PT. PFIZER INDONESIA
Local Product Document

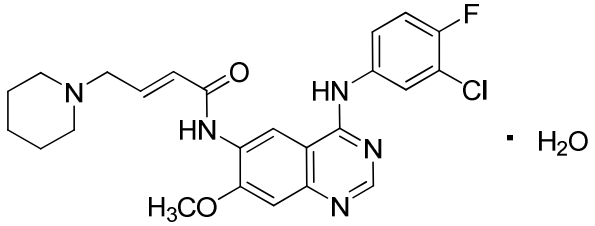
Generic Name: Dacomitinib
Trade Name: DAVIZIM®
CDS Effective Date: July 20, 2020
Supersedes: February 26, 2018

1. NAME OF THE MEDICINAL PRODUCT

DAVIZIM® 15 mg film-coated tablets
DAVIZIM® 30 mg film-coated tablets
DAVIZIM® 45 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dacomitinib monohydrate is a kinase inhibitor with a molecular formula of $C_{24}H_{25}ClFN_5O_2 \cdot H_2O$ and a molecular weight of 487.95 Daltons (or 469.94 Daltons as dacomitinib anhydrate). The chemical structure of dacomitinib monohydrate is:



Dacomitinib is a white to pale yellow powder with pKa values of 5.0 and 8.5.

Each film-coated tablet contains dacomitinib monohydrate equivalent to 15 mg or 30 mg or 45 mg of dacomitinib. For the full list of excipients, see Section 6.1 (List of excipients).

3. PHARMACEUTICAL FORM

Film-coated tablets 15 mg, 30 mg, 45 mg

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DAVIZIM® as monotherapy, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth

factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an approved validated test.

4.2. Posology and method of administration

EGFR mutation status should be established prior to initiation of DAVIZIM® therapy.

Posology

The recommended dose of DAVIZIM® is 45 mg taken orally once daily, until disease progression or unacceptable toxicity occurs. DAVIZIM® can be taken with or without food.

Patients should be encouraged to take their dose at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken and the next prescribed dose should be taken at the usual time the next day.

Dose modifications

Dose modifications may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of DAVIZIM® should be reduced as described in Table 1. Dose modification and management guidelines for specific Adverse Drug Reactions (ADRs) are provided in Table 2.

No starting dose adjustments are required on the basis of patient age, race, gender, or body weight (see Section 5.2 Pharmacokinetic properties).

Table 1. Recommended Dose Modifications for DAVIZIM® Adverse Drug Reactions

Dose Level	**Dose (Once Daily)**
Recommended starting dose	45 mg
First dose reduction	30 mg
Second dose reduction	15 mg

Table 2. Dose Modification and Management for DAVIZIM® Adverse Drug Reactions

Adverse Drug Reactions	**Dose Modification**
Interstitial lung disease (ILD/Pneumonitis)	• Withhold DAVIZIM® during ILD/Pneumonitis diagnostic evaluation. • Permanently discontinue DAVIZIM® if ILD/Pneumonitis is confirmed.

Diarrhea	• For Grade 1 diarrhea, no dose modification is required. Initiate treatment with anti-diarrheal medications (e.g., loperamide) at first onset of diarrhea. Encourage adequate oral fluid intake during diarrhea. • For Grade 2 diarrhea, if not improved to Grade ≤1 within 24 hours while using anti-diarrheal medications (e.g., loperamide) and adequate oral fluid intake, withhold DAVIZIM®. Upon recovery to Grade ≤1, resume DAVIZIM® at the same dose level or consider a reduction of one dose level. • For Grade ≥3 diarrhea, withhold DAVIZIM®. Treat with anti-diarrheal medications (e.g., loperamide), and adequate oral fluid intake or intravenous fluids or electrolytes as appropriate. Upon recovery to Grade ≤1, resume DAVIZIM® with a reduction of 1 dose level.
Rash, erythematous and exfoliative skin conditions	• For Grade 1 rash or erythematous skin conditions, no dose modification is required. Initiate treatment (e.g., antibiotics, topical steroids, and emollients). • For Grade 1 exfoliative skin conditions, no dose modification is required. Initiate treatment (e.g., oral antibiotics and topical steroids). • For Grade 2 rash, erythematous or exfoliative skin conditions, no dose modification is required. Initiate treatment and provide additional treatment (e.g., oral antibiotics and topical steroids). • If Grade 2 rash, erythematous or exfoliative skin conditions persist for 72 hours despite treatment, withhold DAVIZIM®. Upon recovery to Grade ≤1, resume DAVIZIM® at the same dose level or consider a reduction of 1 dose level. • For Grade ≥3 rash, erythematous or exfoliative skin conditions, withhold DAVIZIM®. Initiate or continue treatment and/or provide additional treatment (e.g., broad spectrum oral or intravenous antibiotics and topical steroids). Upon recovery to Grade ≤1, resume DAVIZIM® with a reduction of 1 dose level.
Other	• For Grade 1 or 2 toxicity, no dose modification is required. • For Grade ≥3 toxicity, withhold DAVIZIM® until symptoms resolve to Grade ≤2. Upon recovery, resume DAVIZIM® with a reduction of 1 dose level.

Special populations

Hepatic impairment: No starting dose adjustments are required when administering DAVIZIM® to patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. DAVIZIM® has not been studied in patients with severe (Child-Pugh class C) hepatic impairment (see Section 5.2 Pharmacokinetic properties).

Renal impairment: No starting dose adjustments are required when administering DAVIZIM® to patients with mild or moderate renal impairment (CrCl ≥30 mL/min). Insufficient data are available in patients with severe renal impairment (CrCl <30 mL/min) or requiring hemodialysis to provide dosing recommendations in this patient population. (see Section 5.2 Pharmacokinetic properties)

Elderly population: No starting dose adjustment of DAVIZIM® in elderly (≥65 years of age) patients is required (see Section 5.2 Pharmacokinetic properties).

Pediatric population: The safety and efficacy of DAVIZIM® in children (<18 years of age) have not been established.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Assessment of EGFR mutation status

When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust.

