Dacomitinib Tablets
DACOPLICE ®

1. GENERIC NAME

Dacomitinib Tablets 15 mg, 30 mg and 45 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Dacomitinib monohydrate equivalent to 15 mg or 30 mg or 45 mg of Dacomitinib.

List of Excipients

Microcrystalline Cellulose
Lactose Monohydrate
Sodium Starch Glycolate
Magnesium Stearate
Opadry® II Blue 85F30716 film coating contains;
Polyvinyl Alcohol, Talc, Titanium Dioxide, Macrogol/PEG 3350, FD&C Blue # 2/Indigo Carmine Aluminium
Lake.

All strengths/presentations mentioned in this document might not be available in the market

3 DOSAGE FORM AND STRENGTH

Tablets:

- 45 mg: blue film-coated, immediate release, round biconvex tablet, debossed with “Pfizer” on one side and “DCB45” on the other side.
- 30 mg: blue film-coated, immediate release, round biconvex tablet, debossed with “Pfizer” on one side and “DCB30” on the other side.
- 15 mg: blue film-coated, immediate release, round biconvex tablet, debossed with “Pfizer” on one side and “DCB15” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dacomitinib is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations.

4.2 Posology and Method of Administration

Patient Selection

Select patients for the first-line treatment of metastatic NSCLC with DACOMITINIB based on the presence of an EGFR exon 19 deletion or exon 21 L858R substitution mutation in tumor specimens.

Recommended Dosage

The recommended dosage of DACOMITINIB is 45 mg taken orally once daily, until disease progression or unacceptable toxicity occurs. DACOMITINIB can be taken with or without food *[see sections 4.2. **Dosage Modifications for Acid-Reducing Agents** and section 6.1**. Animal toxicology or pharmacology**]*.

Take DACOMITINIB the same time each day. If the patient vomits or misses a dose, do not take an additional dose or make up a missed dose but continue with the next scheduled dose

.**Dosage Modifications for Adverse Reactions**

Reduce the dose of DACOMITINIB for adverse reactions as described in Table 1. Dosage modifications for specific adverse reactions are provided in Table 2.

Table 1. DACOMITINIB Recommended Dose Reductions for Adverse Reactions

Dose Level	**Dose (Once Daily)**
First dose reduction	30 mg
Second dose reduction	15 mg

Table 2. DACOMITINIB Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity[a]**	**Dosage Modification**
Interstitial lung disease (ILD) *[see section 4.4]*	Any Grade	• Permanently discontinue DACOMITINIB.

Diarrhea *[see section 4.4]*	Grade 2	• Withhold DACOMITINIB until recovery to less than or equal to Grade 1; then resume DACOMITINIB at the same dose level. • For recurrent Grade 2 diarrhea, withhold until recovery to less than or equal to Grade 1; then resume DACOMITINIB at a reduced dose.
	Grade 3 or 4	• Withhold DACOMITINIB until recovery to less than or equal to Grade 1; then resume DACOMITINIB at a reduced dose.
Dermatologic Adverse Reactions *[see Warnings and Precautions (5.3)]*	Grade 2	• Withhold DACOMITINIB for persistent dermatologic adverse reactions; upon recovery to less than or equal to Grade 1, resume DACOMITINIB at the same dose level. • For recurrent persistent Grade 2 dermatologic adverse reactions, withhold until recovery to less than or equal to Grade 1; then resume DACOMITINIB at a reduced dose.
	Grade 3 or 4	• Withhold DACOMITINIB until recovery to less than or equal to Grade 1; then resume DACOMITINIB at a reduced dose.
Other	Grade 3 or 4	• Withhold DACOMITINIB until recovery to less than or equal to Grade 2; then resume DACOMITINIB at a reduced dose.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

Dosage Modifications for Acid-Reducing Agents

Avoid the concomitant use of proton pump inhibitors (PPIs) while taking DACOMITINIB. As an alternative to PPIs, use locally-acting antacids or if using an histamine 2 (H2)-receptor antagonist, administer DACOMITINIB at least 6 hours before or 10 hours after taking an H2-receptor antagonist *[see sections 4.5 and section 5.2]*.

4.3 Contraindications

None

4.4 Special Warnings and Precautions for Use

Interstitial Lung Disease (ILD)

Severe and fatal ILD/pneumonitis occurred in patients treated with DACOMITINIB and occurred in 0.5% of the 394 DACOMITINIB-treated patients; 0.3% of cases were fatal.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Withhold DACOMITINIB and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Permanently discontinue DACOMITINIB if ILD is confirmed *[see section 4.8- Clinical Trials Experience section]*.

Diarrhea

Severe and fatal diarrhea occurred in patients treated with DACOMITINIB. Diarrhea occurred in 86% of the 394 DACOMITINIB-treated patients; Grade 3 or 4 diarrhea was reported in 11% of patients and 0.3% of cases were fatal.

