were > 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger
230 subjects and other reported clinical experience has not identified differences in responses between the elderly and younger patients,
231 but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage
232 in geriatric patients is warranted [see *Clinical Pharmacology* (12.3)].
233

234 **8.6 Hepatic Impairment**

235 Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh
236 A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in
237 Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-
238 matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A
239 subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not
240 been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who
241 have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver
242 impairment (Child-Pugh B or C) [see *Contraindications* (4) and *Clinical Pharmacology* (12.3)].
243

244 **8.7 Renal Impairment**

245 In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and
246 roflumilast N-oxide were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. No dosage
247 adjustment is necessary for patients with renal impairment [see *Clinical Pharmacology* (12.3)].
248

249 **10 OVERDOSAGE**

250 **10.1 Human Experience**

251 No case of overdose has been reported in clinical studies with DALIRESP. During the Phase I studies of DALIRESP, the
252 following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg:
253 headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.
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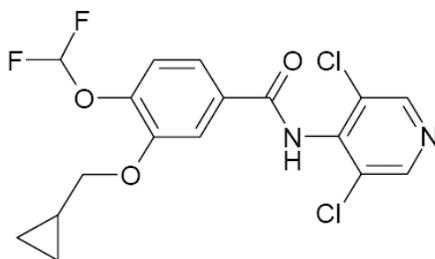
255 **10.2 Management of Overdose**

256 In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since
257 roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether
258 roflumilast is dialyzable by peritoneal dialysis.
259

260 **11 DESCRIPTION**

261 The active ingredient in DALIRESP tablets is roflumilast. Roflumilast and its active metabolite (roflumilast N-oxide) are selective
262 phosphodiesterase 4 (PDE4) inhibitors. The chemical name of roflumilast is N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-
263 difluoromethoxy-benzamide. Its empirical formula is C₁₇H₁₄Cl₂F₂N₂O₃ and the molecular weight is 403.22.
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265 The chemical structure is:
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The drug substance is a white to off-white non-hygroscopic powder with a melting point of 160°C. It is practically insoluble in water and hexane, sparingly soluble in ethanol and freely soluble in acetone.

DALIRESP is supplied as white to off-white, round tablets, embossed with "D" on one side and "500" on the other side. Each tablet contains 500 mcg of roflumilast.

Each tablet of DALIRESP for oral administration contains the following inactive ingredients: lactose monohydrate, corn starch, povidone and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 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 DALIRESP 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.

12.2 Pharmacodynamics

In COPD patients, 4 week treatment with DALIRESP 500 mcg oral once daily reduced sputum neutrophils and eosinophils by 31%, and 42%, respectively. In a pharmacodynamic study in healthy volunteers, DALIRESP 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.

12.3 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%

330 of the radioactivity was recovered in the urine.

331

332 *Special Populations*

333

334 *Hepatic Impairment*

335 Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh
336 A and B (8 subjects in each group). The AUC of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in
337 Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-
338 matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A
339 subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not
340 been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who
341 have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver
342 impairment (Child-Pugh B or C) [see *Contraindications (4) and Use in Specific Populations (8.6)*].

343

344 *Renal Impairment*

345 In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, roflumilast and roflumilast N-oxide
346 AUCs were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. No dosage adjustment is
347 necessary for patients with renal impairment [see *Use in Specific Populations (8.7)*].

348

349 *Age*

350 Roflumilast 500 mcg once daily for 15 days was studied in young, middle aged, and elderly healthy subjects. The exposure in elderly
351 (> 65 years of age) were 27% higher in AUC and 16% higher in C_{max} for roflumilast and 19% higher in AUC and 13% higher in C_{max} for
352 roflumilast-N-oxide than that in young volunteers (18-45 years old). No dosage adjustment is necessary for elderly patients [see *Use in*
353 *Specific Populations (8.5)*].

354

355 *Gender*

356 In a Phase I study evaluating the effect of age and gender on the pharmacokinetics of roflumilast and roflumilast N-oxide, a 39% and
357 33% increase in roflumilast and roflumilast N-oxide AUC were noted in healthy female subjects as compared to healthy male subjects.
358 No dosage adjustment is necessary based on gender.

359

360 *Smoking*

361 The pharmacokinetics of roflumilast and roflumilast N-oxide were comparable in smokers as compared to non-smokers. There was no
362 difference in C_{max} between smokers and non-smokers when roflumilast 500 mcg was administered as a single dose to 12 smokers and
363 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
364 smokers was 17% more than that in non-smokers.

