Rx,

Abemaciclib film coated tablets 50mg, 100mg, 150mg and 200mg

Ramiven®

Qualitative and quantitative composition:

Ramiven® 50 mg film-coated tablets
Each film-coated tablet contains 50 mg abemaciclib.
Beige, oval tablet of 5.2 x 9.5 mm, debossed with "Lilly" on one side and "50" on the other.

Excipients with known effect
Each film-coated tablet contains 14 mg of lactose monohydrate.

Ramiven® 100 mg film-coated tablets
Each film-coated tablet contains 100 mg abemaciclib.
White, oval tablet of 6.6 x 12.0 mm, debossed with "Lilly" on one side and "100" on the other.

Excipients with known effect
Each film-coated tablet contains 28 mg of lactose monohydrate.

Ramiven® 150 mg film-coated tablets
Each film-coated tablet contains 150 mg abemaciclib.
Yellow, oval tablet of 7.5 x 13.7 mm, debossed with "Lilly" on one side and "150" on the other.

Excipients with known effect
Each film-coated tablet contains 42 mg of lactose monohydrate.

Ramiven® 200 mg film-coated tablets
Each film-coated tablet contains 200 mg abemaciclib.
Beige, oval tablet, debossed with "Lilly" on one side and "200" on the other.

Excipients with known effect
Each film-coated tablet contains 56 mg of lactose monohydrate.

Therapeutic Indications

(i) Abemaciclib is indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.
- In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

(ii) As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

Posology and method of administration

Posology

Ramiven® in combination with endocrine therapy
The recommended dose of abemaciclib is 150 mg twice daily when used in combination with endocrine therapy. Please refer to the prescribing information of the endocrine therapy combination partner for the recommended posology.

Monotherapy
Recommended starting dose as monotherapy: 200 mg twice daily.

Ramiven® should be taken continuously as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

If a patient vomits or misses a dose of Ramiven®, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken.

Dose adjustments
Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Tables 1-6.

Table 1. Dose adjustment recommendations for adverse reactions

Dose level	Ramiven® dose combination with Fulvestrant or an Aromatase Inhibitor	Ramiven® dose for monotherapy
Recommended starting dose	150 mg twice daily	200 mg twice daily
First dose reduction	100 mg twice daily	150 mg twice daily
Second dose reduction	50 mg twice daily	100 mg twice daily
Third dose reduction	Not applicable	50 mg twice daily

Table 2. Management recommendations for haematologic toxicities
Complete blood counts should be monitored prior to the start of Ramiven® therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Before treatment initiation, absolute neutrophil counts (ANC) ≥1500/mm^3, platelets ≥100,000/mm^3, and haemoglobin ≥8 g/dL are recommended.

Toxicity[a, b]	Management recommendations
Grade 1 or 2	No dose adjustment required.
Grade 3	Suspend dose until toxicity resolves to Grade 2 or less. Dose reduction is not required.
Grade 3, recurrent; or Grade 4	Suspend dose until toxicity resolves to Grade 2 or less. Resume at next lower dose.
Patient requires administration of blood cell growth factors	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to Grade 2 or less. Resume at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

[a] NCI Common Terminology Criteria for Adverse Events (CTCAE)
[b] ANC: Grade 1: ANC < LLN - 1500/mm^3; Grade 2: ANC 1000 - < 1500/mm^3;
Grade 3: ANC 500 - < 1000/mm^3; Grade 4: ANC < 500/mm^3
LLN = lower limit of normal

Table 3. Management recommendations for diarrhea
At the first sign of loose stools, start treatment with antidiarrheal agents and increase intake of oral fluids.

Toxicity [a]	Management recommendations
Grade 1	No dose adjustment required.
Grade 2	If toxicity does not resolve within 24 hours to Grade 1 or less, suspend dose until resolution. Dose reduction is not required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose.
Grade 3 or 4 or requires hospitalization	

[a] NCI CTCAE

Table 4. Management recommendations for increased aminotransferases
Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum bilirubin should be monitored prior to the start of Ramiven® therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.

Toxicity [a]	Management recommendations
Grade 1 (> ULN-3.0 x ULN) Grade 2 (> 3.0-5.0 x ULN)	No dose adjustment required.
Persistent or Recurrent Grade 2, or Grade 3 (> 5.0-20.0 x ULN)	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 4 (> 20.0 x ULN)	Discontinue abemaciclib.
Elevation in AST and/or ALT >3 x ULN WITH total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue abemaciclib.

[a] NCI CTCAE
ULN = upper limit of normal

Table 5: Management recommendations for Interstitial Lung Disease (ILD)/Pneumonitis

CTCAE Grade	Ramiven® Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at *next lower dose.*
Grade 3 or 4	Discontinue abemaciclib.

Table 6. Management recommendations for non-haematologic toxicities (excluding diarrhea, increased aminotransferases, and interstitial lung disease (ILD)/pneumonitis)

Toxicity [a]	Management recommendations
Grade 1 or 2.	No dose adjustment required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures to baseline or Grade 1 within 7 days	Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose.
Grade 3 or 4	

[a] NCI CTCAE

CYP3A4 inhibitors
Concomitant use of strong CYP3A4 inhibitors should be avoided. If strong CYP3A4 inhibitors cannot be avoided, the abemaciclib dose should be reduced to 100 mg twice daily.