Withhold DACOMITINIB for Grade 2 or greater diarrhea until recovery to less than or equal to Grade 1 severity, then resume DACOMITINIB at the same or a reduced dose depending on the severity of diarrhea *[see sections 4.2. Posology and method of administration and 4.8. Clinical trial experience]*. Promptly initiate anti-diarrheal treatment (loperamide or diphenoxylate hydrochloride with atropine sulfate) for diarrhea.

Dermatologic Adverse Reactions

Rash and exfoliative skin reactions occurred in patients treated with DACOMITINIB. Rash occurred in 78% of the 394 DACOMITINIB-treated patients; Grade 3 or 4 rash was reported in 21% of patients. Exfoliative skin reactions of any severity were reported in 7% of patients. Grade 3 or 4 exfoliative skin reactions were reported in 1.8% of patients.

Withhold DACOMITINIB for persistent Grade 2 or any Grade 3 or 4 dermatologic adverse reaction until recovery to less than or equal to Grade 1 severity, then resume DACOMITINIB at the same or a reduced dose depending on the severity of the dermatologic adverse reaction *[see sections 4.2 Posology and method of administration and 4.8. Clinical trial experience]*. The incidence and severity of rash and exfoliative skin reactions may increase with sun exposure. At the time of initiation of DACOMITINIB, initiate use of moisturizers and appropriate measures to limit sun exposure. Upon development of Grade 1 rash, initiate treatment with topical antibiotics and topical steroids. Initiate oral antibiotics for Grade 2 or more severe dermatologic adverse reactions.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, DACOMITINIB can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of dacomitinib to pregnant rats during the period of organogenesis resulted in an increased incidence of post-implantation loss and reduced fetal body weight at doses resulting in exposures near the exposure at the 45 mg human dose. The absence of EGFR signaling has been shown to result in embryolethality as well as post-natal death in animals.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with DACOMITINIB and for at least 17 days after the final dose *[see section 4.6]*.

4.5 Drug Interactions

Effect of Other Drugs on DACOMITINIB

Concomitant use with a PPI decreases dacomitinib concentrations, which may reduce DACOMITINIB efficacy. Avoid the concomitant use of PPIs with DACOMITINIB. As an alternative to PPIs, use locally-acting antacids or an H2-receptor antagonist. Administer

DACOMITINIB at least 6 hours before or 10 hours after taking an H2-receptor antagonist *[see section 4.2 and section 5.3]*.

Effect of DACOMITINIB on CYP2D6 Substrates
Concomitant use of DACOMITINIB increases the concentration of drugs that are CYP2D6 substrates *[see section 5.2]* which may increase the risk of toxicities of these drugs. Avoid concomitant use of DACOMITINIB with CYP2D6 substrates where minimal increases in concentration of the CYP2D6 substrate may lead to serious or life-threatening toxicities.

4.6 Use in special population

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, DACOMITINIB can cause fetal harm when administered to a pregnant woman *[see section 5.1]*. There are no available data on DACOMITINIB use in pregnant women. In animal reproduction studies, oral administration of dacomitinib to pregnant rats during the period of organogenesis resulted in an increased incidence of post-implantation loss and reduced fetal body weight at doses resulting in exposures near the exposure at the 45 mg human dose *(see Data)*. The absence of EGFR signaling has been shown to result in embryolethality as well as post-natal death in animals *(see Data)*. Advise pregnant women of the potential risk to a fetus *[see section 4.6. Use in Special population]*.

Data

Animal Data

Daily oral administration of dacomitinib to pregnant rats during the period of organogenesis resulted in an increased incidence of post-implantation loss, maternal toxicity, and reduced fetal body weight at 5 mg/kg/day (approximately 1.2 times the exposure based on area under the curve [AUC] at the 45 mg human dose).

Disruption or depletion of EGFR in mouse models has shown EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/post-natal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling in mice can prevent implantation, and can cause embryo-fetal loss during various stages of gestation (through effects on placental development), developmental anomalies, early death in surviving fetuses, and adverse developmental outcomes in multiple organs in embryos/neonates.

Lactation

Risk Summary

There is no information regarding the presence of dacomitinib or its metabolites in human milk or their effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants from DACOMITINIB, advise women not to breastfeed during treatment with DACOMITINIB and for at least 17 days after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating DACOMITINIB *[see section 4.6. Use in special population]*

Contraception

DACOMITINIB can cause fetal harm when administered to a pregnant woman *[see section 4.6. Use in special population]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with DACOMITINIB and for at least 17 days after the final dose.

Pediatric Use

The safety and effectiveness of DACOMITINIB in pediatrics have not been established.