365

366 *Race*

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

371

372 *Drug Interactions*

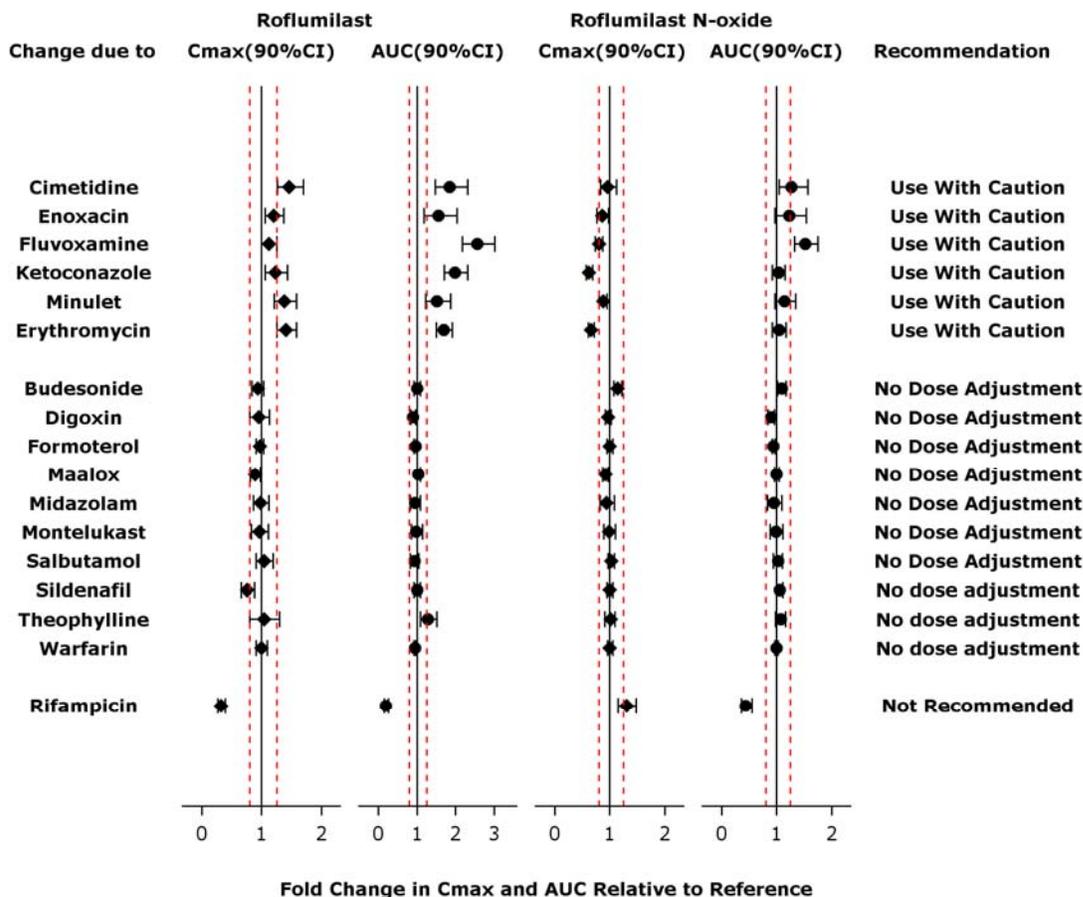
373 Drug interaction studies were performed with roflumilast and other drugs likely to be coadministered or drugs commonly used as
374 probes for pharmacokinetic interaction [see *Drug Interactions*]. No significant drug interactions were observed when 500 mcg oral
375 roflumilast was administered with inhaled salbutamol, formoterol, budesonide and oral montelukast, digoxin, theophylline, warfarin,
376 sildenafil, midazolam, or antacids.

377

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

379

380



381
 382 Figure 1. Effect of concomitant drugs on the exposure of roflumilast and roflumilast N-oxide. Note that the dashed lines indicate the
 383 lower and higher bounds (0.8-1.25) of the 90% confidence interval of the geometric mean ratio of C_{max} or AUC for roflumilast or
 384 roflumilast N-oxide for Treatment (DALIRESP+Coadministered Drug) vs. Reference (DALIRESP). The dosing regimens of
 385 coadministered drugs was: Midazolam:2mg po SD; Erythromycin:500mg po TID; Ketoconazole:200mg po BID; Rifampicin:600mg po
 386 QD; Fluvoxamine:50mg po QD; Digoxin:250ug po SD; Maalox:30mL po SD; Salbutamol:0.2mg pi TID; Cimetidine:400mg po BID;
 387 Formoterol:40ug po BID; Budesonide:400ug po BID; Theophylline:375mg po BID; Warfarin:250mg po SD; Enoxacin:400mg po BID;
 388 Sildenafil:100mg SD; Minulet (combination oral contraceptive):0.075mg gestodene/0.03mg ethinylestradiol po QD; Montelukast:10mg
 389 po QD

391 Drug interactions considered to be significant are described in more detail below [also see Drug Interactions (5.4) and Drug
 392 Interactions (7)].

393
 394 Inhibitors of CYP3A4 and CYP1A2:

395 Erythromycin: In an open-label crossover study in 16 healthy volunteers, the coadministration of CYP 3A4 inhibitor erythromycin (500
 396 mg three times daily for 13 days) with a single oral dose of 500 mcg DALIRESP resulted in 40% and 70% increase in C_{max} and AUC for
 397 roflumilast, respectively, and a 34% decrease and a 4% increase in C_{max} and AUC for roflumilast N-oxide, respectively.