The warnings and precautions listed below are based on pooled data from 255 patients who received DAVIZIM® 45 mg once daily for first-line treatment of NSCLC with EGFR-activating mutations across clinical studies.

Interstitial lung disease (ILD)/Pneumonitis

ILD/pneumonitis, including a fatal event, has been reported in patients receiving DAVIZIM® (see Section 4.8 Undesirable effects – ILD).

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (e.g., dyspnea, cough, fever) should be performed to exclude ILD/pneumonitis. Treatment with DAVIZIM® should be withheld pending investigation of these symptoms. If ILD/pneumonitis is confirmed, DAVIZIM® should be permanently discontinued and appropriate treatment instituted as necessary (see Section 4.2 Posology and method of administration – Table 2).

Diarrhoea

Diarrhoea, including severe diarrhoea, has been very commonly reported during treatment with DAVIZIM®. Diarrhoea may result in dehydration with or without renal impairment,

which could be fatal if not adequately treated. Across the clinical experience of 255 patients, there was one case (0.4%) of diarrhea which was not adequately treated and was fatal.

Proactive management of diarrhea should start at the first sign of diarrhea especially within the first 2 weeks of starting DAVIZIM®, including adequate hydration combined with anti-diarrheal medications and continued until loose bowel movements cease for 12 hours.

Anti-diarrheal medications (e.g., loperamide) should be used and, if necessary, escalated to the highest recommended approved dose. Patients may require dosing interruption and/or dose reduction of therapy with DAVIZIM®. Patients should maintain adequate oral hydration and patients who become dehydrated may require administration of intravenous fluids and electrolytes (see Section 4.2 Posology and method of administration- Table 2).

Rash, erythematous and exfoliative skin conditions

Rash, erythematous and exfoliative skin conditions have been reported in patients treated with DAVIZIM® (see Section 4.8 Undesirable effects- Rash, erythematous and exfoliative skin conditions).

For prevention of dry skin, initiate treatment with moisturizers, and upon development of rash, initiate treatment with topical antibiotics, emollients, and topical steroids. Start oral antibiotics and topical steroids in patients who develop exfoliative skin conditions. Consider adding broad spectrum oral or intravenous antibiotics if any of these conditions worsen to greater than or equal to Grade 2 severity. Rash, erythematous and exfoliative skin conditions may occur or worsen in areas exposed to the sun. Advise patients to use protective clothing and sunscreen before exposure to the sun. Patients may require dosing interruption and/or dose reduction of therapy with dacomitinib.

Hepatotoxicity and transaminases increased

Transaminases increased (alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased) have been reported during treatment with DAVIZIM® (see Section 4.8 Undesirable effects). Among NSCLC patients treated with dacomitinib 45 mg daily, there have been isolated reports of hepatotoxicity in 4 (1.6%) patients. Across the dacomitinib program, hepatic failure led to a fatal outcome in 1 patient. Therefore, periodic liver function testing is recommended. In patients who develop severe elevations in transaminases while taking dacomitinib, treatment should be interrupted.

Medicinal products metabolised by cytochrome P450 (CYP)2D6

DAVIZIM® may increase exposure (or decrease exposure of active metabolites) of other medicinal products metabolised by CYP2D6. Concomitant use of medicinal products

predominantly metabolised by CYP2D6 should be avoided unless such products are considered necessary.

Other forms of interactions

Concomitant use of proton pump inhibitors (PPIs) with dacomitinib should be avoided.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains (symbol) less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

4.5. Interaction with other medicinal products and other forms of interaction

Co-administration of dacomitinib and CYP2D6 substrates

Co-administration of single 45 mg oral dose of dacomitinib increased the mean exposure (AUC and C_{max}) of dextromethorphan, a probe CYP2D6 substrate, 855% and 874%, respectively, compared with administration of dextromethorphan alone. These results suggest that dacomitinib may increase exposure of other medicinal products (or decrease exposure to active metabolites) primarily metabolised by CYP2D6. Concomitant use of medicinal products predominantly metabolised by CYP2D6 should be avoided (see Section 4.4 Special warnings and precautions for use). If concomitant use of such medicinal products is considered necessary, they should follow their respective labels for dose recommendation regarding co-administration with strong CYP2D6 inhibitors.

Effect of cytochrome P450 (CYP)2D6 inhibitors on dacomitinib

Coadministration of dacomitinib with strong inhibitors of CYP2D6 did not result in clinically relevant changes in exposure of dacomitinib. Dose adjustment of DAVIZIM® is not required in patients taking a strong CYP2D6 inhibitor.

Effect of DAVIZIM® on drugs metabolized by CYP2D6

Dacomitinib is a strong inhibitor of CYP2D6 (see Section 5.2 Pharmacokinetic properties). Dose reduction may be needed for coadministered drugs that are predominantly metabolized by CYP2D6, including but not limited to amitriptyline, atomoxetine, desipramine, dextromethorphan, doxepin, fluvoxamine, methoxyphenamine, metoprolol, or

nebivolol. Coadministration of DAVIZIM® with CYP2D6 substrates with a narrow therapeutic index, including to but not limited to procainamide, pimozide, and thioridazine, should be avoided. Drugs with active metabolites formed via CYP2D6, such as codeine and tramadol, should be replaced by an alternative within the therapeutic class as their exposure with the coadministration of dacomitinib may be subtherapeutic.

Coadministration with medicinal products that increase gastric pH

The aqueous solubility of dacomitinib is pH dependent, with low (acidic) pH resulting in higher solubility. Proton pump inhibitors (PPIs) should be avoided while receiving treatment with DAVIZIM®.

Based on data from observations in 8 cancer patients in Study A7471001, there was no apparent effect of local antacid administration on C_{max} and AUC_{inf} of dacomitinib. Local antacids may be used if needed.

If the use of a histamine-2 (H2) receptor antagonist is needed, DAVIZIM® should be administered 2 hours before or at least 10 hours after taking a H2 receptor antagonist. Based on pooled data in patients, there was no apparent effect of histamine-2 (H2) receptor antagonists on steady-state trough concentration of dacomitinib (geometric mean ratio of 86% (90% CI: 73; 101) (see Section 5.2 Pharmacokinetic properties).