Geriatric Use

Of the total number of patients (N=394) in five clinical studies with EGFR mutation-positive NSCLC who received DACOMITINIB at a dose of 45 mg orally once daily [ARCHER 1050 (N=227), Study A7471009 (N=38), Study A7471011 (N=83), Study A7471028 (N=16), and Study A7471017 (N=30)] 40% were 65 years of age and older.

Exploratory analyses across this population suggest a higher incidence of Grade 3 and 4 adverse reactions (67% versus 56%, respectively), more frequent dose interruptions (53% versus 45%, respectively), and more frequent discontinuations (24% versus 10%, respectively) for adverse reactions in patients 65 years or older as compared to those younger than 65 years.

Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min estimated by Cockcroft-Gault). The recommended dose of DACOMITINIB has not been established for patients with severe renal impairment (CLcr <30 mL/min) *[see section 5.2]*.

Hepatic Impairment

No dose adjustment is recommended in patients with mild (total bilirubin ≤upper limit of normal [ULN] with AST >ULN or total bilirubin >1 to 1.5 × ULN with any AST) or moderate (total bilirubin >1.5 to 3 × ULN and any AST) hepatic impairment. The recommended dose of DACOMITINIB has not been established for patients with severe hepatic impairment (total bilirubin >3 to 10 × ULN and any AST) *[see section 5.2]*.

4.7 Effects on Ability to Drive and Use Machines

No data

4.8 Undesirable Effects

The following adverse drug reactions are described elsewhere in the labeling:
- Interstitial Lung Disease *[see section 4.4]*
- Diarrhea *[see section 4.4]*
- Dermatologic Adverse Reactions *[see section 4.4]*

Clinical Trials Experience

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 data in the Special Warnings and Precautions for use section reflect exposure to DACOMITINIB in 394 patients with first-line or previously treated NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations who received DACOMITINIB at the recommended dose of 45 mg once daily in 4 randomized, active-controlled trials [ARCHER 1050 (N=227), Study A7471009 (N=38), Study A7471011 (N=83), and Study A7471028 (N=16)] and one single-arm trial [Study A7471017 (N=30)]. The median duration of exposure to DACOMITINIB was 10.8 months (range 0.07-68) *[see section 4.4]*.

The data described below reflect exposure to DACOMITINIB in 227 patients with EGFR mutation-positive, metastatic NSCLC enrolled in a randomized, active-controlled trial (ARCHER 1050*)*; 224 patients received gefitinib 250 mg orally once daily in the active control arm *[see Clinical Studies]*. Patients were excluded if they had a history of ILD, interstitial pneumonitis, or brain metastases. The median duration of exposure to DACOMITINIB was 15 months (range 0.07-37).

The most common (>20%) adverse reactions in patients treated with DACOMITINIB were diarrhea (87%), rash (69%), paronychia (64%), stomatitis (45%), decreased appetite (31%), dry skin (30%), decreased weight (26%), alopecia (23%), cough (21%), and pruritus (21%).

Serious adverse reactions occurred in 27% of patients treated with DACOMITINIB. The most common (≥1%) serious adverse reactions were diarrhea (2.2%) and interstitial lung disease (1.3%). Dose interruptions occurred in 57% of patients treated with DACOMITINIB. The most frequent (>5%) adverse reactions leading to dose interruptions were rash (23%), paronychia (13%), and diarrhea (10%). Dose reductions occurred in 66% of patients treated with DACOMITINIB. The most frequent (>5%) adverse reactions leading to dose reductions were rash (29%), paronychia (17%), and diarrhea (8%).

Adverse reactions leading to permanent discontinuation of DACOMITINIB occurred in 18% of patients. The most common (>0.5%) adverse reactions leading to permanent discontinuation of DACOMITINIB were: rash (2.6%), interstitial lung disease (1.8%), stomatitis (0.9%), and diarrhea (0.9%).

Tables 3 and 4 summarize the most common adverse reactions and laboratory abnormalities, respectively, in ARCHER 1050. ARCHER 1050 was not designed to demonstrate a statistically significant difference in adverse reaction rates for DACOMITINIB or for gefitinib for any adverse reaction or laboratory value listed in Table 3 or 4.