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

402
 403 Fluvoxamine: In an open-label crossover study in 16 healthy volunteers, the coadministration of dual CYP 3A4/1A2 inhibitor
 404 fluvoxamine (50 mg daily for 14 days) with a single oral dose of 500 mcg DALIRESP showed a 12% and 156% increase in roflumilast
 405 C_{max} and AUC along with a 210% decrease and 52% increase in roflumilast N-oxide C_{max} and AUC, respectively.

406
 407 Enoxacin: In an open-label crossover study in 16 healthy volunteers, the coadministration of dual CYP 3A4/1A2 inhibitor enoxacin (400
 408 mg twice daily for 12 days) with a single oral dose of 500 mcg DALIRESP resulted in an increased C_{max} and AUC of roflumilast by 20%
 409 and 56%, respectively. Roflumilast N-oxide C_{max} was decreased by 14% while roflumilast N-oxide AUC was increased by 23%.

410
 411 Cimetidine: In an open-label crossover study in 16 healthy volunteers, the coadministration of a dual CYP 3A4/1A2 inhibitor cimetidine
 412 (400 mg twice daily for 7 days) with a single dose of 500 mcg oral DALIRESP resulted in a 46% and 85% increase in roflumilast C_{max}
 413 and AUC; and a 4% decrease in C_{max} and 27% increase in AUC for roflumilast N-oxide, respectively.

414 Oral Contraceptives containing Gestodene and Ethinyl Estradiol:
415 In an open-label crossover study in 20 healthy adult volunteers, coadministration of a single oral dose of 500 mcg DALIRESP with
416 repeated doses of a fixed combination oral contraceptive containing 0.075 mg gestodene and 0.03 mg ethinyl estradiol to steady state
417 caused a 38% increase and 12 % decrease in C_{max} of roflumilast and roflumilast N-oxide, respectively. Roflumilast and roflumilast N-
418 oxide AUCs were increased by 51% and 14%, respectively.
419

420 Inducers of CYP enzymes:

421 Rifampicin: In an open-label, three-period, fixed-sequence study in 15 healthy volunteers, coadministration of the strong CYP3A4
422 inducer rifampicin (600 mg once daily for 11 days) with a single oral dose of 500 mcg DALIRESP resulted in reduction of roflumilast
423 C_{max} and AUC by 68% and 79%, respectively; and an increase of roflumilast N-oxide C_{max} by 30% and reduced roflumilast N-oxide
424 AUC by 56%.
425

426 13 NONCLINICAL TOXICOLOGY

427 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

429 Long-term studies were conducted in hamsters and mice with roflumilast to evaluate its carcinogenic potential. In 2-year oral gavage
430 carcinogenicity studies, roflumilast treatment resulted in dose-related, statistically significant increases in the incidence of
431 undifferentiated carcinomas of nasal epithelium in hamsters at ≥ 8 mg/kg/day (approximately 11 times the MRHD based on summed
432 AUCs of roflumilast and its metabolites). The tumorigenicity of roflumilast appears to be attributed to a reactive metabolite of 4-amino-
433 3,5-dichloro-pyridine N-oxide (ADCP N-oxide). No evidence of tumorigenicity was observed in mice at roflumilast oral doses up to 12
434 and 18 mg/kg/day in females and males, respectively (approximately 10 and 15 times the MRHD, respectively, based on summed
435 AUCs of roflumilast and its metabolites).
436

437 Roflumilast tested positive in an *in vivo* mouse micronucleus test, but negative in the following assays: Ames test for bacterial gene
438 mutation, *in vitro* chromosome aberration assay in human lymphocytes, *in vitro* HPRT test with V79 cells, an *in vitro* micronucleus test
439 with V79 cells, DNA adduct formation assay in rat nasal mucosa, liver and testes, and *in vivo* mouse bone marrow chromosome
440 aberration assay. Roflumilast N-oxide was negative in the Ames test and *in vitro* micronucleus test with V79 cells.
441

442 In a human spermatogenesis study, roflumilast 500 mcg had no effects on semen parameters or reproductive hormones during the 3-
443 month treatment period and the following 3-month off-treatment period. In a fertility study, roflumilast decreased fertility rates in male
444 rats at 1.8-mg/kg/day (approximately 29 times the MRHD on a mg/m^2 basis). These rats also showed increases in the incidence of
445 tubular atrophy, degeneration in the testis and spermiogenic granuloma in the epididymides. No effect on male rat fertility rate or
446 reproductive organ morphology was observed at 0.8 mg/kg/day (approximately 13 times the MRHD on a mg/m^2 basis). No effect on
447 female fertility was observed up to the highest roflumilast dose of 1.5 mg/kg/day in rats (approximately 24 times the MRHD on a mg/m^2
448 basis).
449

450 14 CLINICAL STUDIES

451 14.1 Chronic Obstructive Pulmonary Disease (COPD)