Effect of dacomitinib on drug transporters

Based on *in vitro* data, dacomitinib may have the potential to inhibit the activity of P-glycoprotein (P-gp) (in the gastrointestinal [GI] tract), Breast Cancer Resistance Protein (BCRP) (systemically and GI tract), and organic cation transporter (OCT)1 at clinically relevant concentrations (see Section 5.2 Pharmacokinetic properties).

4.6. Fertility, pregnancy and lactation

Fertility

Fertility studies have not been performed with DAVIZIM®. Nonclinical safety studies showed reversible epithelial atrophy in the cervix and vagina of rats (see Section 5.3 Preclinical safety data).

Woman of childbearing potential/Contraception

Women of childbearing potential should be advised to avoid becoming pregnant while receiving DAVIZIM®. Women of childbearing potential who are receiving this medicinal product should use adequate contraceptive methods during therapy and for at least 17 days (5 half-lives) after completing therapy.

Pregnancy

DAVIZIM® may cause fetal harm when administered to a pregnant woman based on its mechanism of action. In pregnant rats or rabbits, effects were limited to lower maternal body weight gain and food consumption in rats and rabbits, and lower fetal body weights in rats only (see Section 5.3 Preclinical safety data).

There are no data on the use of dacomitinib in pregnant women. Studies in animals have shown limited effects on reproductive toxicity (lower maternal body weight gain and food consumption in rats and rabbits, and lower foetal body weight and higher incidence of unossified metatarsals in rats only) (see Section 5.3 Preclinical safety data). Based on its mechanism of action, dacomitinib may cause foetal harm when administered to a pregnant woman. Dacomitinib should not be used during pregnancy.

Female patients taking DAVIZIM® during pregnancy or who become pregnant while taking DAVIZIM® should be apprised of the potential hazard to the fetus.

Lactation

It is not known whether dacomitinib and its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious ADRs in breastfed infants from exposure to dacomitinib, mothers should be advised against breastfeeding while receiving DAVIZIM®.

4.7. Effects on ability to drive and use machines

No studies on the effects of DAVIZIM® on the ability to drive or operate machinery have been conducted. However, patients experiencing fatigue while taking DAVIZIM® should exercise caution when driving or operating machinery.

4.8. Undesirable effects

The ADRs described in this section are based on pooled data from 255 patients who received DAVIZIM® 45 mg once daily as starting dose for first-line treatment of NSCLC with EGFR-activating mutations across clinical studies as defined in Table 3 footnotes [a] through [j]. The median duration of treatment with DAVIZIM® across the pooled data set was 66.7 weeks.

The most common (>20%) ADRs in patients receiving DAVIZIM® were diarrhea (88.6%), rash (82.4%), stomatitis (71.8%), nail disorder (65.5%), dry skin (33.3%), decreased appetite (31.8%), conjunctivitis (25.5%), weight decreased (24.3%), alopecia (23.1%), and nausea (20.4%). Serious ADRs were reported in 6.7% of patients treated with DAVIZIM®. The most frequently (≥1%) reported serious ADRs in patients receiving DAVIZIM® were

diarrhea (2.0%), interstitial lung disease (1.2%), rash (1.2%), and decreased appetite (1.2%).

ADRs leading to dose reduction were reported in 52.2% of patients treated with DAVIZIM®. The most frequently reported (>5%) reasons for dose reductions due to any ADRs in patients receiving DAVIZIM® were rash (32.9%), nail disorder (16.5%), and diarrhea (7.5%).

ADRs leading to permanent discontinuation were reported in 6.7% of patients treated with DAVIZIM®. The most common (>0.5%) reasons for permanent discontinuations associated with ADRs in patients receiving DAVIZIM® were rash (2.4%), interstitial lung disease (2.0%), and diarrhea (0.8%).

Tabulated list of adverse drug reactions

Table 3 presents adverse reactions for DAVIZIM®. Adverse reactions are listed according to system organ class (SOC). Within each SOC, the adverse reactions are ranked by frequency, with the most frequent reactions first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions reported in dacomitinib clinical studies (N=255)

System organ class	**Very common**	**Common**
Metabolism and nutrition disorders	Decreased appetite Hypokalaemia[a]	Dehydration
Nervous system disorders		Dysgeusia
Eye disorders	Conjunctivitis[b]	Keratitis
Respiratory, thoracic and mediastinal disorders		Interstitial lung disease*[c]
Gastrointestinal disorders	Diarrhoea* Stomatitis[d] Vomiting Nausea	
Skin and subcutaneous tissue disorders	Rash[e] Palmar-plantar erythrodysaesthesia syndrome Skin fissures Dry skin[f] Pruritus[g] Nail disorder[h]	Skin exfoliation[i] Hypertrichosis

Table 3. Adverse reactions reported in dacomitinib clinical studies (N=255)

System organ class	Very common	Common
	Alopecia	
General disorders and administration site conditions	Fatigue Asthenia	
Investigations	Transaminases increased[j] Weight decreased	

Data based on pool of 255 patients who received DAVIZIM® 45 mg once daily as starting dose for first-line treatment of NSCLC with EGFR-activating mutations across clinical studies.

* Fatal events were reported.
[a] Hypokalaemia includes the following preferred terms (PTs): Blood potassium decreased, Hypokalaemia.
[b] Conjunctivitis includes the following PTs: Blepharitis, Conjunctivitis, Dry eye, Noninfective conjunctivitis.
[c] Interstitial lung disease includes the following PTs: Interstitial lung disease, Pneumonitis.
[d] Stomatitis includes the following PTs: Aphthous ulcer, Cheilitis, Dry mouth, Mucosal inflammation, Mouth ulceration, Oral pain, Oropharyngeal pain, Stomatitis.
[e] Rash (also referred to as Rash and erythematous skin conditions) includes the following PTs: Acne, Dermatitis acneiform, Erythema, Erythema multiforme, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular.
[f] Dry skin includes the following PTs: Dry skin, Xerosis.
[g] Pruritus includes the following PTs: Pruritus, Rash pruritic.
[h] Nail disorder includes the following PTs: Ingrowing nail, Nail bed bleeding, Nail bed inflammation, Nail discolouration, Nail disorder, Nail infection, Nail toxicity, Onychoclasis, Onycholysis, Onychomadesis, Paronychia.
[i] Skin exfoliation (also referred to as Exfoliative skin conditions) includes the following PTs: Exfoliative rash, Skin exfoliation.
[j] Transaminases increased includes the following PTs: Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminases increased.