Table 3. Adverse Reactions Occurring in ≥10% of Patients Receiving DACOMITINIB in ARCHER 1050*

Adverse Reaction	DACOMITINIB (N=227)		Gefitinib (N=224)	
	All Grades[a] %	Grades 3 and 4 %	All Grades %	Grades 3 and 4 %
Gastrointestinal				
Diarrhea[b]	87	8	56	0.9
Stomatitis[c]	45	4.4	19	0.4
Nausea	19	1.3	22	0.4
Constipation	13	0	14	0
Mouth ulceration	12	0	6	0
Skin and Subcutaneous Tissue				
Rash[d]	69	23	47	0.4
Paronychia[e]	64	8	21	1.3
Dry skin[f]	30	1.8	19	0.4
Alopecia	23	0.4	13	0
Pruritus[g]	21	0.9	15	1.3
Palmar-plantar erythrodysesthesiasyndrome	15	0.9	3.1	0
Dermatitis	11	1.8	4	0.4
Metabolism and Nutrition				
Decreased appetite	31	3.1	25	0.4
Decreased weight	26	2.2	17	0.4
Respiratory				
Cough	21	0	19	0.4
Nasal mucosal disorder[h]	19	0	4.9	0
Dyspnea	13	2.2	13	1.8
Upper respiratory tract infection	12	1.3	13	0
Chest pain	10	0	14	0
Eye				
Conjunctivitis	19	0	4	0
Musculoskeletal				
Pain in extremity	14	0	12	0
Musculoskeletal pain	12	0.9	13	0
General				
Asthenia	13	2.2	13	1.3
Psychiatric				
Insomnia	11	0.4	15	0

* National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

[a] Grades 1 through 5 are included in All Grades.

[b] One Grade 5 (fatal) event in the DACOMITINIB arm.

[c] Stomatitis includes mucosal inflammation and stomatitis.

[d] Rash includes dermatitis acneiform, rash, and rash maculo-papular.

[e] Paronychia includes nail infection, nail toxicity, onychoclasis, onycholysis, onychomadesis, paronychia.

[f] Dry skin includes dry skin, xerosis.

[g] Pruritus includes pruritus, pruritus generalized, rash pruritic.

[h] Nasal mucosal disorder includes epistaxis, nasal inflammation, nasal mucosal disorder, nasal mucosal ulcer, rhinitis.

Additional adverse reactions (All Grades) that were reported in <10% of patients who received DACOMITINIB in ARCHER 1050 include:

General: fatigue 9%
Skin and subcutaneous tissue: skin fissures 9%,
hypertrichosis 1.3%,
skin exfoliation/exfoliative skin reactions 3.5%
Gastrointestinal: vomiting 9%
Nervous system: dysgeusia 7%
Respiratory: interstitial lung disease 2.6%
Ocular: keratitis 1.8%
Metabolism and nutrition: dehydration 1.3%

Table 4. Laboratory Abnormalities Worsening from Baseline in >20% of Patients in ARCHER 1050*

Laboratory Test Abnormality[a]	DACOMITINIB		Gefitinib	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)
Hematology				
Anemia	44	0.9	26	2.7
Lymphopenia	42	6	35	2.7
Chemistry				
Hypoalbuminemia	44	0	34	0
Increased ALT	40	1.4	63	13
Hyperglycemia	36	1.0	38	2.5
Increased AST	35	0.5	57	8
Hypocalcemia	33	1.4	28	2.0
Hypokalemia	29	7	18	2.0
Hyponatremia	26	2.9	20	1.5
Increased creatinine	24	0	16	0.5
Increased alkaline phosphatase	22	0.5	21	2.0
Hypomagnesemia	22	0.5	9	0
Hyperbilirubinemia	16	0.5	22	0.5

ALT=alanine aminotransferase; AST=aspartate aminotransferase.
*NCI CTCAE v4.03, except for increased creatinine which only includes patients with creatinine increase based on upper limit of normal definition.

[a] Based on the number of patients with available baseline and at least one on-treatment laboratory test.

4.9 Overdose

No data

5. PHARMACOLOGICAL PROPERTIES

5.1. Mechanism of Action

Dacomitinib is an irreversible inhibitor of the kinase activity of the human EGFR family (EGFR/HER1, HER2, and HER4) and certain EGFR activating mutations (exon 19 deletion or the exon 21 L858R substitution mutation). *In vitro* dacomitinib also inhibited the activity of DDR1, EPHA6, LCK, DDR2, and MNK1 at clinically relevant concentrations.

Dacomitinib demonstrated dose-dependent inhibition of EGFR and HER2 autophosphorylation and tumor growth in mice bearing subcutaneously implanted human tumor xenografts driven by HER family targets including mutated EGFR. Dacomitinib also exhibited antitumor activity in orally-dosed mice bearing intracranial human tumor xenografts driven by EGFR amplifications.

5.2 Pharmacodynamic Properties

Cardiac Electrophysiology

The effect of dacomitinib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 32 patients with advanced NSCLC. Dacomitinib had no large effect on QTc (i.e., >20 ms) at maximum dacomitinib concentrations achieved with DACOMITINIB 45 mg orally once daily.