453 The efficacy and safety of DALIRESP (roflumilast) in COPD was evaluated in 8 randomized double-blind, controlled, parallel group
454 clinical trials in 9394 adult patients (4425 receiving DALIRESP 500 mcg) 40 years of age and older with COPD. Of the 8 trials, two
455 were placebo-controlled dose selection trials (Trials 1 and 2) of 6 months duration that evaluated the efficacy of DALIRESP 250 mcg
456 and 500 mcg once daily, four were placebo-controlled 1-year trials (Trials 3, 4, 5, and 6) primarily designed to evaluate the efficacy of
457 DALIRESP on COPD exacerbations, and two were 6-month efficacy trials (Trials 7 and 8) which assessed the effect of DALIRESP as
458 add-on therapy to a long-acting beta agonist or long-acting anti-muscarinic. The 8 trials enrolled patients with nonreversible obstructive
459 lung disease ($FEV_1/FVC \leq 70\%$ and $\leq 12\%$ or 200 mL improvement in FEV_1 in response to 4 puffs of a buterol/sa butamol) but the
460 severity of airflow obstruction at baseline was different among the trials. Patients enrolled in the dose selection trials had the full range
461 of COPD severity (FEV_1 30-80% predicted); median age of 63 years, 73% male, and 99% Caucasian. Patients enrolled in the four
462 exacerbation trials had severe COPD ($FEV_1 \leq 50\%$ predicted); median age of 64 years, 74% male, and 90% Caucasian. Patients
463 enrolled in the two 6-month efficacy trials had moderate to severe COPD (FEV_1 40-70% predicted); median age of 65 years, 68%
464 male, and 97% Caucasian. COPD exacerbations and lung function (FEV_1) were co-primary efficacy outcome measures in the four 1-
465 year trials. In the two 6-month supportive efficacy trials, lung function (FEV_1) alone was the primary efficacy outcome measure.
466

467 The two 6-month dose-selection efficacy trials (Trials 1 and 2) explored doses of 250 mcg and 500 mcg once daily in a total of 1929
468 patients (751 and 724 on DALIRESP 250 and 500 mcg, respectively). The selection of the 500 mcg dose was primarily based on
469 nominal improvements in lung function (FEV_1) over the 250 mcg dose. The once daily dosing regimen was primarily based on the
470 determination of a plasma half-life of 17 hours for roflumilast and 30 hours for its active metabolite roflumilast N-oxide [see *Clinical*
471 *Pharmacology* (12.3)].
472

473 *Effect on Exacerbations*

474 The effect of DALIRESP 500 mcg once daily on COPD exacerbations was evaluated in four 1-year trials (Trials 3, 4, 5, and 6).
475

476 Two of the trials (Trials 3 and 4) conducted initially enrolled a population of patients with severe COPD ($FEV_1 \leq 50\%$ of predicted)
477 inclusive of those with chronic bronchitis and/or emphysema who had a history of smoking of at least 10 pack years. Inhaled
478 corticosteroids were allowed as concomitant medications and used in 61% of both DALIRESP and placebo-treated patients and short-
479 acting beta agonists were allowed as rescue therapy. The use of long-acting beta agonists, long-acting anti-muscarinics, and
480 theophylline were prohibited. The rate of moderate or severe COPD exacerbations was a co-primary endpoint in both trials. There was
481 not a symptomatic definition of exacerbation in these 2 trials. Exacerbations were defined in terms of severity requiring treatment with
482 a moderate exacerbation defined as treatment with systemic glucocorticosteroids in Trial 3 or systemic glucocorticosteroids and/or
483 antibiotics in Trial 4 and a severe exacerbation defined as requiring hospitalizations and/or leading to death in Trial 3 or requiring

484 hospitalization in Trial 4. The trials randomized 1176 patients (567 on DALIRESP) in Trial 3 and 1514 patients (760 on DALIRESP) in
 485 Trial 4. Both trials failed to demonstrate a significant reduction in the rate of COPD exacerbations.
 486

487 Exploratory analyses of the results of Trials 3 and 4 identified a subpopulation of patients with severe COPD associated with chronic
 488 bronchitis and COPD exacerbations within the previous year that appeared to demonstrate a better response in the reduction of the
 489 rate of COPD exacerbations compared to the overall population. As a result, two subsequent trials (Trial 5 and Trial 6) were conducted
 490 that enrolled patients with severe COPD but associated with chronic bronchitis, at least one COPD exacerbation in the previous year,
 491 and at least a 20 pack-year smoking history. In these trials, long-acting beta agonists and short-acting anti-muscarinics were allowed
 492 and were used by 44% and 35% of patients treated with DALIRESP and 45% and 37% of patients treated with placebo, respectively.
 493 The use of inhaled corticosteroids was prohibited. As in trials 3 and 4, the rate of moderate exacerbations (defined as requiring
 494 intervention with systemic glucocorticosteroids) or severe exacerbations (defined as leading to hospitalization and/or to death) was a
 495 co-primary endpoint.
 496

497 Trial 5 randomized a total of 1525 patients (765 on DALIRESP) and Trial 6 randomized a total of 1571 patients (772 on DALIRESP). In
 498 both trials, DALIRESP 500 mcg once daily demonstrated a significant reduction in the rate of moderate or severe exacerbations
 499 compared to placebo (Table 2). These two trials provide the evidence to support the use of DALIRESP for the reduction of COPD
 500 exacerbations.
 501