In patients who have had their dose reduced to 100 mg abemaciclib twice daily and in whom co-administration of a strong CYP3A4 inhibitor cannot be avoided, the abemaciclib dose should be further reduced to 50 mg twice daily.

In patients who have had their dose reduced to 50 mg abemaciclib twice daily and in whom co-administration of a strong CYP3A4 inhibitor cannot be avoided, the abemaciclib dose may be continued with close monitoring of signs of toxicity. Alternatively, the abemaciclib dose may be reduced to 50 mg once daily or discontinued.

If the CYP3A4 inhibitor is discontinued, the abemaciclib dose should be increased to the dose used prior to the initiation of the CYP3A4 inhibitor (after 3 to 5 half-lives of the CYP3A4 inhibitor).

Special populations
Elderly
No dose adjustment is required based on age (see section 'Pharmacokinetic properties').

Renal impairment
No dose adjustments are necessary in patients with mild or moderate renal impairment. There are no data regarding abemaciclib administration in patients with severe renal impairment, end stage renal disease, or in patients on dialysis (see section 'Pharmacokinetic properties'). Abemaciclib should be administered with caution in patients with severe renal impairment, with close monitoring for signs of toxicity.

Hepatic impairment
No dose adjustments are necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. In patients with severe (Child Pugh C) hepatic impairment, a decrease in dosing frequency to once daily is recommended (see section 'Pharmacokinetic properties').

Paediatric population
The safety and efficacy of abemaciclib in children and adolescents aged less than 18 years has not been established. No data are available.

Method of administration
Ramiven® is for oral use.
The dose can be taken with or without food. It should not be taken with grapefruit or grapefruit juice (see section Drugs interactions).
Patients should take the doses at approximately the same times every day.
The tablet should be swallowed whole (patients should not chew, crush, or split tablets before swallowing).

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

Special warnings and precautions for use

Neutropenia
Neutropenia was reported in patients receiving abemaciclib. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see section 'Posology and method of administration'). Fatal events occurred in <1% of patients. Patients should be instructed to report any episode of fever to their healthcare provider.

Infections/infestations
Infections were reported in patients receiving abemaciclib plus endocrine therapy at a higher rate than in patients treated with placebo plus endocrine therapy. Lung infection was reported in patients receiving abemaciclib without concurrent neutropenia. Fatal events occurred in < 1% of patients. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.

Venous thromboembolism
Venous thromboembolic events were reported in 5.3% of patients treated with abemaciclib plus fulvestrant or aromatase inhibitors, compared to 0.8% of patients treated with placebo plus fulvestrant or aromatase inhibitors. Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate.

Increased aminotransferases
Increases in ALT and AST were reported in patients receiving abemaciclib. Based on the level of ALT or AST elevation, abemaciclib may require dose modification (see section 'Posology and method of administration').

Diarrhea
Diarrhea is the most common adverse reaction. Across clinical studies, median time to onset of the first diarrhoea event was approximately 6 to 8 days, and median duration of diarrhoea was 9 to 12 days (Grade 2) and 6 to 8 days (Grade 3). Diarrhea can be associated with dehydration. Patients should start treatment with antidiarrheal agents such as loperamide at the first sign of loose stools, increase oral fluids and notify their healthcare provider. Dose modification is recommended for patients who develop ≥Grade 2 diarrhoea (see section 'Posology and method of administration').

Interstitial Lung Disease (ILD)/Pneumonitis
Interstitial lung disease (ILD)/pneumonitis was reported in patients receiving abemaciclib. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and treat as medically appropriate. Based on the grade of ILD/pneumonitis, abemaciclib may require dose modification (Posology and method of administration). Permanently discontinue abemaciclib in patients with Grade 3 or 4 ILD/pneumonitis.

Concomitant use of inducers of CYP3A4
Concomitant use of CYP3A4 inducers should be avoided due to the risk of decreased efficacy of abemaciclib (see section 'Drug interactions').

Visceral crisis
There are no data on the efficacy and safety of abemaciclib in patients with visceral crisis.

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Drug interactions

Effects of other medicinal products on the pharmacokinetics of abemaciclib
Abemaciclib is primarily metabolised by CYP3A4.

CYP3A4 inhibitors
Co-administration of abemaciclib with CYP3A4 inhibitors can increase plasma concentrations of abemaciclib. In patients with advanced and/or metastatic cancer, co-administration of the CYP3A4 inhibitor clarithromycin resulted in a 3.4-fold increase in the plasma exposure of abemaciclib and a 2.5-fold increase in the combined unbound potency adjusted plasma exposure of abemaciclib and its active metabolites.

Use of strong CYP3A4 inhibitors together with abemaciclib should be avoided. If strong CYP3A4 inhibitors need to be co-administered, the dose of abemaciclib should be reduced (see section 'Posology and method of administration'), followed by careful monitoring of toxicity. Examples of strong CYP3A4 inhibitors include, but not limited to: clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole or voriconazole. Avoid grapefruit or grapefruit juice.