Exposure-Response Relationships

Higher exposures, across the range of exposures with the recommended dose of 45 mg daily, correlated with an increased probability of Grade ≥3 adverse events, specifically dermatologic toxicities and diarrhea

5.3 Pharmacokinetic Properties

The maximum dacomitinib plasma concentration (C_{max}) and AUC at steady state increased proportionally over the dose range of DACOMITINIB 2 mg to 60 mg orally once daily (0.04 to 1.3 times the recommended dose) across dacomitinib studies in patients with cancer. At a dose of 45 mg orally once daily, the geometric mean [coefficient of variation (CV%)] C_{max} was 108 ng/mL (35%) and the $AUC_{0\text{-}24h}$ was 2213 ng•h/mL (35%) at steady state in a dose-finding clinical study conducted in patients with solid tumors. Steady state was achieved within 14 days following repeated dosing and the estimated geometric mean (CV%) accumulation ratio was 5.7 (28%) based on AUC.

Absorption

The mean absolute bioavailability of dacomitinib is 80% after oral administration. The median dacomitinib time to reach maximum concentration (T_{max}) occurred at approximately 6.0 hours

(range 2.0 to 24 hours) after a single oral dose of DACOMITINIB 45 mg in patients with cancer.

Effect of Food

Administration of DACOMITINIB with a high-fat, high-calorie meal (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate and fat, respectively) had no clinically meaningful effect on dacomitinib pharmacokinetics.

Distribution

The geometric mean (CV%) volume of distribution of dacomitinib (Vss) was 1889 L (18%). In vitro binding of dacomitinib to human plasma proteins is approximately 98% and is independent of drug concentrations from 250 ng/mL to 1000 ng/mL.

Elimination

Following a single 45 mg oral dose of DACOMITINIB in patients with cancer, the mean (CV%) plasma half-life of dacomitinib was 70 hours (21%), and the geometric mean (CV%) apparent plasma clearance of dacomitinib was 24.9 L/h (36%).

Metabolism

Hepatic metabolism is the main route of clearance of dacomitinib, with oxidation and glutathione conjugation as the major pathways. Following oral administration of a single 45 mg dose of [^{14}C] dacomitinib, the most abundant circulating metabolite was O-desmethyl dacomitinib, which had similar in vitro pharmacologic activity as dacomitinib. The steady-state plasma trough concentration of O-desmethyl dacomitinib ranges from 7.4% to 19% of the parent. *In vitro* studies indicated that cytochrome P450 (CYP) 2D6 was the major isozyme involved in the formation of O-desmethyl dacomitinib, while CYP3A4 contributed to the formation of other minor oxidative metabolites.

Excretion

Following a single oral 45 mg dose of [^{14}C] radiolabeled dacomitinib, 79% of the radioactivity was recovered in feces (20% as dacomitinib) and 3% in urine (<1% as dacomitinib).

Specific Populations

Patients with Renal Impairment

Based on population pharmacokinetic analyses, mild (60 mL/min ≤CLcr <90 mL/min; N=590) and moderate (30 mL/min ≤CLcr <60 mL/min; N=218) renal impairment did not alter dacomitinib pharmacokinetics, relative to the pharmacokinetics in patients with normal renal function (CLcr ≥90 mL/min; N=567). The pharmacokinetics of dacomitinib has not been adequately characterized in patients with severe renal impairment (CLcr <30 mL/min) (N=4) or studied in patients requiring hemodialysis.

Patients with Hepatic Impairment

In a dedicated hepatic impairment trial, following a single oral dose of 30 mg DACOMITINIB, dacomitinib exposure (AUC_{inf} and C_{max}) was unchanged in subjects with mild hepatic impairment (Child-Pugh A; N=8) and decreased by 15% and 20%, respectively in subjects with moderate hepatic impairment (Child-Pugh B; N=9) when compared to subjects with normal hepatic function (N=8). Based on this trial, mild and moderate hepatic impairment had no clinically important effects on pharmacokinetics of dacomitinib. In addition, based on a population pharmacokinetic analysis of 1381 patients, in which 158 patients had mild hepatic impairment (total bilirubin ≤ULN and AST >ULN, or total bilirubin >1 to 1.5 × ULN with any AST) and 5 patients had moderate hepatic impairment (total bilirubin >1.5 to 3 × ULN and any AST), no effects on pharmacokinetics of dacomitinib were observed. The effect of severe hepatic impairment (total bilirubin >3 to 10 × ULN and any AST) on dacomitinib pharmacokinetics is unknown *[see Section 4.2]*

Drug Interaction Studies

Clinical Studies

Effect of Acid-Reducing Agents on Dacomitinib
Coadministration of a single 45 mg dose of DACOMITINIB with multiple doses of rabeprazole (a proton pump inhibitor) decreased dacomitinib C_{max} by 51% and AUC0-96h by 39% *[see sections 4.2 and 4.8]*.