502 **Table 2. Effect of DALIRESP on Rate of Moderate or Severe Exacerbations**

Study	Exacerbations Per Patient-Year			RR ²	95% CI	Percent Reduction ³
	DALIRESP	Placebo	Absolute Reduction ¹			
Trial 5	1.1	1.3	0.2	0.85	0.74, 0.98	15
Trial 6	1.2	1.5	0.3	0.82	0.71, 0.94	18

- 505 1. Absolute reduction measured as difference between placebo and roflumilast treated patients.
 506 2. RR is Rate Ratio.
 507 3. Percent reduction is defined as 100 (1-RR).
 508

509 For patients in Trials 5 and 6 who received concomitant long-acting beta agonists or short-acting anti-muscarinics, reduction of
 510 moderate or severe exacerbations with DALIRESP was similar to that observed for the overall populations of the two trials.
 511

512 *Effect on Lung Function*

513 While DALIRESP is not a bronchodilator, all 1-year trials (Trials 3, 4, 5, and 6) evaluated the effect of DALIRESP on lung function as
 514 determined by the difference in FEV₁ between DALIRESP and placebo-treated patients (pre-bronchodilator FEV₁ measured prior to
 515 study drug administration in three of the trials and post-bronchodilator FEV₁ measured 30 minutes after administration of 4 puffs of
 516 albuterol/salbutamol in one trial) as a co-primary endpoint. In each of these trials DALIRESP 500 mcg once daily demonstrated a
 517 statistically significant improvement in FEV₁ which averaged approximately 50 mL across the four trials. Table 3 shows FEV₁ results
 518 from Trials 5 and 6 which had demonstrated a significant reduction in COPD exacerbations.
 519
 520
 521

522 **Table 3. Effect of DALIRESP on FEV₁**

Study	Change in FEV ₁ from Baseline, mL			
	DALIRESP	Placebo	Effect ¹	95% CI
Trial 5	46	8	39	18, 60
Trial 6	33	-25	58	41, 75

523 ¹ Effect measured as difference between DALIRESP and placebo treated patients.
 524

525 Lung function was also evaluated in two 6-month trials (Trials 7 and 8) to assess the effect of DALIRESP when administered as add-
 526 on therapy to treatment with a long-acting beta agonist or a long-acting anti-muscarinic. These trials were conducted in a different
 527 population of COPD patients [moderate to severe COPD (FEV₁ 40 to 70% of predicted) without a requirement for chronic bronchitis or
 528 frequent history of exacerbations] from that for which efficacy in reduction of exacerbations has been demonstrated and provide safety
 529 support to the DALIRESP COPD program.
 530

531 No trials have been conducted to assess the effects of DALIRESP on COPD exacerbations when added to a fixed-dose combination
 532 product containing a long-acting beta agonist and inhaled corticosteroid.
 533
 534
 535
 536

537 **16 HOW SUPPLIED/STORAGE AND HANDLING**

538
539 **16.1 How Supplied**

540 DALIRESP is supplied as white to off-white, round tablets, embossed with "D" on one side and "500" on the other side. Each tablet
541 contains 500 mcg of roflumilast.

542
543 DALIRESP tablets are available in bottles containing 30 tablets - NDC 0456-0095-30 or 90 tablets - NDC 0456-0095-90.

544
545 **16.2 Storage and Handling**

546 Store DALIRESP 500 mcg tablets at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled
547 Room Temperature].

548
549 **17 PATIENT COUNSELING INFORMATION**

550 See FDA-approved Medication Guide.

551
552
553 **17.1 Bronchospasm**

554 DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm. [see Warnings and Precautions (5.1)].

555
556 **17.2 Psychiatric Events including Suicidality**

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

564
565 Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully
566 weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of
567 the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if
568 such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing
569 treatment with DALIRESP if such events occur [see Warnings and Precautions (5.2)].

570
571 **17.3 Weight Decrease**

572 Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with
573 DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo. In two placebo-controlled clinical trials of one year
574 duration in which weight was prospectively assessed, 20% of patients receiving roflumilast experienced moderate weight loss (defined
575 as between 5-10% of body weight) compared to 7% of patients who received placebo and 7% of patients who received roflumilast
576 compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment
577 discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients
578 treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight
579 loss should be evaluated, and discontinuation of DALIRESP should be considered [see Warnings and Precautions (5.3)].

580
581 **17.4 Drug Interactions**

582 The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure which may result in a
583 decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g.
584 rifampicin, phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended [see Drugs That Induce Cytochrome P450
585 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3)].