No dose adjustment is necessary for patients treated with moderate or weak CYP3A4 inhibitors. There should, however be close monitoring for signs of toxicity.

CYP3A4 inducers
Co-administration of abemaciclib with the strong CYP3A4 inducer rifampicin decreased the plasma concentration of abemaciclib by 95% and unbound potency adjusted plasma concentration of abemaciclib plus its active metabolites by 77% based on $AUC_{0-\infty}$. Concomitant use of strong CYP3A4 inducers (including, but not limited to: carbamazepine, phenytoin, rifampicin and St. John's wort) should be avoided due to the risk of decreased efficacy of abemaciclib.

Effects of abemaciclib on the pharmacokinetics of other medicinal products
Medicinal products that are substrates of transporters
Abemaciclib and its major active metabolites inhibit the renal transporters organic cation transporter 2 (OCT2), multidrug and extrusion toxin protein (MATE1), and MATE2-K. *In vivo* interactions of abemaciclib with clinically relevant substrates of these transporters, such as dofetilide or creatinine, may occur (see section 'Undesirable effects'). In a clinical drug interaction study with metformin (substrate of OCT2, MATE1 and 2) co-administered with 400 mg abemaciclib, a small but not clinically relevant increase (37%) in metformin plasma exposure was observed. This was found to be due to reduced renal secretion with unaffected glomerular filtration.

In healthy subjects, co-administration of abemaciclib and the P-glycoprotein (P-gp) substrate loperamide resulted in an increase in loperamide plasma exposure of 9% based on $AUC_{0-\infty}$ and 35% based on C_{max}. This was not considered to be clinically relevant. However, based on the *in vitro* inhibition of P-gp and breast cancer resistance protein (BCRP) observed with abemaciclib, *in vivo* interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin or dabigatran etexilate, may occur.

In a clinical study in patients with breast cancer, there was no clinically-relevant pharmacokinetic drug interaction between abemaciclib and anastrozole, fulvestrant, exemestane, letrozole or tamoxifen.

It is currently unknown whether abemaciclib may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives are advised to add a barrier method.

Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females
Women of childbearing potential should use highly effective contraception methods (e.g. double-barrier contraception) during treatment and for at least 3 weeks after completing therapy (see section drugs interactions).

Pregnancy
There are no data from the use of abemaciclib in pregnant women. Studies in animals have shown reproductive toxicity (see section preclinical safety data). Ramiven® is not recommended during pregnancy and in women of child-bearing potential not using contraception.

Breast-feeding
It is unknown whether abemaciclib is excreted in human milk. A risk to newborns/infants cannot be excluded. Patients receiving abemaciclib should not breast-feed.

Fertility
The effect of abemaciclib on fertility in humans is unknown. In animal studies, no effects on female reproductive organs were observed. However, cytotoxic effects to the male reproductive tract in rats and dogs indicate that abemaciclib may impair fertility in males (see section preclinical safety data).

Effects on ability to drive and use machines
Ramiven® has minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue or dizziness during treatment with abemaciclib (see section Undesirable effects).

Undesirable effects

Summary of the safety profile
The most commonly occurring adverse reactions are diarrhea, infections, neutropenia, anaemia, fatigue, nausea, vomiting and decreased appetite.

RAMIVEN® Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)
Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting
Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer. Patients received 200 mg RAMIVEN® orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months. Ten patients (8%) discontinued study treatment from adverse reactions due to (1 patient each) abdominal pain, arterial thrombosis, aspartate aminotransferase (AST) increased, blood creatinine increased, chronic kidney disease, diarrhea, ECG QT prolonged, fatigue, hip fracture, and lymphopenia. Fortynine percent of patients had dose reductions due to an adverse reaction. The most frequent adverse reactions that led to dose reductions were diarrhea (20%), neutropenia (11%), and fatigue (9%). Deaths during treatment or during the 30-day follow up were reported in 2% of patients. Cause of death in these patients was due to infection. The most common reported adverse reactions (≥20%) were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia (Table 7). Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib [see section Posology and Method of administration].

Table 7: Adverse Reactions (≥10% of Patients) in MONARCH 1

	RAMIVEN® N=132		
	All Grades (%)	Grade 3 %	Grade 4 %
Gastrointestinal Disorders			
Diarrhea	90	20	0
Nausea	64	5	0
Abdominal pain	39	2	0
Vomiting	35	2	0
Constipation	17	<1	0
Dry mouth	14	0	0
Stomatitis	14	0	0
Infections & Infestations			
Infections	31	5	2
General Disorders and Administration Site Conditions			
Fatigue[a]	65	13	0
Pyrexia	11	0	0
Blood and Lymphatic System Disorders			
Neutropenia[b]	37	19	5
Anemia[c]	25	5	0
Thrombocytopenia[d]	20	4	0
Leukopenia[e]	17	5	<1
Metabolism and Nutrition Disorders			
Decreased appetite	45	3	0
Dehydration	10	2	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	19	0	0
Musculoskeletal and Connective Tissue			
Arthralgia	15	0	0
Nervous System Disorder			
Headache	20	0	0
Dysgeusia	12	0	0
Dizziness	11	0	0
Skin and Subcutaneous Tissue Disorders			
Alopecia	12	0	0
Investigations			
Creatinine Increased	13	<1	0
Weight decreased	14	0	0

[a] Includes asthenia, fatigue.
[b] Includes neutropenia, neutrophil count decreased
[c] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
[d] Includes platelet count decreased, thrombocytopenia
[e] Includes leukopenia, white blood cell count decreased.

