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.

CLINICAL PARTICULARS

Therapeutic Indications

Early Breast Cancer

Ramiven® in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence (see section pharmacodynamic property).

In pre- or perimenopausal women, aromatase inhibitor therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

Advanced or Metastatic Breast Cancer

Ramiven® 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.

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

Ramiven® therapy should be initiated and supervised by physicians experienced in the use of anti-cancer therapies.

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.

Duration of treatment

Early Breast Cancer

Ramiven® should be taken continuously for two years, or until disease recurrence or unacceptable toxicity occurs.

Advanced or Metastatic Breast Cancer

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 1-7.

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/mm3, platelets >100,000/mm3, 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/mm3; Grade 2: ANC 1000 - < 1500/mm3; Grade 3: ANC 500 - < 1000/mm3; Grade 4: ANC < 500/mm3 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 aminostransferase (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

Toxicity [a]	Management recommendations
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.

[a] *NCI CTCAE*

Table 6. Management recommendations for venous thromboembolic events (VTEs)

Toxicity[a]	Management recommendations
Early Breast Cancer	
All Grades (1, 2, 3, or 4)	Suspend dose and treat as clinically indicated. Abemaciclib may be resumed when the patient is clinically stable.
Advanced or metastatic breast cancer	
Grade 1 or 2	No dose modification is required.
Grade 3 or 4	Suspend dose and treat as clinically indicated. Abemaciclib may be resumed when the patient is clinically stable.

[a] NCI CTCAE

Table 7. Management recommendations for non-haematologic toxicities (excluding diarrhea, increased aminotransferases, and ILD/pneumonitis and VTEs)

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 of neutropenic sepsis occurred in <1% of patients with metastatic breast cancer. 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 endocrine therapy. Lung infection was reported in patients receiving abemaciclib without concurrent neutropenia. Fatal events occurred in < 1% of patients with metastatic breast cancer. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.

Venous thromboembolism

Venous thromboembolic events were reported in patients treated with abemaciclib plus endocrine therapy . Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate. Based on the grade of VTE, abemaciclib may require dose modification (see section Posology and method of administration).

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 7 to 12 days (Grade 2) and 5 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

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".

Interaction with other medicinal products and other forms of interaction

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 AUC0-∞. 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 4.4). 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.

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 **Interaction with other medicinal products and other forms of interaction**).

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. While in rats no effects on male fertility were noted, cytotoxic effects to the male reproductive tract in mice, rats, and dogs indicate that abemaciclib may impair fertility in males. No adverse effects on female reproductive organs in mice, rats, or dogs, nor effects on female fertility and early embryonic development in rats were observed (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 Ramiven (see section Undesirable effects).

Undesirable effects
Summary of the safety profile
The most commonly occurring adverse reactions are diarrhea, infections, neutropenia, leukopenia, anaemia, fatigue, nausea, vomiting, alopecia and decreased appetite.
Of the most common adverse reactions, Grade ≥ 3 events were less than 5 % with the exception of neutropenia, leukopenia, and diarrhoea.

Tabulated list of adverse reactions

In the following table, 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 the phase 3 studies of abemaciclib in combination with endocrine therapy[a] (N = 3 559)

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Infections [b]		
Blood and lymphatic system disorders	Neutropenia Leukopenia Anaemia Thrombocytopenia		Febrile neutropenia [e]
	Lymphopenia [h]		
Metabolism and nutrition disorders	Decreased appetite		
Nervous system disorders	Headache [f] **Dysgeusia** [g] **Dizziness** [g]		
Eye disorders		**Lacrimation increased**	
Vascular disorders		**Venous thromboembolism** [c]	
Respiratory, thoracic and mediastinal disorders		**ILD/pneumonitis** [d]	
Gastrointestinal disorders	Diarrhoea Vomiting Nausea Stomatitis [f]	Dyspepsia [f]	
Skin and subcutaneous tissue disorders	**Alopecia** [g] **Pruritus** [g] **Rash** [g]	**Nail disorder** [f] **Dry skin** [e]	
Musculoskeletal and connective tissue disorders		**Muscular weakness** [e]	
General disorders and administration site conditions	Pyrexia [e] Fatigue		
Investigations	**Alanine aminotransferase increased** [g] **Aspartate aminotransferase increased** [g]		

[a] Abemaciclib in combination with anastrozole, letrozole, exemestane, tamoxifen, or fulvestrant.