Description of selected adverse drug reactions

Very common adverse reactions in patients occurring in at least 10% of patients in Study ARCHER 1050 are summarised by National Cancer Institute-Common Toxicity Criteria (NCI CTC) Grade in Table 4.

Table 4. Very common adverse reactions in Phase 3 Study ARCHER 1050 (N=451)

	Dacomitinib (N=227)			Gefitinib (N=224)		
Adverse Reactions[a]	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Metabolism and nutrition disorders						
Decreased appetite	30.8	3.1	0.0	25.0	0.4	0.0
Hypokalemia[b]	10.1	4.0	0.9	5.8	1.8	0.0
Eye disorders						
Conjunctivitis[c]	23.3	0.0	0.0	8.9	0.0	0.0
Gastrointestinal disorders						
Diarrhoea[d]	87.2	8.4	0.0	55.8	0.9	0.0
Stomatitis[e]	69.6	4.4	0.4	33.5	0.4	0.0
Nausea	18.9	1.3	0.0	21.9	0.4	0.0
Skin and subcutaneous tissue disorders						
Rash[f]	77.1	24.2	0.0	57.6	0.9	0.0
Palmar-plantar erythrodysaesthesia syndrome	14.5	0.9	0.0	3.1	0.0	0.0
Dry skin[g]	29.5	1.8	0.0	18.8	0.4	0.0
Pruritus[h]	20.3	0.9	0.0	14.3	1.3	0.0
Nail disorder[i]	65.6	7.9	0.0	21.4	1.3	0.0
Alopecia	23.3	0.4	0.0	12.5	0.0	0.0
General disorders and administration site conditions						
Asthenia	12.8	2.2	0.0	12.5	1.3	0.0
Investigations						
Transaminases increased[j]	23.8	0.9	0.0	40.2	9.8	0.0
Weight decreased	25.6	2.2	0.0	16.5	0.4	0.0

[a] Only adverse reactions with ≥ 10% incidence in the dacomitinib arm are included.
[b] Hypokalaemia includes the following preferred terms (PTs): Blood potassium decreased, Hypokalaemia.
[c] Conjunctivitis includes the following PTs: Blepharitis, Conjunctivitis, Dry eye, Noninfective conjunctivitis.
[d] 1 fatal event was reported in the dacomitinib arm.
[e] Stomatitis includes the following PTs: Aphthous ulcer, Cheilitis, Dry mouth, Mucosal inflammation, Mouth ulceration, Oral pain, Oropharyngeal pain, Stomatitis.
[f] Rash includes the following PTs: Acne, Dermatitis acneiform, Erythema, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular.
[g] Dry skin includes the following PTs: Dry skin, Xerosis.
[h] Pruritus includes the following PTs: Pruritus, Rash pruritic.
[i] Nail disorder includes the following PTs: Ingrowing nail, Nail discolouration, Nail disorder, Nail infection, Nail toxicity, Onychoclasis, Onycholysis, Onychomadesis, Paronychia.
[j] Transaminases increased includes the following PTs: Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminases increased.

Interstitial lung disease (ILD)/Pneumonitis

ILD/Pneumonitis adverse drug reactions were reported in 2.7% of patients receiving DAVIZIM®, and Grade ≥3 ILD/pneumonitis adverse drug reactions were reported in 0.8%, including a fatal event (0.4%) (see Section 4.4 Special warnings and precautions for use).

The median time to the first episode of any grade ILD/pneumonitis was 16 weeks and the median time to the worst episode of ILD/pneumonitis was 16 weeks in patients receiving DAVIZIM®. The median duration of any grade and Grade ≥3 ILD/pneumonitis was 13 weeks. and 1.5 weeks, respectively (see Section 4.4 Special warnings and precautions for use).

Diarrhea

Diarrhea was the most frequently reported adverse drug reaction in patients receiving DAVIZIM® (88.6%) and Grade ≥3 diarrhea adverse reactions were reported in 9.4% of patients. In a clinical study, one patient (0.4%) was inadequately treated and had a fatal outcome (see Section 4.4 Special warnings and precautions for use).

The median time to the first episode of any grade diarrhea was 1 week and the median time to the worst episode of diarrhea was 2 weeks in patients receiving DAVIZIM®. The median duration of any grade and Grade ≥3 diarrhea was 20 weeks and 1 week, respectively (see Section 4.4 Special warnings and precautions for use).

Skin-related adverse reactions

Rash, erythematous and exfoliative skin condition adverse reactions were reported in 79.2% and 5.5%, respectively, of patients receiving DAVIZIM®. Skin-related adverse reactions were Grades 1 to 3. Grade 3 rash and erythematous skin condition adverse reactions were the most frequently reported Grade 3 adverse reactions (25.5%). Grade 3 exfoliative skin conditions were reported in 0.8% of patients (see Section 4.4 Special warnings and precautions for use).

The median time to the first episode of any grade rash and erythematous skin conditions was approximately 2 weeks and the median time to the worst episode of rash and erythematous skin conditions was 7 weeks in patients receiving DAVIZIM®. The median duration of any grade and Grade ≥ 3 rash and erythematous skin conditions was 53 weeks and 2 weeks, respectively. The median time to the first episode of any grade exfoliative skin conditions was 6 weeks and the median time to the worst episode of exfoliative skin conditions was 6 weeks. The median duration of any grade and Grade ≥ 3 exfoliative skin conditions was 10 weeks and approximately 2 weeks, respectively (see Section 4.4 Special warnings and precautions for use).

Transaminases increased

Transaminases increased (alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased) were reported in 22.0% of patients receiving DAVIZIM® and were Grades 1 to 3, with the majority Grade 1 (18.4%) (see Section 4.4 Special warnings and precautions for use).