586
587 Manufactured by:

588
589 Nycomed GmbH
590 Production Site Oranienburg
591 Lehnitzstrasse 70 – 98
592 16515 Oranienburg
593 Germany

594
595 Manufactured for:

596
597 Forest Pharmaceuticals, Inc.
598 Subsidiary of Forest Laboratories, Inc.
599 St. Louis, MO 63045, USA

600
601 Component Code Number:

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MEDICATION GUIDE
DALIRESP® (da'-li-resp)
(roflumilast)
Tablets

Read this Medication Guide before you start taking DALIRESP® and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about DALIRESP?

DALIRESP can cause serious side effects. Tell your healthcare provider right away if you have any of the symptoms listed below while taking DALIRESP.

- 1. DALIRESP may cause mental health problems including suicidal thoughts and behavior.** Some people taking DALIRESP may develop mood or behavior problems including:
 - thoughts of suicide or dying
 - attempt to commit suicide
 - trouble sleeping (insomnia)
 - new or worse anxiety
 - new or worse depression
 - acting on dangerous impulses
 - other unusual changes in your behavior or mood

- 2. Weight loss.** DALIRESP can cause weight loss. You should check your weight on a regular basis. You will also need to see your healthcare provider regularly to have your weight checked. If you notice that you are losing weight, call your healthcare provider. Your healthcare provider may ask you to stop taking DALIRESP if you lose too much weight.

DALIRESP may affect the way other medicines work, and other medicines may affect how DALIRESP works. Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

What is DALIRESP?

DALIRESP is a prescription medicine used in adults with severe Chronic Obstructive Pulmonary Disease (COPD) to decrease the number of flare-ups or the worsening of COPD symptoms (exacerbations).

DALIRESP is not a bronchodilator and should not be used for treating sudden breathing problems. Your healthcare provider may give you other medicine to use for sudden breathing problems.

It is not known if DALIRESP is safe and effective in children.

Who should not take DALIRESP?

Do not take DALIRESP if you:

- have certain liver problems. Talk with your healthcare provider before you take DALIRESP if you have liver problems.

What should I tell my healthcare provider before taking DALIRESP?

Before you take DALIRESP, tell your healthcare provider if you:

- have or have had a history of mental health problems including depression and suicidal behavior.
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if DALIRESP will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.

- 661 • are breastfeeding or plan to breastfeed. It is not known if DALIRESP passes into your breast milk. You and your
662 healthcare provider should decide if you will take DALIRESP or breastfeed. You should not do both.

663

664 **How should I take DALIRESP?**

665

- 666 • Take DALIRESP exactly as your healthcare provider tells you to take it.
667 • DALIRESP can be taken with or without food.
668 • If you take more than your prescribed dose of DALIRESP, call your healthcare provider or go to the nearest hospital
669 emergency room right away.

670

671 **What are the possible side effects of DALIRESP?**

672

673 **DALIRESP can cause serious side effects, including:**

674

675 See **“What is the most important information I should know about DALIRESP?”**

676 **The most common side effects of DALIRESP include:**

677

- 678 • diarrhea
679 • weight loss
680 • nausea
681 • headache
682 • back pain
683 • flu like symptoms
684 • problems sleeping (insomnia)
685 • dizziness
686 • decreased appetite

687

688 Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

689 These are not all the possible side effects of DALIRESP.

690 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

691

692 **How do I store DALIRESP Tablets?**

- 693 • **Store DALIRESP at 68°F to 77°F (20°C to 25°C)** ; excursions permitted to 15° - 30°C (59° - 86°F). [See USP
694 Controlled Room Temperature].

695

696 **Keep DALIRESP Tablets and all medicines out of the reach of children.**

697

698 **General information about DALIRESP**

699

700 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DALIRESP for a
701 condition for which it was not prescribed. Do not give DALIRESP to other people, even if they have the same symptoms that
702 you have. It may harm them.

703 This Medication Guide summarizes the most important information about DALIRESP. For more information about
704 DALIRESP, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about
705 DALIRESP that is written for health professionals.

706 For more information about DALIRESP call 1-800-678-1605.

707

708 **What are the ingredients in DALIRESP?**

709

710 **Active ingredient:** roflumilast

711 **Inactive ingredients:** lactose monohydrate, corn starch, povidone and magnesium stearate.

712

713 Rx only

714 Manufactured by:

715 Nycomed GmbH

716 Production Site Oranienburg
717 Lehnitzstrasse 70 – 98
718 16515 Oranienburg
719 Germany

720
721 Manufactured for:
722 Forest Pharmaceuticals, Inc.
723 Subsidiary of Forest Laboratories, Inc.
724 St. Louis, MO 63045, USA
725

726 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

727

728 Rev. XX/2011

DOSAGE: The recommended dose for adults is one tablet (500 mcg) by mouth once a day. See package insert for full Prescribing Information. Keep this and all drugs out of the reach of children.

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Daliresp® is a registered trademark of Nycomed GmbH.
Licensed from Nycomed GmbH.

Manufactured by:
Nycomed GmbH
Production site Oranienburg
Lehn tzstrasse 70-98
16515 Oranienburg, Germany

Manufactured for:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045, USA

Rx Only

NDC 0456-0095-30

Daliresp 
(roflumilast) tablets

500 mcg per tablet

Dispense the accompanying
Medication Guide to each patient

30 Tablets



FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045



N 3

Rev 02/2011



Reference ID: 2911527

DOSAGE: The recommended dose for adults is one tablet (500 mcg) by mouth once a day. See package insert for full Prescribing Information. Keep this and all drugs out of the reach of children.