[b] Infections include all reported Preferred Terms that are part of the System Organ Class Infections and Infestations.

[c] Venous thromboembolic events include deep vein thrombosis (DVT), pulmonary embolism, cerebral venous sinus thrombosis, subclavian, axillary vein thrombosis, DVT inferior vena cava and pelvic venous thrombosis.

[d] Interstitial lung disease (ILD)/pneumonitis for early breast cancer (EBC) include all reported Preferred Terms that are part of the MedDRA SMQ interstitial lung disease. For metastatic breast cancer (mBC) Preferred Terms include interstitial lung disease, pneumonitis, organising pneumonia, pulmonary fibrosis and bronchiolitis obliterans.

[e] Considered ADRs in the mBC setting only (MONARCH 2 and MONARCH 3).

[f] Considered ADRs in the EBC setting only (monarchE).

[g] Common frequency in the EBC setting (monarchE), very common in the mBC setting (MONARCH 2 and MONARCH 3).

[h] Common frequency in mBC setting (MONARCH 2 and MONARCH 3), very common in the EBC setting (monarchE).

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. The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were diarrhea, neutropenia, fatigue, and leukopenia. Deaths due to adverse reactions 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 (2 patients) or pneumonitis (1 patient).
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. Forty-nine 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%).

The most common reported adverse reactions (≥20%) were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia (Table 9) and laboratory abnormalities in (Table 10). Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib [see section Posology and Method of administration].

Table 9: 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	4.5	0
Abdominal pain	39	2.3	0
Vomiting	35	1.5	0
Constipation	17	0.8	0
Dry mouth	14	0	0
Stomatitis	14	0	0
Infections and Infestations			
Infections	31	4.5	0
General Disorders and Administration Site Conditions			
Fatigue[a]	65	13	0
Pyrexia	11	0	0
Metabolism and Nutrition Disorders			
Decreased appetite	45	3.0	0
Dehydration	10	2.3	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	19	0	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	15	0	0
Nervous System Disorders			
Headache	20	0	0
Dysgeusia	12	0	0
Dizziness	11	0	0
Skin and Subcutaneous Tissue Disorders			
Alopecia	12	0	0
Investigations			
Weight decreased	14	0	0

[a] Includes asthenia, fatigue.

Table 10: Laboratory Abnormalities for Patients Receiving Ramiven® in MONARCH 1

	Ramiven® N=132		
	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	99	0.8	0
White blood cell decreased	91	28	0
Neutrophil count decreased	88	22	4.6
Anemia	69	0	0
Lymphocyte count decreased	42	13	0.8
Platelet count decreased	41	2.3	0
ALT Increased	31	3.1	0
AST Increased	30	3.8	0