The median time to the first episode of any grade of transaminases increased was approximately 12 weeks and the median time to the worst episode of transaminases increased was 12 weeks in patients receiving dacomitinib. The median duration of any grade and Grade ≥ 3 transaminases increased was 11 weeks and 1 week, respectively.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

The highest dose of dacomitinib studied in a limited number of patients was 105 mg (6 doses every 12 hours every 14 days). The adverse drug reactions observed at doses greater than 45 mg once a day were primarily gastrointestinal, dermatological, and constitutional (e.g., fatigue, malaise, and weight loss). There were no overdoses reported in the dacomitinib clinical trials.

There is no known antidote for dacomitinib. The treatment of DAVIZIM® overdose should consist of symptomatic treatment and general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of action

Dacomitinib is a pan-human epidermal growth factor receptor (HER) (EGFR/HER1, HER2, and HER4) inhibitor, with clinical activity against mutated EGFR with deletions in exon 19 or the L858R substitution in exon 21. Dacomitinib binds selectively and irreversibly to its HER family targets thereby providing prolonged inhibition. Dacomitinib demonstrates dose-dependent target inhibition and antitumor efficacy in mice bearing human tumor xenografts driven by HER family targets including mutated EGFR.

Dacomitinib distributes to the brain in mice, with brain and plasma average concentrations approximately equal following oral dosing. Dacomitinib exhibits target inhibition and antitumor efficacy in orally-dosed dacomitinib- versus control-treated mice bearing intracranial human tumor xenografts driven by EGFR.

Clinical efficacy

DAVIZIM® in first-line treatment of NSCLC patients with EGFR-activating mutations (ARCHER 1050)

The efficacy and safety of DAVIZIM® was demonstrated in a Phase 3 study (ARCHER 1050) conducted in patients with locally advanced or metastatic NSCLC harboring activating mutations of EGFR. A total of 452 patients were randomized 1:1 to DAVIZIM® or gefitinib in a multicenter, multinational, randomized, open-label Phase 3 study. Treatment was administered orally on a continuous daily basis until disease progression, institution of new anticancer therapy, intolerable toxicity, withdrawal of consent, death, or investigator decision dictated by protocol compliance, whichever occurred first. Stratification factors at randomization were race (Japanese versus mainland Chinese versus other East Asian versus non-East Asian, as stated by the patient) and EGFR mutation status (exon 19 deletion versus the L858R mutation in exon 21). EGFR mutation status was determined by a standardized and commercially available test kit.

The primary endpoint of the study was progression-free survival (PFS) as determined by blinded Independent Radiology Central (IRC) review. Key secondary endpoints included Objective Response Rate (ORR), Duration of Response (DoR), Overall Survival (OS), and patient-reported outcomes (PROs).

The demographic characteristics of the overall study population were 60% female, median age at enrollment of 62 years, baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 (30%), or 1 (70%), 59% with exon 19 deletion, and 41% with L858R mutation in exon 21; 23% White, 77% Asian, and less than 1% Black.

A statistically significant and clinically meaningful improvement in PFS as determined by the IRC was demonstrated for patients randomized to DAVIZIM® compared with those randomized to gefitinib, see Table 5 and Figure 1.

Subgroup analyses of PFS per IRC review based on baseline characteristics were consistent with those from the primary analysis of PFS.

The pre-specified final analysis of OS demonstrated that dacomitinib resulted in a significant improvement in OS versus gefitinib, see Table 5 and Figure 2.

Table 5. Efficacy Results From ARCHER 1050 in Patients With Previously Untreated NSCLC With EGFR-activating Mutations – ITT Population*

	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]	0.589 (0.469, 0.739)	
2-sided p-value[b]	<0.0001	
Progression-Free Survival (per Investigator assessment)		
Number of patients with event, n (%)	140 (61.7%)	177 (78.7%)
Median PFS in months (95% CI)	16.6 (12.9, 18.4)	11.0 (9.4, 12.1)
HR (95% CI)[a]	0.622 (0.497, 0.779)	
2-sided p-value[b]	<0.0001	
Overall Survival		
Number of patients with event, n (%)	103 (45.4)	117 (52.0)
Median OS in months (95% CI)	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR (95% CI)[a]	0.760 (0.582, 0.993)	
2-sided p-value[b]	0.0438	
Objective Response Rate (per IRC)		
Objective Response Rate % (95% CI)	74.9% (68.7, 80.4)	71.6% (65.2, 77.4)
2-sided p-value[c]	0.3883	
Duration of Response in Responders (per IRC)		
Number of responders per IRC review, n (%)	170 (74.9)	161 (71.6)
Median DoR in months (95% CI)	14.8 (12.0, 17.4)	8.3 (7.4, 9.2)
HR (95% CI)[a]	0.403 (0.307, 0.529)	
2-sided p-value[b]	<0.0001	
Duration of Response[d] (per IRC)		
Median DoR in months (95% CI)	9.3 (8.2, 12.0)	6.4 (4.6, 6.5)
HR (95% CI)[a]	0.530 (0.426, 0.659)	
2-sided p-value[b]	<0.0001	

*Data based on data cut-off date of 29 July 2016 except for pre-specified final OS analysis which is based on the data cut-off date of 17 February 2017.

Abbreviations: CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; IRC=independent radiologic central; ITT= intent-to-treat; IWRS= interactive web response system; N/n=total number; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; DoR=duration of response.

a. From stratified Cox Regression. The stratification factors were Race (Japanese versus mainland Chinese and other East Asian versus non-East Asian) and EGFR mutation status (exon 19 deletion versus the L858R mutation in exon 21) at randomization per IWRS.