Tabulated list of adverse reactions
In the following tables, adverse reactions are listed in order of MedDRA body system organ class and frequency. Frequency gradings are: 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), very rare (< 1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 8 Adverse reactions reported in phase 3 studies of abemaciclib in combination with endocrine therapy (N=768)

System organ class *Frequency* Preferred term	Abemaciclib plus endocrine therapy[a]		
	All Grades Toxicity (%)	Grade 3 Toxicity (%)	Grade 4 Toxicity (%)
Infections and infestations			
Very common			
Infections[b]	43.6	5.2	1.0
Blood and lymphatic system disorders			
Very common			
Neutropenia	45.1	22.9	2.5
Leukopenia	25.7	8.5	0.3
Anaemia	30.1	7.0	0.1
Thrombocytopenia	14.3	2.2	1.0
Common			
Lymphopenia	7.3	3.0	0.1
Uncommon			
Febrile neutropenia	0.9	0.7	0.1
Metabolism and nutrition disorders			
Very common			
Decreased appetite	26.4	1.3	0
Nervous system disorders			
Very common			
Dysgeusia	14.3	0	0
Dizziness	12.9	0.5	0
Eye disorders			
Common			
Lacrimation increased	6.8	0.1	0
Vascular disorders			
Common			
Venous thromboembolism[c]	5.3	1.7	0.3
Respiratory, Thoracic and Mediastinal Disorders			
Common			
Interstitial Lung Disease (ILD)/Pneumonitis	3.4	0.4	0.1
Gastrointestinal disorders			
Very common			
Diarrhea	84.6	11.7	0
Vomiting	27.7	1.2	0
Nausea	43.5	2.1	0
Skin and subcutaneous tissue disorders			
Very common			
Alopecia	20.7	0	0
Pruritus	13.5	0	0
Rash	12.9	1.0	0
Common			
Dry skin	9.0	0	0
Musculoskeletal and connective tissue disorders			
***Commo**n*			
Muscular weakness	8.3	0.5	0
General disorders and administration site conditions			
***Very commo**n*			
Fatigue	40.5	2.3	0
Pyrexia	10.7	0.1	0
Investigations			
Very common			
Alanine aminotransferase increased	15.1	4.8	0.3
Aspartate aminotransferase increased	14.2	2.9	0

[a] Abemaciclib in combination with letrozole, anastrozole, or fulvestrant.
[b] Infections includes all PTs that are part of the System Organ Class Infections and infestations.
[c] Venous thromboembolic events include DVT, pulmonary embolism, cerebral venous sinus thrombosis, subclavian, axillary vein thrombosis, DVT inferior vena cava and pelvic venous thrombosis

PP-AL-IN-0096

Item Code PA0085PIN01	Previous Item Code *(to be destroyed)* PA0085PIN00

PPD Information Box

Start Date 23 JUN 2020	Proof No.: 4	Printing Colours BLACK	Technical Colours Die Cut	Affiliate Barcode: Type: N/A Code: N/A
Technical Information: Layout name ALCPA0066A00	Size (mm): 630 x 350			Other Regulated Elements N/A
	Folded Size (mm) 157,5x175		Overt N/A	
	No. of Pages: 1/2			
BLUE Project No. 39187	Sick Code 5482			

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Operator name: SC Time: 10:24

Description of selected adverse reactions

Neutropenia

Neutropenia was reported frequently (45.1%). and a Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 28.2% of patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. The median time to onset of Grade 3 or 4 neutropenia was 29 to 33 days, and median time to resolution was 11 to 15 days. Febrile neutropenia was reported in 0.9% patients. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see section 'Posology and method of administration').

Diarrhea

Diarrhea was the most commonly reported adverse reaction (see Table 8). Incidence was greatest during the first month of abemaciclib treatment and was lower subsequently. The median time to onset of the first diarrhea event was approximately 6 to 8 days across studies, and the median duration of diarrhea was 9 to 12 days (Grade 2) and 6 to 8 days (Grade 3) across studies. Diarrhea returned to baseline or lesser grade with supportive treatment such as loperamide and/or dose adjustment (see section 'Posology and method of administration').

Increased aminotransferases

In patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant, ALT and AST elevations were reported frequently (15.1% and 14.2%, respectively). Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 6.1% and 4.2% patients. The median time to onset of Grade 3 or 4 ALT elevation was 57 to 61 days, and median time to resolution was 14 days. The median time to onset of Grade 3 or 4 AST elevation was 71 to 185 days, and median time to resolution was 13 to 15 days. Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see section 'Posology and method of administration').

Creatinine

Although not an adverse reaction, abemaciclib has been shown to increase serum creatinine in 98.3% of patients (based on laboratory findings), 1.9% Grade 3 or 4 (based on laboratory findings). In patients receiving an aromatase inhibitor or fulvestrant alone, 78.4% reported an increase in serum creatinine (all laboratory grades). Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters without affecting glomerular function (as measured by iohexol clearance) (see section drug interactions). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Ramiven®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory disorders: Interstitial lung disease (ILD)/pneumonitis.