Coadministration of DACOMITINIB with a local antacid (Maalox® Maximum Strength, 400 mg/5 mL) did not cause clinically relevant changes dacomitinib concentrations *[see sections 4.2 and 4.8]*.

The effect of H2 receptor antagonists on dacomitinib pharmacokinetics has not been studied *[see sections 4.2 and 4.8]*.

Effect of Strong CYP2D6 Inhibitors on Dacomitinib
Coadministration of a single 45 mg dose of DACOMITINIB with multiple doses of paroxetine (a strong CYP2D6 inhibitor) in healthy subjects increased the total AUC_{last} of dacomitinib plus its active metabolite (O-desmethyl dacomitinib) in plasma by approximately 6%, which is not considered clinically relevant.

Effect of Dacomitinib on CYP2D6 Substrates
Coadministration of a single 45 mg oral dose of DACOMITINIB increased dextromethorphan (a CYP2D6 substrate) C_{max} by 9.7-fold and AUC_{last} by 9.6-fold *[see Drug Interactions (7.2)]*.

In Vitro Studies

Effect of Dacomitinib and O-desmethyl Dacomitinib on CYP Enzymes: Dacomitinib and its metabolite O-desmethyl dacomitinib do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5. Dacomitinib does not induce CYP1A2, CYP2B6, or CYP3A4.

Effect of Dacomitinib on Uridine 5' diphospho-glucuronosyltransferase (UGT) Enzymes: Dacomitinib inhibits UGT1A1. Dacomitinib does not inhibit UGT1A4, UGT1A6, UGT1A9, UGT2B7, or UGT2B15.

Effect of Dacomitinib on Transporter Systems: Dacomitinib is a substrate for the membrane transport protein P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Dacomitinib inhibits P-gp, BCRP, and organic cation transporter (OCT)1. Dacomitinib does not inhibit organic anion transporters (OAT)1 and OAT3, OCT2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3.

CLINICAL STUDIES

The efficacy of DACOMITINIB was demonstrated in a randomized, multicenter, multinational, open-label study (ARCHER 1050; [NCT01774721]). Patients were required to have unresectable, metastatic NSCLC with no prior therapy for metastatic disease or recurrent disease with a minimum of 12 months disease-free after completion of systemic therapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; EGFR exon 19 deletion or exon 21 L858R substitution mutations. EGFR mutation status was prospectively determined by local laboratory or commercially available tests (e.g., therascreen® EGFR RGQ PCR and cobas® EGFR Mutation Test).

Patients were randomized (1:1) to receive DACOMITINIB 45 mg orally once daily or gefitinib 250 mg orally once daily until disease progression or unacceptable toxicity. Randomization was stratified by region (Japanese versus mainland Chinese versus other East Asian versus non-East Asian), and EGFR mutation status (exon 19 deletions versus exon 21 L858R substitution mutation). The major efficacy outcome measure was progression-free survival (PFS) as determined by blinded Independent Radiologic Central (IRC) review per RECIST v1.1. Additional efficacy outcome measures were overall response rate (ORR), duration of response (DoR), and overall survival (OS).

A total of 452 patients were randomized to receive DACOMITINIB (N=227) or gefitinib (N=225). The demographic characteristics were 60% female; median age 62 years (range: 28 to 87), with 40% aged 65 years and older; and 23% White, 77% Asian, and less than 1% Black. Prognostic and tumor characteristics were ECOG performance status 0 (30%) or 1 (70%); 59% with exon 19 deletion and 41% with exon 21 L858R substitution; Stage IIIB (8%) and Stage IV (92%); 64% were never smokers; and 1% received prior adjuvant or neoadjuvant therapy.

ARCHER 1050 demonstrated a statistically significant improvement in PFS as determined by the IRC. Results are summarized in Table 5 and Figures 1 and 2.

The hierarchical statistical testing order was PFS followed by ORR and then OS. No formal testing of OS was conducted since the formal comparison of ORR was not statistically significant.

Table 5. Efficacy Results in ARCHER 1050

DACOMITINIB N=227	Gefitinib N=225	
Progression-Free Survival (per IRC)		
Number of patients with event, n (%)	136 (59.9%)	179 (79.6%)
Median PFS in months (95% CI)	14.7 (11.1, 16.6)	9.2 (9.1, 11.0)
HR (95% CI)[a]	0.59 (0.47, 0.74)	
p-value[b]	<0.0001	
Overall Response Rate (per IRC)		
Overall Response Rate % (95% CI)	75% (69, 80)	72% (65, 77)
p-value[c]	0.39	
Duration of Response in Responders (per IRC)		
Median DoR in months (95% CI)	14.8 (12.0, 17.4)	8.3 (7.4, 9.2)