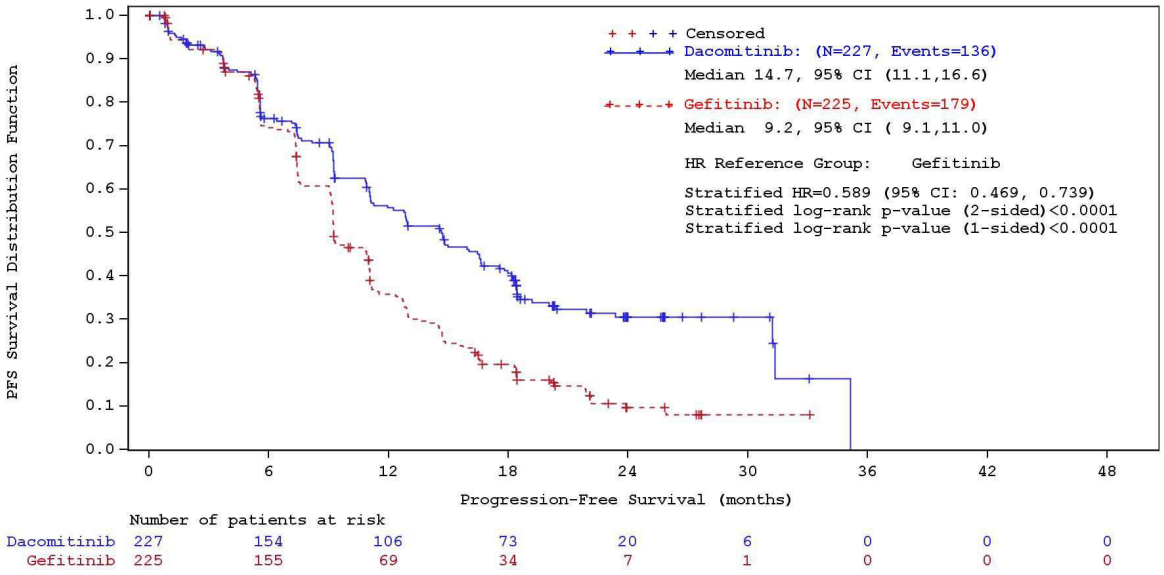
b. Based on the stratified log-rank test. The stratification factors were Race (Japanese versus mainland Chinese and other East Asian versus non-East Asian) and EGFR mutation status (exon 19 deletion versus the L858R mutation in exon 21) at randomization per IWRS.

c. Based on the stratified Cochran-Mantel-Haenszel test. The stratification factors were Race (Japanese versus mainland Chinese and other East Asian versus non-East Asian) and EGFR mutation status (exon 19

deletion versus the L858R mutation in exon 21) at randomization per IWRS.

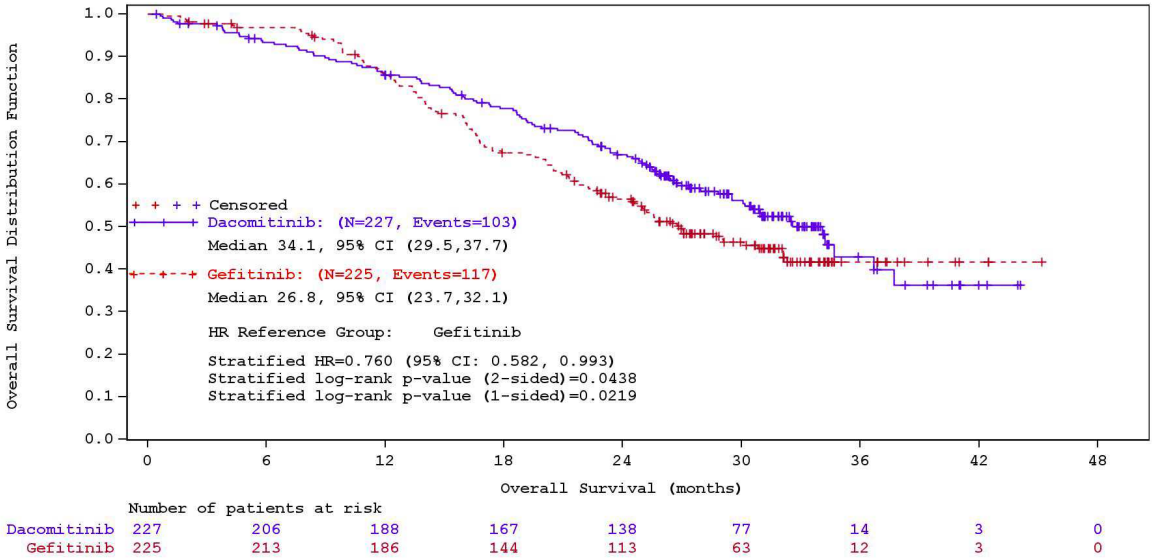
[d.] Analysis was based on the ITT population with patients without response being given a duration of zero and considered an event.

Figure 1. ARCHER 1050 - Kaplan-Meier Curve for PFS per IRC Review – ITT Population



Abbreviations: CI=confidence interval; HR=hazard ratio; IRC=independent radiologic central; ITT=Intent-To-Treat; N=total number; PFS=progression-free survival.

Figure 2. ARCHER 1050 - Kaplan-Meier Curve for OS – ITT Population



Abbreviations: CI=confidence interval; HR=hazard ratio; ITT=Intent-To-Treat; N=total number; OS=overall survival.

Patient-reported outcomes were collected using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (items) (EORTC-QLQ-C30) and its lung cancer module European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer module 13 (items) (EORTC-QLQ-LC13). Dacomitinib resulted in an improvement in the disease-related symptom of pain in chest (p=0.0235) compared to gefitinib. The improvement from baseline was clinically meaningful (≥10 point change from baseline) in pain in chest in the dacomitinib arm.

There was a clinically meaningful improvement from baseline (≥10 point change from baseline) in disease-related symptom of cough in the dacomitinib arm which was similar to the gefitinib arm (p=0.3440).

Improvements from baseline that were not statistically different between the dacomitinib arm and the gefitinib arm were seen in the disease related symptoms of dyspnea (p=0.9411), fatigue (p=0.5490), pain in arm or shoulder (p=0.2854), and pain in other parts (p=0.3288).

5.2. Pharmacokinetic properties

Absorption

Following the administration of a single 45 mg dose of dacomitinib tablets, the mean oral bioavailability of dacomitinib is 80% compared to intravenous administration, with C_{max} occurring 5 to 6 hours after oral dosing. Following dacomitinib 45 mg daily dosing, steady state was reached within 14 days. Food does not alter bioavailability to a clinically meaningful extent. Dacomitinib can be administered with or without food. Dacomitinib is a substrate for the membrane transport proteins P-glycoprotein (P-gp) and Breast Cancer Resistant Protein (BCRP). However, based on the oral bioavailability of 80% these membrane transport proteins are unlikely to have any impact on dacomitinib absorption.