Overdose

In the event of an abemaciclib overdose, fatigue and diarrhea may occur. General supportive care should be provided.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinases inhibitors, ATC code: L01XE50

Mechanism of action

Abemaciclib is a potent and selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), and most active against Cyclin D1/CDK4 in enzymatic assays. Abemaciclib prevents retinoblastoma protein (Rb) phosphorylation, blocking cell cycle progression from the G1 to the S-phase of cell division, leading to suppression of tumour growth. In oestrogen receptor-positive breast cancer cell lines, sustained target inhibition with abemaciclib prevented rebound of Rb phosphorylation resulting in cell senescence and apoptosis. *In vitro*, Rb-negative and Rb-depleted cancer cell lines are generally less sensitive to abemaciclib. In breast cancer xenograft models, abemaciclib dosed daily without interruption at clinically relevant concentrations alone or in combination with anti-oestrogens resulted in reduction of tumour size.

Pharmacodynamic effects

In cancer patients, abemaciclib inhibits CDK4 and CDK6 as indicated by inhibition of phosphorylation of Rb and topoisomerase II alpha, which results in cell cycle inhibition upstream of the G1 restriction point.

Cardiac electrophysiology

The effect of abemaciclib on the QTcF interval was evaluated in 144 patients with advanced cancer. No large change (that is, > 20 ms) in the QTcF interval was detected at the mean observed maximal steady state abemaciclib concentration following a therapeutic dosing schedule.

In an exposure-response analysis in healthy subjects at exposures comparable to a 200 mg twice-daily dose, abemaciclib did not prolong the QTcF interval to any clinically relevant extent.

Clinical efficacy and safety

Randomised Phase 3 Study MONARCH 3: Ramiven® in combination with aromatase inhibitors

The efficacy and safety of Ramiven® in combination with an aromatase inhibitor (anastrozole or letrozole) was evaluated in MONARCH 3, a randomised, double-blind, placebo-controlled phase 3 study in women with HR positive, HER2 negative locally advanced or metastatic breast cancer who had not received prior systemic therapy in this disease setting. Patients were randomised in a 2:1 ratio to receive Ramiven® 150 mg twice daily plus a non-steroidal aromatase inhibitor given daily at the recommended dose versus placebo plus a non-steroidal aromatase inhibitor according to the same schedule. The primary endpoint was investigator-assessed progression-free survival (PFS) evaluated according to RECIST 1.1; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS).

The median age of patients enrolled was 63 years (range 32-88). Approximately 39% of patients had received chemotherapy and 44% had received antihormonal therapy in the (neo) adjuvant setting. Patients with prior (neo)adjuvant endocrine therapy must have completed this therapy at least 12 months before study randomisation. The majority of patients (96%) had metastatic disease at baseline. Approximately 22% of patients had bone-only disease, and 53% patients had visceral metastases.

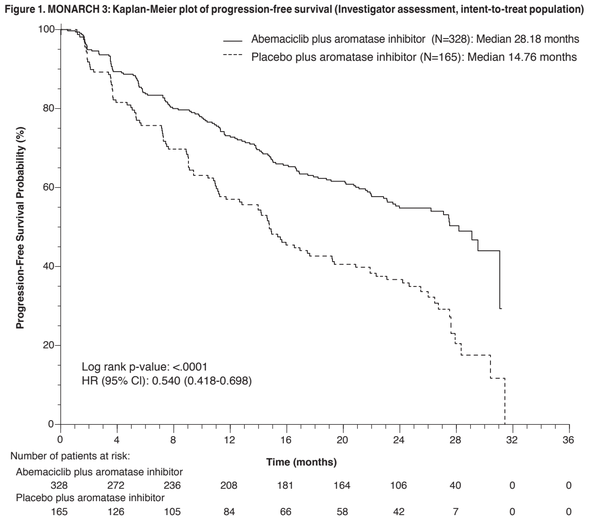
The study met its primary endpoint of improving PFS. Primary efficacy results are summarised in Table 9 and Figure 1.

Table 9 MONARCH 3: Summary of efficacy data (Investigator assessment, intent-to-treat population)

	Ramiven® plus aromatase inhibitor	Placebo plus aromatase inhibitor
Progression-free survival	**N=328**	**N=165**
Investigator assessment, number of events (%)	138 (42.1)	108 (65.5)
Median [months] (95% CI)	28.18 (23.51, NR)	14.76 (11.24, 19.20)
Hazard ratio (95% CI) and p-value	0.540 (0.418, 0.698), p=0.000002	
Independent radiographic review, number of events (%)	91 (27.7)	73 (44.2)
Median [months] (95% CI)	NR (NR, NR)	19.36 (16.37, 27.91)
Hazard ratio (95% CI) and p-value	0.465 (0.339, 0.636); p < 0.000001	
Objective response rate[a] [%] (95% CI)	49.7 (44.3, 55.1)	37.0 (29.6, 44.3)
Duration of response [months] (95% CI)	27.39 (25.74, NR)	17.46 (11.21, 22.19)
Objective response for patients with measurable disease[a]	**N=267**	**N=132**
Objective response rate[b] [%] (95% CI)	61.0 (55.2, 66.9)	45.5 (37.0, 53.9)
Complete response, (%)	3.4	0
Partial response, (%)	57.7	45.5
Clinical benefit rate[c] **(measurable disease)** [%] (95% CI)	79.0 (74.1, 83.9)	69.7 (61.9, 77.5)

[a] Measurable disease defined per RECIST version 1.1
[b] Complete response + partial response
[c] Complete response + partial response + stable disease for ≥ 6 months
N=number of patients; CI=confidence interval; NR=not reached.