Description of selected adverse reactions

Neutropenia

Neutropenia was reported frequently across studies. In the monarchE study, neutropenia was reported in 45.8 % of patients. Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 19.1 % of patients receiving abemaciclib in combination with endocrine therapy with a median time to onset of 30 days, and median time to resolution of 16 days. Febrile neutropenia was reported in 0.3 % patients. In MONARCH 2 and MONARCH 3 studies, neutropenia was reported in 45.1% of patients. 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 9). Incidence was greatest during the first month of abemaciclib treatment and was lower subsequently. In the monarchE study, the median time to onset of the first diarrhoea event of any grade was 8 days. The median duration of diarrhoea was 7 days for Grade 2 and 5 days for Grade 3. In MONARCH 2 and MONARCH 3 studies, the median time to onset of the first diarrhea event of any grade was approximately 6 to 8 days. the median duration of diarrhea was 9 to 12 days for Grade 2 and 6 to 8 days for Grade 3. Diarrhoea 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 the monarchE study, ALT and AST elevations were reported frequently (12.3 % and 11.8 %, respectively) in patients receiving abemaciclib in combination with endocrine therapy. Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 2.6 % and 1.6 % patients. The median time to onset of Grade 3 or 4 ALT elevation was 118 days, and median time to resolution was 14.5 days. The median time to onset of Grade 3 or 4 AST elevation was 90.5 days, and median time to resolution was 11 days. In MONARCH 2 and MONARCH 3 studies, , ALT and AST elevations were reported frequently (15.1% and 14.2%, respectively) in patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. 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 the monarchE study, 99.3 % of patients had serum creatinine elevations (based on laboratory findings), and of these, 0.5 % of patients had Grade 3 or 4 elevations. In patients receiving endocrine therapy alone, 91.0 % reported an increase in serum creatinine (all laboratory grades). In MONARCH 2 and MONARCH 3 studies, 98.3% of patients had serum creatinine elevations (based on laboratory findings), and of these, 1.9% of patients had Grade 3 or 4 elevation. 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. (See section: Special warnings and precautions for use)

Overdose

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinases inhibitors, ATC code: L01XEF03

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

Ramiven®

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PPD Information Box

Technical Information: ■ BLACK ☐ DIECUT

Previous Item Code (to be destroyed)
PA008SPIN03

Lilly

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

Early Breast Cancer

Randomised Phase 3 Study monarchE: Ramiven®in combination with endocrine therapy

The efficacy and safety of Ramiven® in combination with adjuvant endocrine therapy was evaluated in monarchE, a randomised, open label, two cohort, phase 3 study, in women and men with HR-positive, HER2-negative, node positive early breast cancer at high risk of recurrence. High risk of recurrence in Cohort 1 was defined by clinical and pathological features: either ≥ 4 pALN (positive axillary lymph nodes), or 1-3 pALN and at least one of the following criteria: tumor size ≥ 5 cm or histological grade 3.

A total of 5 637 patients were randomised in a 1:1 ratio to receive 2 years of Ramiven® 150 mg twice daily plus physician's choice of standard endocrine therapy, or standard endocrine therapy alone.

Randomization was stratified by prior chemotherapy, menopausal status, and region. Men were stratified as postmenopausal. Patients had completed definitive locoregional therapy (with or without neoadjuvant or adjuvant chemotherapy).

Patients must have recovered from the acute side effects of any prior chemotherapy or radiotherapy. A washout period of 21 days after chemotherapy and 14 days after radiotherapy prior to randomization was required. Patients were allowed to receive up to 12 weeks of adjuvant endocrine therapy prior to randomisation. Adjuvant treatment with fulvestrant was not allowed as standard endocrine therapy. Patients with Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 were eligible. Patients with history of VTEs were excluded from the study. After the end of the study treatment period, in both treatment arms patients continued to receive adjuvant endocrine therapy for a cumulative duration of at least 5 years and up to 10 years, if medically appropriate. LHRH agonists were given when clinically indicated to pre- and perimenopausal women, and men.

Among the 5 637 randomised patients, 5 120 were enrolled in Cohort 1, representing 91 % of the ITT population. In Cohort 1, patient demographics and baseline tumour characteristics were balanced between treatment arms. The median age of patients enrolled was approximately 51 years (range, 22-89 years), 15 % of patients were 65 or older, 99 % were women, 71 % were Caucasian, 24 % were Asian, and 5 % Other. Forty three percent of patients were pre- or perimenopausal. Most patients received prior chemotherapy (36 % neoadjuvant, 62 % adjuvant), and prior radiotherapy (96 %). Initial endocrine therapy received by patients included letrozole (39 %), tamoxifen (31 %), anastrozole (22 %), or exemestane (8 %).