Distribution

Dacomitinib is extensively distributed throughout the body with a mean steady state volume of distribution of 27 L/kg (patient of 70 kg) [coefficient of variation (CV%): 18%] following intravenous administration. In plasma, dacomitinib binds to albumin and α_1-acid glycoprotein and the fraction unbound is approximately 2% *in vitro* and *ex vivo* in healthy volunteers.

Metabolism

O-desmethyl dacomitinib accounted for 16% of human plasma radioactivity and is formed

mainly by CYP2D6 and to a lesser extent CYP2C9. The inhibition of CYP2D6 translated into approximately a 90% reduction in metabolite exposure and an approximate 37% increase in dacomitinib exposure.

In humans, dacomitinib undergoes oxidation and glutathione conjugation as the major metabolic pathways. Following oral administration of a single 45 mg dose of [^{14}C] dacomitinib, the most abundant circulating metabolite was O-desmethyl dacomitinib. This metabolite exhibited *in vitro* pharmacologic activity that was similar to that of dacomitinib in the *in vitro* biochemical assays. In feces, dacomitinib, O-desmethyl dacomitinib, a cysteine conjugate of dacomitinib, and a mono-oxygenated metabolite of dacomitinib were the major drug-related components. *In vitro* studies indicated that CYP2D6 was the major CYP isozyme involved in the formation of O-desmethyl dacomitinib, while CYP3A4 contributed to the formation of other minor oxidative metabolites.

Elimination

The plasma half-life of dacomitinib ranges from 54 to 80 hours. Dacomitinib showed a clearance of 20.0 L/hr with an inter-individual variability of 32% (CV%). In 6 healthy male subjects given a single-oral dose of [^{14}C] radiolabeled dacomitinib, a median of 82% of the total administered radioactivity was recovered in 552 hours; feces (79% of dose) was the major route of excretion, with 3% of the dose recovered in urine, of which < 1% of the administered dose was unchanged dacomitinib.

Drug interactions

Coadministration of dacomitinib and CYP2D6 inhibitors

Coadministration of a single 45 mg oral dose of dacomitinib in the presence of paroxetine (30 mg), a potent CYP2D6 inhibitor, resulted in a 37% increase in dacomitinib exposures (AUC). The change in dacomitinib disposition due to paroxetine coadministration is unlikely to be clinically relevant and dose adjustment of dacomitinib is not required upon concomitant administration with a CYP2D6 inhibitor.

Coadministration of dacomitinib and CYP2D6 substrates

Coadministration of single 45 mg oral dose of dacomitinib increased the mean exposure (AUC and C_{max}) of dextromethorphan, a probe CYP2D6 substrate, 855% and 874%, respectively, compared with administration of dextromethorphan alone. These results suggest that dacomitinib may increase exposure of other drugs (or decrease exposure to active metabolites) primarily metabolized by CYP2D6. Administration of drugs which are highly dependent on CYP2D6 metabolism may require dose adjustment, or substitution with an alternative medication. Clinical monitoring for exaggerated or decreased drug effects is also recommended.

Coadministration of dacomitinib with agents that increase gastric pH

The aqueous solubility of dacomitinib is pH dependent, with low (acidic) pH resulting in higher solubility. Data from a study in healthy subjects indicated that coadministration of a single 45 mg dacomitinib dose with multiple doses of the PPI rabeprazole 40 mg decreased dacomitinib C_{max} and AUC_{inf} (area under the concentration-time curve from time 0 to infinity) by approximately 51% and 30%, respectively when compared to a single 45 mg dose of DAVIZIM® administered alone. PPIs should be avoided while receiving treatment with DAVIZIM®.

Based on data from observations in 8 cancer patients from Study A7471001, there was no apparent effect of local antacid administration on C_{max} and AUC_{inf} of dacomitinib. Based on data from 16 cancer patients across multiple studies, there was no apparent effect of H2 receptor antagonists on steady-state trough concentrations of dacomitinib.

Effect of dacomitinib and O-desmethyl dacomitinib on CYP enzymes

In vitro, dacomitinib and its metabolite O-desmethyl dacomitinib have a low potential to inhibit the activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5 at clinically relevant concentrations, but they may inhibit the activity of CYP2D6.
In vitro, dacomitinib has a low potential to induce CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

Effect of dacomitinib on drug transporters

In vitro, dacomitinib has a low potential to inhibit the activities of drug transporters P-gp (systemically), organic anion transporters (OAT)1 and OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3, but may inhibit the activity of P-gp (in the gastrointestinal [GI] tract), BCRP (systemically and GI tract), and OCT1 at clinically relevant concentrations.

Effect of dacomitinib on UGT enzymes

In vitro, dacomitinib has a low potential to inhibit uridine-diphosphate glucuronosyltransferase (UGT)1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15, but may inhibit UGT1A1 at clinically relevant concentrations.

Special populations

Age, race, gender, body weight

Based on population pharmacokinetic analyses, patient age, race, gender, and body weight do not have a clinically relevant effect on predicted steady state trough concentration of dacomitinib.

Patients with hepatic impairment

In a dedicated hepatic impairment trial, following a single-oral dose of 30 mg DAVIZIM®, dacomitinib exposure (AUC and C_{max}) was unchanged in mild hepatic impairment (Child-Pugh A; N=8) and decreased by 15% and 20%, respectively in moderate hepatic impairment (Child-Pugh B; N=9) when compared to subjects with normal hepatic function (N=8). Dacomitinib pharmacokinetics has not been studied in subjects with severe hepatic impairment (Child-Pugh class C). In addition, based on a population pharmacokinetic analysis using data from 1381 patients, that included 158 patients with mild hepatic impairment defined by National Cancer institute (NCI) criteria [total bilirubin ≤Upper Limit of Normal (ULN) and Aspartate Aminotransferase (AST) > ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST; N=158], mild hepatic impairment had no effect on the pharmacokinetics of dacomitinib. From the small number of patients in the moderate group [total bilirubin >1.5 to 3 × ULN and any AST; N=5], there is no evidence for a change in dacomitinib pharmacokinetics.