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

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Lehn tzstrasse 70-98
16515 Oranienburg, Germany

Manufactured for:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045, USA

Rx Only

NDC 0456-0095-90

Daliresp 
(roflumilast) tablets

500 mcg per tablet

Dispense the accompanying
Medication Guide to each patient

90 Tablets

 **FOREST PHARMACEUTICALS, INC.**
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045



Rev 02/2011

Reference ID: 2911527

DOSAGE: The recommended dose for adults is one tablet (500 mcg) by mouth once a day. See package insert for full Prescribing Information. Keep this and all drugs out of the reach of children.

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

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Lehn tzstrasse 70-98
16515 Oranienburg, Germany

Manufactured for:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045, USA

Rx Only

Professional Sample
Not for Sale

Daliresp 
(roflumilast) tablets

500 mcg per tablet

Dispense the accompanying
Medication Guide to each patient

30 Tablets



FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045



Rev 02/2011

Reference ID: 2911527

PRINT SIDE

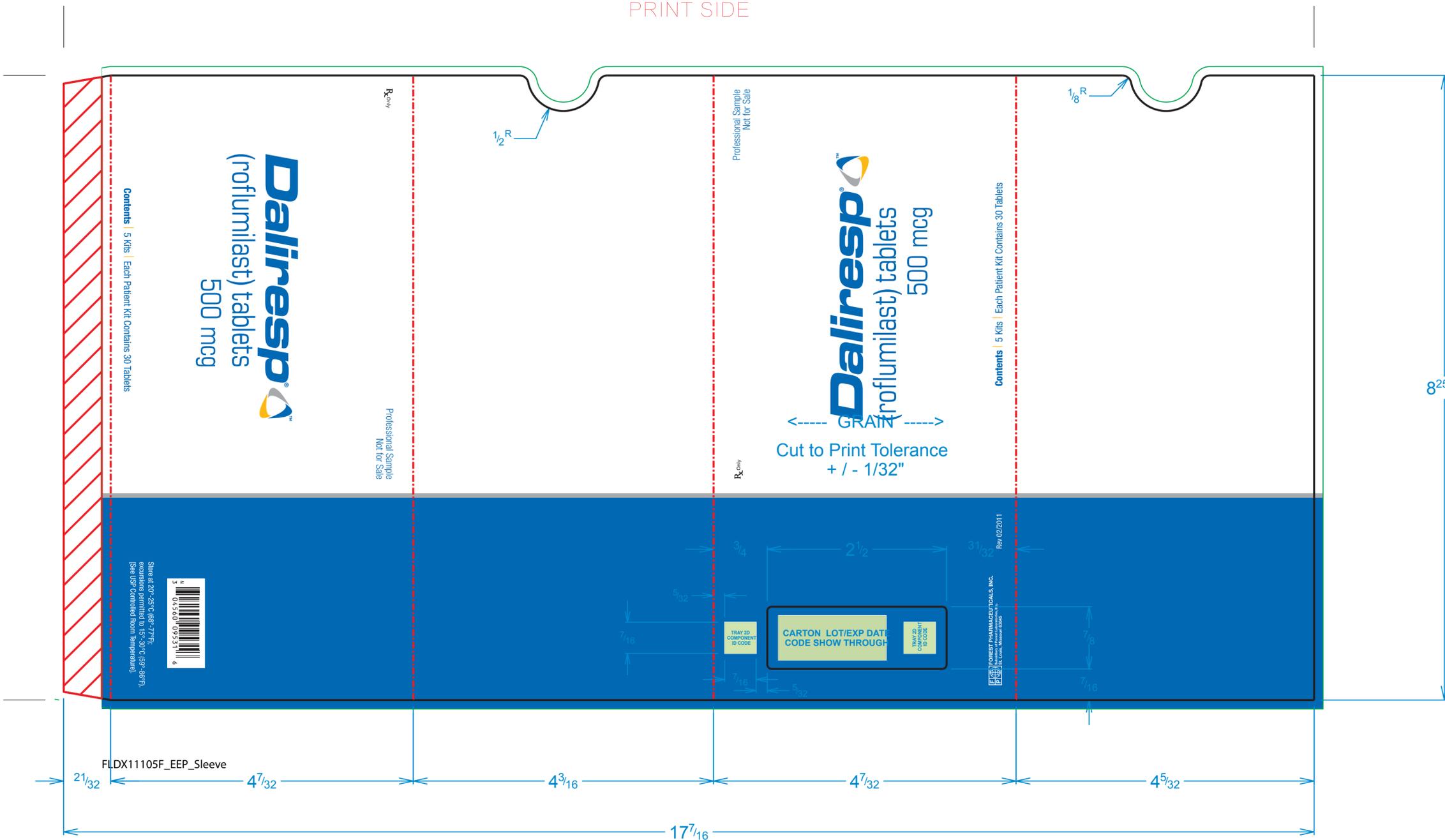
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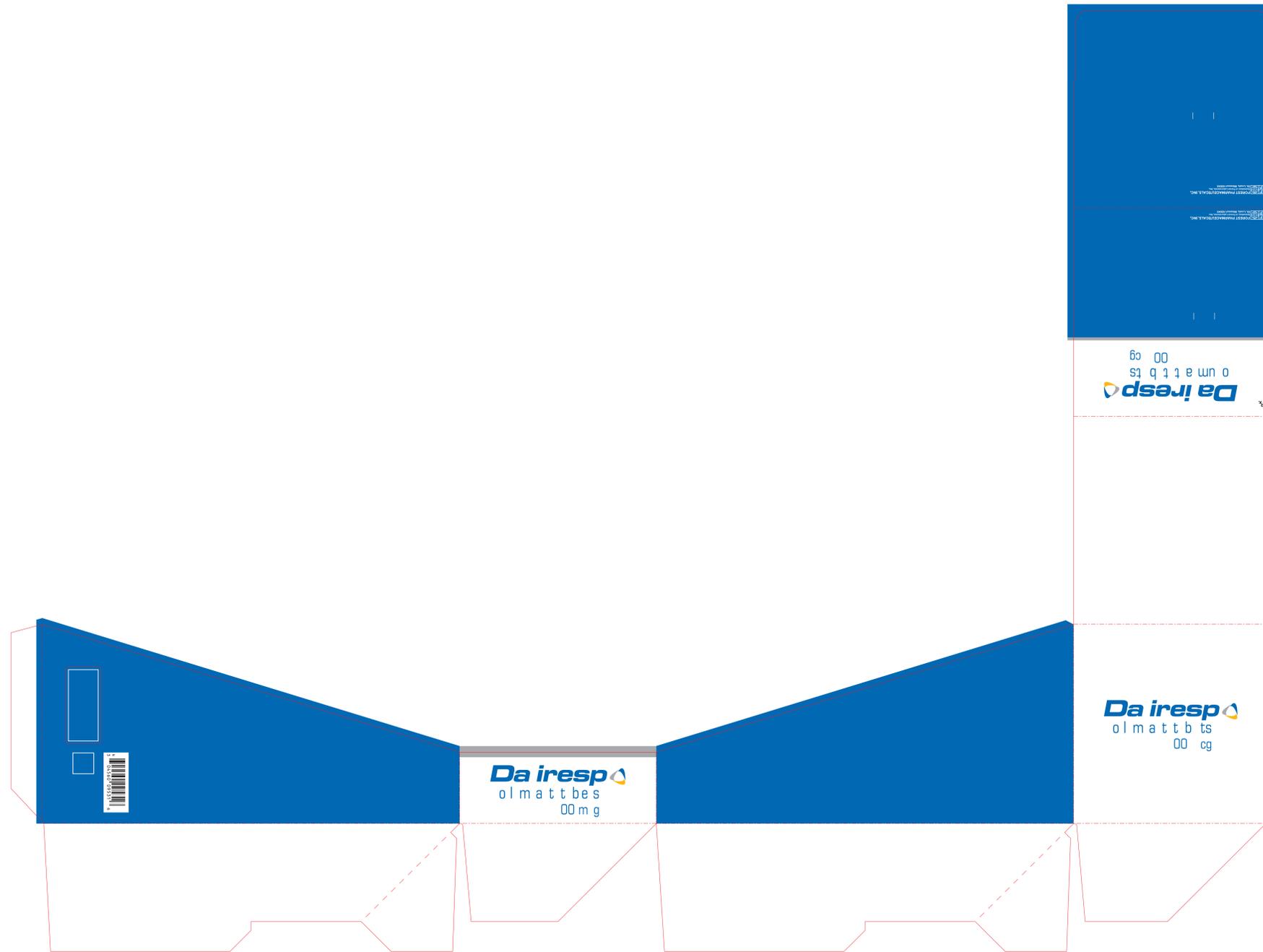
OUTSIDE BLEED: 

DIMENSIONS: 

NON VARNISH: 









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Manufactured by:
Nycomed GmbH
Production site: Osnabrück
Lindemannstrasse 10-18
16815 Osnabrück, Germany

Manufactured for:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045, USA

Rev 02/2011 RMC 17136

- **DOSAGE:** The recommended dose for adults is one tablet (500 mcg) by mouth once a day.
- Keep this and all drugs out of the reach of children.
- Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].
- See package insert for full Prescribing Information.

Daliresp
(roflumilast) tablets
500 mcg

Daliresp
(roflumilast) tablets
500 mcg

 FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

Rx Only

Professional Sample
Not for Sale

Daliresp
(roflumilast) tablets

500 mcg per tablet

Provide the accompanying
Medication Guide to each patient

 FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

7 Tablets

Daliresp
(roflumilast) tablets
500 mcg

 FOREST PHARMACEUTICALS, INC.
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Reference ID: 2911527