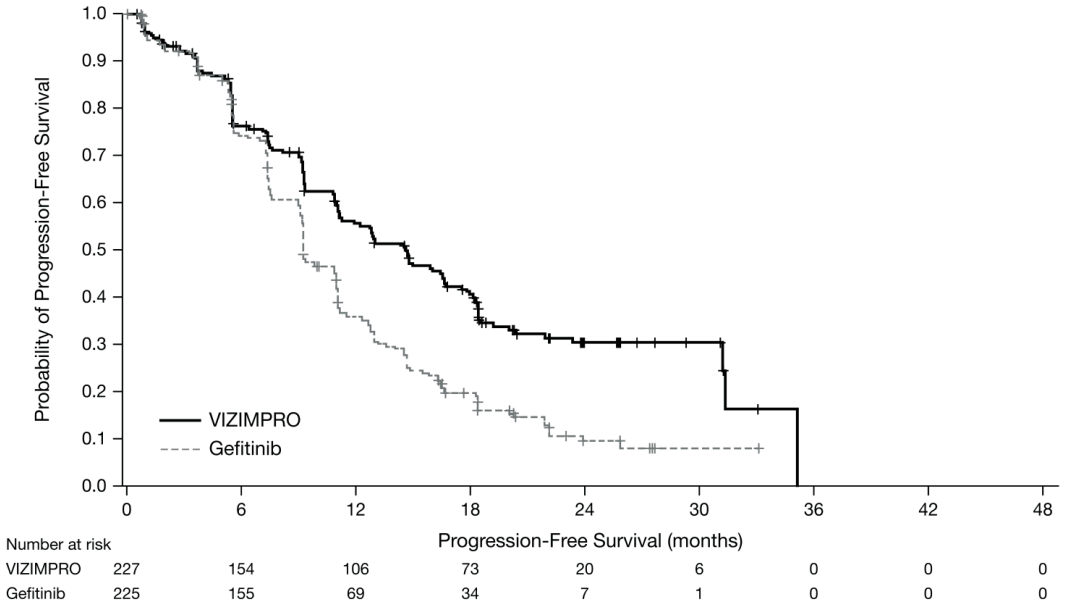
CI=confidence interval; DoR=duration of response; HR=hazard ratio; IRC=Independent Radiologic Central; N/n=total number; PFS=progression-free survival.

a. From stratified Cox Regression.

b. Based on the stratified log-rank test.

c. Based on the stratified Cochran-Mantel-Haenszel test.

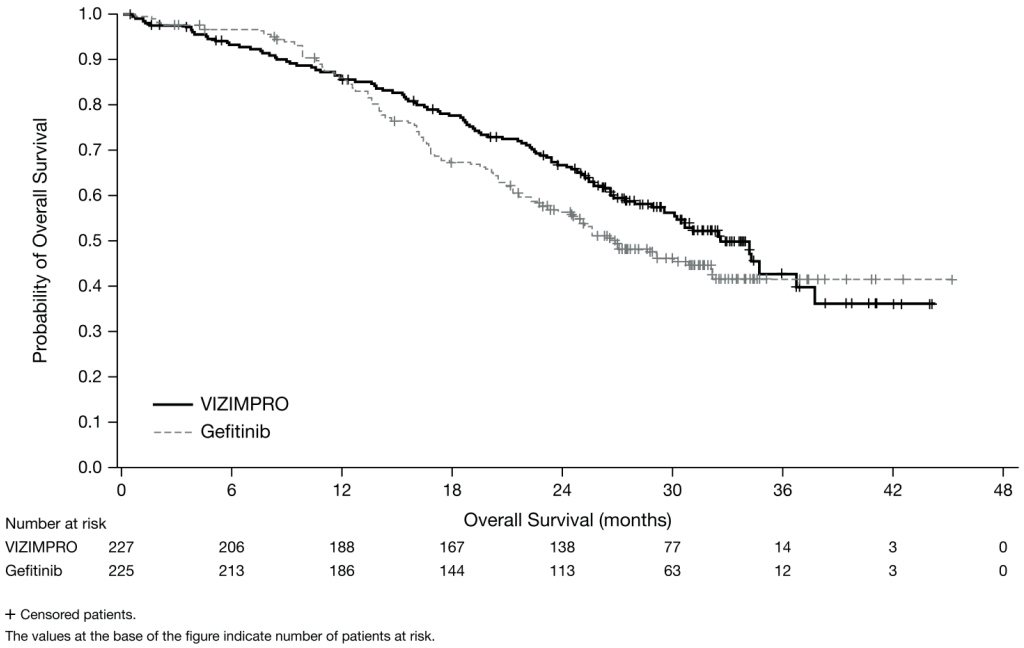
Figure 1. Kaplan-Meier Curve for PFS per IRC Review in ARCHER 1050



+ Censored patients.