Figure 1. MONARCH 3: Kaplan-Meier plot of progression-free survival (Investigator assessment, intent-to-treat population)



Progression-free survival (PFS) was significantly prolonged in the Ramiven® plus aromatase inhibitor (AI) arm, (Hazard Ratio [HR] of 0.540 [95% CI, 0.418 to 0.698]); median PFS was 28.18 months in the Ramiven® plus AI arm and was 14.76 months in the placebo plus AI arm. These results correspond to a clinically meaningful reduction in the risk of disease progression or death of 46% for patients treated with abemaciclib plus an aromatase inhibitor.

Overall survival was not mature at the final PFS analysis (93 events observed across the two arms). The HR was 1.057 (95% CI: 0.683, 1.633), p=0.8017.

A series of prespecified subgroup PFS analyses showed consistent results across patient subgroups including age (< 65 or ≥65 years), disease site, disease staging (de novo metastatic vs recurrent metastatic vs locally advanced recurrent), presence of measurable disease, progesterone receptor status, and baseline ECOG performance status. A reduction in the risk of disease progression or death was observed in patients with visceral disease, (HR of 0.567 [95% CI: 0.407, 0.789]), median PFS 21.6 months versus 14.0 months; in patients with bone-only disease (HR 0.565, [95% CI: 0.306, 1.044]); and in patients with measurable disease (HR 0.517, [95% CI: 0.392, 0.681]).

Randomised Phase 3 Study MONARCH 2: Ramiven® in combination with fulvestrant

The efficacy and safety of Ramiven® in combination with fulvestrant was evaluated in MONARCH 2, a randomised, double-blind, placebo-controlled phase 3 study in women with HR positive, HER2 negative locally advanced or metastatic breast cancer. Patients were randomised in a 2:1 ratio to receive Ramiven® 150 mg twice daily plus fulvestrant 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose, versus placebo plus fulvestrant according to the same schedule. The primary endpoint was investigator-assessed PFS evaluated according to RECIST 1.1; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS).

The median age of patients enrolled was 60 years (range, 32-91 years). In each treatment arm the majority of patients were white, and had not received chemotherapy for metastatic disease. 17% of patients were pre/perimenopausal on ovarian suppression with a GnRH agonist. Approximately 56% patients had visceral metastases. Approximately 25% of patients had primary endocrine resistance (progression on endocrine therapy within the first 2 years of adjuvant endocrine therapy or within the first 6 months of first line endocrine therapy for metastatic breast cancer) and for the majority, endocrine resistance developed later. 59% of patients had most recent endocrine therapy in the (neo) adjuvant setting, and 38% in metastatic setting.

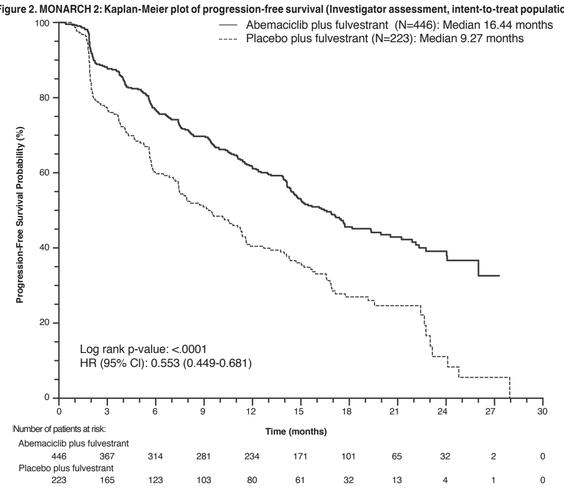
The study met its primary endpoint of improving PFS. Primary efficacy results are summarised in Table 10 and Figure 2.