Sixty-five percent of the patients had 4 or more positive lymph nodes, 41 % had Grade 3 tumour, and 24 % had pathological tumour size ≥ 5 cm at surgery.

The primary endpoint was invasive disease-free survival (IDFS) in ITT population defined as the time from randomization to the first occurrence of ipsilateral invasive breast tumour recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary non- breast invasive cancer, or death attributable to any cause. Key secondary endpoint was distant relapse free survival (DRFS) in ITT population defined as time from randomization to the first occurrence of distant recurrence, or death attributable to any cause.

The primary objective of the study was met at the pre-planned interim analysis (16 Mar 2020 cut-off). A statistically significant improvement in IDFS was observed in patients who received Ramiven® plus endocrine therapy versus endocrine therapy alone in the ITT population. The approval was granted for the large subpopulation, Cohort 1.

In a further analysis (01 April 2021 cut-off), 91 % of the patients in Cohort 1 were off the 2 year study treatment period and the median duration of follow-up was 27.7 months.

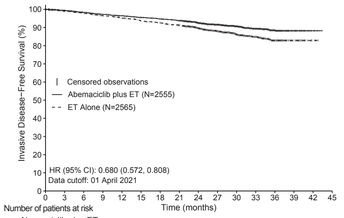
Efficacy results in Cohort 1 are summarised in Table 11 and Figure 1.

Table 11. monarchE: Summary of efficacy data (Cohort 1 population)

	Ramiven® plus endocrine therapy N = 2 555	Endocrine therapy alone N = 2 565
Invasive disease-free survival (IDFS)		
Number of patients with event (n, %)	218 (8.5)	318 (12.4)
Hazard ratio (95 % CI)	0.680 (0.572, 0.808)	
IDFS at 24 months (%, 95 % CI)	92.6 (91.4, 93.5)	89.6 (88.3, 90.8)
Distant relapse free survival (DRFS)		
Number of patients with an event (n, %)	179 (7.0)	266 (10.4)
Hazard ratio (95 % CI)	0.669 (0.554, 0.809)	
DRFS at 24 months (%, 95 % CI)	94.1 (93.0, 95.0)	91.2 (90.0, 92.3)

Abbreviation: CI = confidence interval;
Data cut-off date 01 Apr 2021

Figure 1. monarchE: Kaplan-Meier plot of IDFS (Investigator assessment, Cohort 1 population)



Abbreviations: CI = confidence interval; ET = endocrine therapy; HR = hazard ratio; IDFS = invasive disease-free survival; N = number of patients in the population.
Data cut-off date 01 April 2021

Benefit was observed across patient subgroups defined by geographic region, menopausal status and prior chemotherapy within Cohort 1.

Advanced or Metastatic Breast Cancer

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 nonsteroidal 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 12 and Figure 2.

Table 12 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[b] [%] (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)

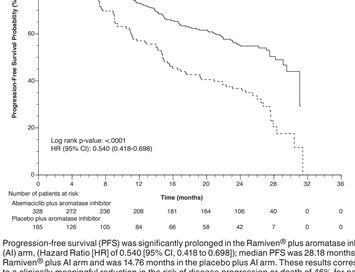
[a] Measurable disease defined per RECIST version 1.1

[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 2. 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.

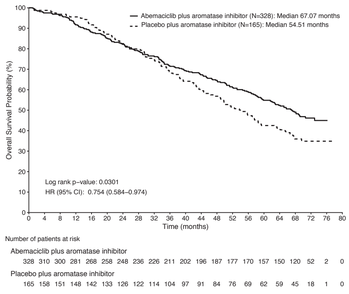
Overall survival was not mature at the final PFS analysis (93 events observed across the two arms). The HR was 1.057 (95% CI: 0.683, 1.633), p=0.8017.