Patients with renal impairment

Approximately 3% of a single [^{14}C] 45 mg dose was excreted in the urine. No clinical studies have been conducted in patients with impaired renal function. Based on population pharmacokinetic analyses, mild (60 mL/min ≤CrCl <90 mL/min; N=590) and moderate (30 mL/min ≤CrCl <60 mL/min; N=218) renal impairment, did not alter dacomitinib pharmacokinetics, relative to subjects with normal (CrCl ≥90 mL/min; N=567) renal function. From the small number of patients with severe renal impairment (CrCl <30 mL/min; N=4), there is no evidence for a change in dacomitinib pharmacokinetics. The pharmacokinetics of dacomitinib have not been studied in patients requiring hemodialysis.

Exposure response relationships

No clear relationship between dacomitinib exposure and efficacy could be characterised over the exposure range studied. Significant exposure-safety relationship was defined for Grade ≥ 3 rash/dermatitis acneiform, other skin toxicities, diarrhoea and Grade ≥ 1 stomatitis.

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 did not prolong QTc to any clinically relevant extent at therapeutic maximum concentrations expected following 45 mg once daily.

5.3. Preclinical safety data

Repeated-dose toxicity

In oral repeated-dose toxicity studies for up to 6 months in rats and 9 months in dogs, the primary toxicities were identified in the skin/hair (dermal changes in rats and dogs, atrophy/dysplasia of hair follicles in rats), kidney (papillary necrosis often accompanied by tubular degeneration, regeneration, dilatation and/or atrophy and changes in urinary markers indicative of renal injury in rats, erosion or ulceration of the pelvic epithelium with associated inflammation without changes indicative of renal dysfunction in dogs), eye (cornea epithelial atrophy in rats and dogs, corneal ulcers/erosions with red/swollen conjunctiva(e), conjunctivitis, elevated third eyelid, increased squinting, partially closed eyes, lacrimation, and/or ocular discharge in dogs), and digestive system (enteropathy in rats and dogs, erosions/ulcers of the mouth with reddened mucous membranes in dogs), and atrophy of epithelial cells of other organs in rats. In addition, hepatocellular necrosis with transaminase increases and hepatocellular vacuolation were observed in rats only. These effects were reversible with the exception of hair follicles and kidney changes. All effects occurred at systemic exposure below that in humans at the recommended dose of 45 mg once daily.

Genotoxicity

Dacomitinib was tested using a series of genetic toxicology assays. Dacomitinib is not mutagenic in a bacterial reverse mutation (Ames) assay, and not clastogenic or aneugenic in the *in vivo* bone marrow micronucleus assay in male and female rats. Dacomitinib was clastogenic in the *in vitro* human lymphocyte chromosome aberration assay at cytotoxic concentrations. Dacomitinib is not directly reactive toward DNA as evidenced by the negative response in the bacterial reverse mutation assay and did not induce chromosome damage in a bone marrow micronucleus assay at concentrations up to approximately 60-70 times the unbound AUC or C_{max} at the recommended human dose. Thus, dacomitinib is not expected to be genotoxic at clinically relevant exposure concentrations.

Carcinogenicity

Carcinogenicity studies have not been performed with DAVIZIM®.

Impairment of fertility

Fertility studies have not been performed with DAVIZIM®. In repeat-dose toxicity studies with DAVIZIM®, effects on reproductive organs were observed in female rats given ≥0.5 mg/kg/day for 6 months (approximately 0.3 times the unbound AUC at the recommended human dose) and were limited to reversible epithelial atrophy in the cervix and vagina. There was no effect on reproductive organs in male rats given ≤2 mg/kg/day for 6 months (approximately 1.1 times the unbound AUC at the recommended human

dose), or in dogs given ≤1 mg/kg/day for 9 months (approximately 0.3 times the unbound AUC at the recommended human dose).

Developmental toxicity

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses up to 5 mg/kg/day and 4 mg/kg/day dacomitinib, respectively, during the period of organogenesis. Maternal body weight gain and food intake were lower at 5 mg/kg/day and 4 mg/kg/day in pregnant rats and rabbits, respectively. The maternally toxic dose of 5 mg/kg/day was fetotoxic in rats, resulting in reduced fetal body weights and higher incidence of unossified metatarsals. At the maternally toxic dose of 4 mg/kg/day in rabbits, there was no evidence of developmental toxicity. At 5 mg/kg/day in rats and 4 mg/kg/day in rabbits, the maternal systemic exposures were approximately 2.4 and 0.3 times, respectively, the unbound AUC at the recommended human dose during the period of organogenesis.

Phototoxicity

A phototoxicity study with dacomitinib in pigmented rats showed no phototoxicity potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Magnesium stearate

Film coating

Opadry II Blue 85F30716 containing:
Polyvinyl alcohol – partially hydrolysed (E1203)
Talc (E553b)
Titanium dioxide (E171)
Macrogol (E1521)
Indigo Carmine Aluminium Lake (E132)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

5 years

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

Aluminium/aluminium blister containing 10 film-coated tablets. Each pack contains 10 film-coated tablets.

6.6. Special precautions for disposal and other handling

Dacomitinib has the potential to be a very persistent, bioaccumulative and toxic substance (see Section 5.3 Preclinical safety data). Any unused product or waste should be disposed in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
Pfizer Manufacturing Deutschland GmbH,
Betriebsstätte Freiburg, Germany

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

8. MARKETING AUTHORISATION NUMBER(S)

DAVIZIM® 15 mg, box of 1 blister @ 10 film-coated tablets; Reg. No.:DKI2090702017A1.
DAVIZIM® 30 mg, box of 1 blister @ 10 film-coated tablets; Reg. No.:DKI2090702017B1.
DAVIZIM® 45 mg, box of 1 blister @ 10 film-coated tablets; Reg. No.:DKI2090702017C1.

HARUS DENGAN RESEP DOKTER

9. DATE OF REVISION OF THE TEXT

Jan 2021