The values at the base of the figure indicate number of patients at risk.

Figure 2. Kaplan-Meier Curve for OS in ARCHER 1050



Number at risk									
VIZIMPRO	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

+ Censored patients.
The values at the base of the figure indicate number of patients at risk.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

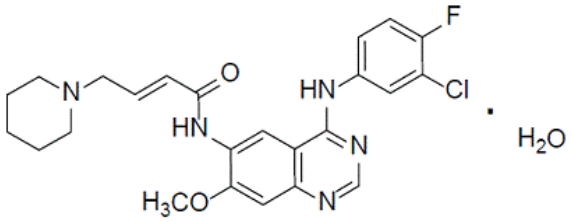
Carcinogenicity studies have not been performed with DACOMITINIB.

Dacomitinib was not mutagenic in a bacterial reverse mutation (Ames) assay or clastogenic in an in vitro human lymphocyte chromosome aberration assay or clastogenic or aneugenic in an in vivo rat bone marrow micronucleus assay.

Daily oral administration of dacomitinib at doses ≥0.5 mg/kg/day to female rats (approximately 0.14 times the exposure based on AUC at the 45 mg human dose) resulted in reversible epithelial atrophy in the cervix and vagina. Oral administration of dacomitinib at 2 mg/kg/day to male rats (approximately 0.6 times the human exposure based on AUC at the 45 mg clinical dose) resulted in reversible decreased secretion in the prostate gland.

7. DESCRIPTION

Dacomitinib is an oral kinase inhibitor with a molecular formula of C24H25ClFN5O2 · H2O and a molecular weight of 487.95 Daltons. The chemical name is: (2E)-N-{4-[(3-Chloro-4-fluorophenyl)amino]-7methoxyquinazolin-6-yl}-4-(piperidin-1-yl)but-2-enamide monohydrate and its structural formula is:



Dacomitinib is a white to pale yellow powder.

Dacomitinib tablets contain 45, 30, or 15 mg of dacomitinib with the following inactive ingredients in the tablet core; lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating consists of Opadry II® Blue 85F30716 containing: Polyvinyl alcohol – partially hydrolyzed, Talc, Titanium dioxide, Macrogol/PEG 3350, and FD&C Blue #2/Indigo Carmine Aluminum Lake.

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

Not applicable

8.2. Shelf Life

60 months

8.3. Packaging information

30 tablets in high-density polyethylene (HDPE) bottles containing 1g desiccant with polypropylene (PP) closure with heat induction seal liner .

10 tablets per blister pack of aluminium foil with aluminium foil liding; 3 blisters strips per carton.

8.4. Special and Handling instruction

Store below 30°C. Keep out of reach of children

9. Patient Counselling Information

Interstitial Lung Disease (ILD)

- Advise patients of the risks of severe or fatal ILD, including pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see special 4.4. Warnings and Precautions for use]*.

Diarrhea

- Advise patients to contact their healthcare provider at the first signs of diarrhea. Advise patients that intravenous hydration and/or anti-diarrheal medication (e.g., loperamide) may be required to manage diarrhea *[see special 4.4. Warnings and Precautions for use)]*.

Dermatologic Adverse Reactions

- Advise patients to initiate use of moisturizers and to minimize sun exposure with protective clothing and use of sunscreen at the time of initiation of Dacomitinib. Advise patients to contact their healthcare provider immediately to report new or worsening rash, erythematous and exfoliative reactions *[see 4.4. special Warning and Precautions for use]*.

Drug Interactions

- Advise patients to avoid use of PPIs while taking Dacomitinib. Short-acting antacids or H2 receptor antagonists may be used if needed. Advise patients to take Dacomitinib at least 6 hours before or 10 hours after taking an H2-receptor antagonist *[see Drug Interactions (4.5)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential that Dacomitinib can result in fetal harm and to use effective contraception during treatment with Dacomitinib and for 17 days after the last dose of Dacomitinib. Advise females of reproductive potential to contact their healthcare provider with a known or suspected pregnancy *[see Use in SpecialPopulations (4.6)]*.

Lactation

- Advise women not to breastfeed during treatment with Dacomitinib and for 17 days after the last dose of Dacomitinib *[see Use in SpecialPopulations (4.6)]*.

10. Details of manufacturer

M/s. Pfizer Manufacturing Deutschland GmbH Betriebsstatte Freiburg Mooswaldallee 1, Freiburg - 79090 (Germany)

Imported and marketed in India by
Pfizer Products India Private Limited,
The Capital- B Wing, 1802, 18th Floor, Plot No. C-70, G Block,
Bandra Kurla Complex, Bandra (East), Mumbai 400 051,
India

11. Details of permission or licence number with date
IMP-ND-168-2019 dated 03-Jan- 2020

12. Date of revision
Jan 2020