Table 10 MONARCH 2: Summary of efficacy data (Investigator assessment, intent-to-treat population)

	Ramiven® plus fulvestrant	Placebo plus fulvestrant
Progression-free survival	**N=446**	**N=223**
Investigator assessment, number of events (%)	222 (49.8)	157 (70.4)
Median [months] (95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 12.7)
Hazard ratio (95% CI) and p-value	0.553 (0.449, 0.681), p=0.0000001	
Independent radiographic review, number of events (%)	164 (36.8)	124 (55.6)
Median [months] (95% CI)	22.4 (18.3, NR)	10.2 (5.8, 14.0)
Hazard ratio (95% CI) and p-value	0.460 (0.363, 0.584); p < .000001	
Objective response rate[a] [%] (95% CI)	35.2 (30.8, 39.6)	16.1 (11.3, 21.0)
Duration of response [months] (95%CI)	NR (18.05, NR)	25.6 (11.9, 25.6)
Objective response for patients with measurable disease[a]	**N=318**	**N=164**
Objective response rate[b] [%] (95% CI)	48.1 (42.6, 53.6)	21.3 (15.1, 27.6)
Complete response, (%)	3.5	0
Partial response, (%)	44.7	21.3
Clinical benefit rate[c] **(measurable disease)** [%] (95% CI)	73.3 (68.4, 78.1)	51.8 (44.2, 59.5)

[a] Measurable disease defined per RECIST version 1.1
[b] Complete response + partial response
[c] Complete response + partial response + stable disease for ≥ 6 months
N=number of patients; CI=confidence interval; NR=not reached.

Figure 2. MONARCH 2: Kaplan-Meier plot of progression-free survival (Investigator assessment, intent-to-treat population)



Median PFS was significantly prolonged in the Ramiven® plus fulvestrant arm (HR of 0.553 [95% CI 0.449, 0.681]); median PFS was 16.4 months versus 9.3 months in the placebo plus fulvestrant arm. These results correspond to a clinically meaningful reduction in the risk of disease progression or death of 44.7% and a 7.2 month improvement in median PFS for patients treated with Ramiven® plus fulvestrant. Ramiven® plus fulvestrant prolonged progression-free survival with neither a clinically meaningful or significant detriment to health-related quality of life.

A series of prespecified subgroup PFS analyses showed consistent results across patient subgroups including age (< 65 or ≥ 65 years), race, geographic region, disease site, endocrine therapy resistance, presence of measurable disease, progesterone receptor status, and menopausal status. A reduction in the risk of disease progression or death was observed in patients with visceral disease, (HR of 0.481 [95% CI: 0.369, 0.627]), median PFS 14.7 months versus 6.5 months; in patients with bone-only disease (HR of 0.543 [95% CI: 0.355, 0.833]); patients with measurable disease (HR of 0.523 [95% CI: 0.412, 0.644]). In patients who were pre/perimenopausal, the hazard ratio was 0.415 (95% CI: 0.246, 0.698); in patients who were progesterone receptor negative, the HR was 0.509 (95% CI: 0.325, 0.797).

In a sub-population with locally advanced or metastatic disease that had not received prior endocrine therapy, the PFS was also consistent.

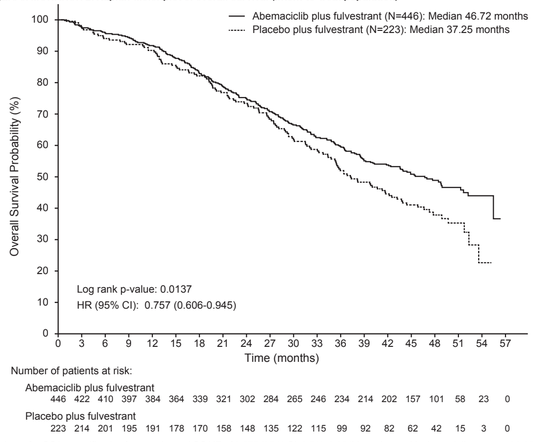
Overall survival (OS) analysis in the ITT population showed a statistically significant improvement in patients receiving Ramiven® plus fulvestrant compared with those receiving placebo plus fulvestrant. The overall survival results are summarized in Table 11 and Figure 3.

Table 11. MONARCH 2: Summary of overall survival data (Intent-to-treat population)

	Ramiven® plus fulvestrant	Placebo plus fulvestrant
Overall survival	N=446	N=223
Number of events (n, %)	211 (47.3)	127 (57.0)
Median OS [months] (95 % CI)	46.7 (39.2, 52.2)	37.3 (34.4, 43.2)
Hazard ratio (95 % CI)	0.757 (0.606, 0.945)	
p-value	0.0137	

N = number of patients; CI = confidence interval; OS = overall survival

Figure 3. MONARCH 2: Kaplan-Meier plot of overall survival (Intent-to-treat population)



Analyses for OS by stratification factors showed OS HR of 0.675 (95 % CI: 0.511, 0.891) in patients with visceral disease, and 0.686 (95 % CI: 0.451, 1.043) in patients with primary endocrine resistance.

Ramiven® Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

MONARCH 1 (NCT02102490) was a single-arm, open-label, multicenter study in women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. A total of 132 patients received 200 mg Ramiven® orally twice daily on a continuous schedule until development of progressive disease or unmanageable toxicity.

Patient median age was 58 years (range, 36-89 years), and the majority of patients were White (85%). Patients had an Eastern Cooperative Oncology Group performance status of 0 (55% of patients) or 1 (45%). The median duration of metastatic disease was 27.6 months. Ninety percent (90%) of patients had visceral metastases, and 51% of patients had 3 or more sites of metastatic disease. Fifty-one percent (51%) of patients had had one line of chemotherapy in the metastatic setting. Sixty-nine percent (69%) of patients had received a taxane-based regimen in the metastatic setting and 55% had received capecitabine in the metastatic setting. Table 12 provides the efficacy results from MONARCH 1.