A series of prespecified subgroup PFS analyses showed consistent results across patient subgroups including age (< 65 or >65 years), disease site, disease setting (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]).

At the first OS interim analysis, 197 events were observed across the two arms and the HR was 0.786 (95 % CI: 0.589, 1.049).

At the second OS interim analysis, 255 events were observed across the two arms. Median OS was 67.1 months in the abemaciclib plus AI arm and 54.5 months in the placebo plus AI arm. As the observed HR of 0.754 (95 % CI: 0.584, 0.974) did not reach statistical significance (Figure 3), the study continues to fully characterise overall survival.

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



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 13 and Figure 4.

Table 13 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 < 0.000001	
Objective response rate[b] [%] (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)

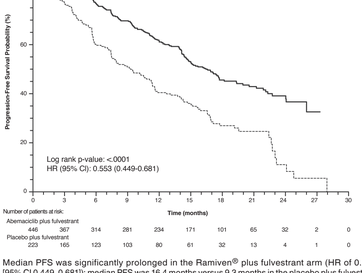
[a] *Measurable disease defined per RECIST version 1.1*

[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 4. 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.

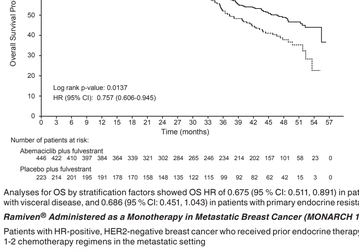
Overall survival (OS) analysis in the ITT population showed a statistically significant improvement in patients receiving Ramiven® plus fulvestrant compared with those receiving placebo plus fulvestrant. The overall survival results are summarized in Table 14 and Figure 5

Table 14. 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 5. 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 15 provides the efficacy results from MONARCH 1.

Table 15: 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 Tmax 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 Cmax 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 Cmax and AUC, respectively. A high-fat meal increased combined AUC of abemaciclib and its active metabolites by 9% and increased Cmax 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 [14C] -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 AUC0-∞ 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 occurred in the gastrointestinal tract and haematolymphopoietic organ and male reproductive tract in mice, rats and dogs in studies up to 13 weeks duration. Effects in eyes and heart valves occurred only in rodents at clinically relevant exposure levels. Effects in lung and skeletal muscle occurred only in rodents at exposure levels least 2-fold higher than human exposure levels. Effects in kidney occurred only in rodents at exposure levels at least 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, with the exception of male reproductive track effects.

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

Abemaciclib was assessed for carcinogenicity in 2 year studies in rats and mice. In male rats, daily oral administration of abemaciclib resulted in benign testicular interstitial cell adenomas at exposures approximately 1.5 times human clinical exposure. In addition, interstitial cell hyperplasia was observed at exposures approximately 0.1 times human clinical exposure. It is unknown if these effects will translate to humans. There were no neoplastic findings in mice or in female rats that were due to administration of abemaciclib.

Impairment of fertility

Abemaciclib may impair fertility in males of reproductive potential. In repeat-dose toxicity studies up to 3 months duration, abemaciclib-related findings in the testis, epididymis, prostate, and seminal vesicle included decreased organ weights, intratubular cellular debris, hypospermia, tubular dilatation, atrophy, and degeneration/necrosis. These effects occurred in rats and dogs at exposures approximately 2 and 0.02 times human clinical exposure, respectively. In a rat male fertility study, abemaciclib had no effects on reproductive performance.

In a rat female fertility and early embryonic development study and in repeat-dose toxicity studies, abemaciclib did not have any effect on reproductive performance or any important effects on the female reproductive tract indicative of a risk of impaired fertility in females.

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, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red.

Incompatibilities

Not applicable

Shelf-life

36 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.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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Avda. de la Industria, 30, 28108 Alcobendas, Madrid, Spain.

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Date of revision: 03 Jun 2022

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