Table 12: Efficacy Results in MONARCH 1 (Intent-to-Treat Population)

	Ramiven® 200 mg N = 132	
	Investigator assessed	Independent Review
Objective Response Rate[a,b],n (%)	26 (19.7)	23 (17.4)
95% CI (%)	13.3, 27.5	11.4, 25.0
Median Duration of response	8.6 months	7.2 months
95% CI (%)	5.8, 10.2	5.6, NR

Abbreviations: CI = confidence interval, NR = not reached.
[a] All responses were partial responses.
[b] Based upon confirmed responses.

Pharmacokinetic properties

Absorption

Abemaciclib absorption is slow, with a T_{max} of 8 hours and a mean absolute bioavailability of approximately 45 %. In the therapeutic dose range of 50-200 mg, the increase in plasma exposure (AUC) and C_{max} is approximately dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and abemaciclib accumulated with a geometric mean accumulation ratio of 3.7 (58% CV) and 5.8 (65% CV) based on C_{max} and AUC, respectively. A high-fat meal increased combined AUC of abemaciclib and its active metabolites by 9% and increased C_{max} by 26%. These changes were not considered to be clinically relevant. Therefore, abemaciclib can be taken with or without food.

Distribution

Abemaciclib is highly bound to plasma proteins in humans (mean bound fraction approximately 96% to 98%). The geometric mean systemic volume of distribution is approximately 750 L (69% CV), indicating distribution of abemaciclib into tissues.

Concentrations of abemaciclib and its active metabolites in cerebrospinal fluid are comparable to unbound plasma concentrations.

Biotransformation

Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolised to several metabolites primarily by cytochrome P450 (CYP) 3A4. The primary biotransformation is hydroxylation to a metabolite that circulates with an AUC that is 77% of parent drug. In addition, N-desethyl and N-desethylhydroxy metabolites circulate at AUCs that are 39% and 15% of parent drug. These circulating metabolites are active with similar potency to abemaciclib.

Elimination

The geometric mean hepatic clearance (CL) of abemaciclib was 21.8 L/h (39.8% CV), and the mean plasma elimination half-life for abemaciclib in patients was 24.8 hours (52.1% CV). After a single oral dose of [^{14}C] -abemaciclib, approximately 81% of the dose was excreted in faeces and 3.4% excreted in urine. The majority of the dose eliminated in faeces was metabolites.

Special populations

Age, gender, and body weight

Age, gender, and body weight had no effect on the exposure of abemaciclib in a population pharmacokinetic analysis in patients with cancer (135 males and 859 females; age range 24-91 years; and body weight range 36-175 kg).

Hepatic impairment

Abemaciclib is metabolised in the liver. Mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment had no effect on the exposure of abemaciclib. In subjects with severe hepatic impairment (Child Pugh C), the $AUC_{0-\infty}$ of abemaciclib and potency adjusted unbound abemaciclib plus its active metabolites increased 2.1-fold and 2.4-fold, respectively. The half-life of abemaciclib increased from 24 to 55 hours (see section posology and method of administration).

Renal impairment

Renal clearance of abemaciclib and its metabolites is minor. Mild and moderate renal impairment had no effect on the exposure of abemaciclib. There are no data in patients with severe renal impairment, end stage renal disease or in patients on dialysis.

Preclinical safety data

The primary target organ findings of potential relevance to humans included gastrointestinal and haematolymphopoietic organ effects in rats and dogs in studies up to 13 weeks duration. Effects in lung and skeletal muscle occurred only in rats at exposure levels approximately 2-fold higher than human exposure levels and effects in kidney occurred only in rats at exposure levels approximately 6-fold higher than human exposure levels. Complete or partial recovery was observed for all target organs at the end of the 28-day recovery period.

Genotoxicity

Abemaciclib was not mutagenic in a bacterial reverse mutation (Ames) assay, was not clastogenic in an *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes, and was not clastogenic in an *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

Specific animal studies to test abemaciclib for carcinogenic potential have not been performed.

Developmental toxicity

Abemaciclib was teratogenic and caused decreased foetal weight at maternal exposures similar to the recommended human dose.

List of excipients:

Tablet core
croscarmellose sodium
lactose monohydrate
microcrystalline cellulose
colloidal hydrated silica
sodium stearyl fumarate

Film coating
polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide yellow, iron oxide red

Incompatibilities

Not applicable

Shelf-life

24 months

Packaging information

PCTFE/PE/PVC blisters sealed with an aluminium foil in a calendar blister card, in packs of 14 or 168 film coated tablets.

Aluminium/aluminium perforated unit dose blisters of 7x2 and 7x4 film coated tablets.

Not all pack sizes may be marketed.

Storage and handling instructions

Store below 30°C.

Manufactured by:

M/s. Lilly, S.A.
Avda. de la Industria, 30, 28108 Alcobendas, Madrid, Spain.

Imported by:

M/s. Eli Lilly and Company (India) Pvt. Ltd.
Bldg. No. 14, Gala, No. 1 to 4, 1st Fl, Arihant Comm.Complex, Opp. Koper Bus Stop,
Purna Bhiwandi, Thane, Maharashtra-421302

Marketed By:

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