DRUP – Drug specific study manual for ABEMACICLIB (Verzenios)

1. Drug specific in- and exclusion criteria

Abemaciclib specific criteria are highlighted in light grey.

Inclusion criteria	Yes	No	n.a.
1. Patients must be ≥18 years of age.			
2. Histologically-proven locally advanced or metastatic solid tumor, multiple myeloma or B cell non-Hodgkin lymphoma, with symptomatic disease progression or progression according to RECIST-criteria after standard anti-cancer therapy, or for whom no such treatment is available or indicated.			
a. <u>For patients with a primary brain tumor</u>: histologically confirmed recurrent or de novo primary brain tumor , with unequivocal progression after prior therapy, at least 3 months after radiotherapy (either first line chemo-radiotherapy or re-irradiation), and with stable or decreasing dosage of steroids for at least 7 days prior to the baseline MRI scan.			
3. Presence of an oncogenic mutation that can potentially be targeted by abemaciclib (please refer to the list of drugs and acceptable profiles for further definitions). A complete sequencing report, confirming the actionable mutation, has to be submitted for patient enrollment.			
4. ECOG performance status 0-2			
5. Patients must have normal organ and bone marrow function measured within 4 weeks prior to administration of study treatment as defined below:			
a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L			
b. Hemoglobin > 5.0 mmol/l Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion.			
c. Platelet count ≥ 100 x 109/L			
d. Total bilirubin < 1.5 x ULN. Patients with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted.			
e. AST (SGOT) and ALT (SGPT) ≤ 3 x institutional ULN (≤ 5 x ULN in the presence of documented liver metastases at baseline)			
f. Serum creatinine ≤ 1.5 × ULN or calculated or measured creatinine clearance ≥ 30 mL/min/1.73 m2			
6. Objectively measurable disease (by physical or radiographic examination, according to RECIST v1.1 for patients with solid tumors, or according to IMWG, Lugano, RANO or GCIG criteria, resp., for patients with multiple myeloma, non-Hodgkin lymphoma, glioblastoma or ovarian cancer in case of CA125-based evaluation).			

Inclusion criteria	**Yes**	**No**	**n.a.**
7. A new (obtained ≤2 months before inclusion, and without any type of anti-cancer therapy within those ≤2 months) fresh frozen tumor biopsy specimen for extensive biomarker testing is mandatory before the start of treatment with a targeted agent included in the protocol. Alternatively, fresh frozen tumor tissue acquired in the context of a standard care procedure may be used, provided that no systemic anti-cancer treatment was given between the procedure and start of study treatment within DRUP. The following exceptions are made: a) An exception is made for patients with a primary brain tumor, only if the mandatory DRUP pre-treatment biopsy for biomarker analysis cannot safely be obtained: i. The fresh frozen tumor biopsy sample may be replaced by fresh frozen tumor tissue, obtained earlier from recurrent disease, as part of standard of care surgical procedure (i.e., performed at progression) ii. If no fresh frozen tumor tissue is available for NGS, and the risk of obtaining a new tumor biopsy is considered too high, no biopsy will be required. In this case, the study coordinators must be informed in advance, and there will be no reimbursement for the biopsy procedure. b) In case WGS is performed on tumor tissue outside the context of a clinical trial before inclusion, and without any type of anti-cancer therapy between the collection of tissue and inclusion in DRUP, this can replace the DRUP pre-treatment biopsy, provided that the patient gives consent to use his/her WGS data for biomarker analysis in DRUP. c) An exception is made for patients that underwent an allogeneic hematopoietic stem cell transplantation prior to study enrollment, since this will prevent a correct WGS analysis due to a mismatch between the biopsy specimen and the required blood sample			
8. Ability to understand and the willingness to sign a written informed consent document.			
9. For orally administered drugs, the patient must be able to swallow and tolerate oral medication and must have no known malabsorption syndrome.			
10. Women of child-bearing potential and men must agree to use adequate double-barrier contraception for the duration of study participation, and for four months following completion of study therapy. For women of childbearing potential: negative serum pregnancy test within 7 days of the first dose. *NB: drug-drug interaction studies of abemaciclib with oral contraceptives have not been conducted.*			

Exclusion criteria	Yes	No	n.a.
1. Patients who are eligible for on-label treatment or ongoing trials with abemaciclib are excluded from treatment with abemaciclib within the DRUP trial.			
2. Patients who have previously been treated with CDK4/6 inhibitors.			
3. Known hypersensitivity to abemaciclib or any of the excipients of the product.			
4. Concomitant use of strong CYP3A inhibitors (e.g. clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice).			
5. Concomitant use of strong CYP3A inducers (e.g. carbamazepine, enzalutamide, phenytoin, rifampin, and St. John's Wort).			
6. Patients with rare hereditary problems of galactose intolerance.			
7. Ongoing toxicity > grade 2, other than alopecia or grade 2 peripheral neuropathy.			
8. Patients that are receiving any other anti-cancer therapy (cytotoxic, biologic, radiation, or hormonal other than for replacement). Required wash out period prior to starting study treatment is at least 21 days for chemotherapy and at least two weeks for all other anti-cancer therapies. An exception is made for patients suffering from CRPC, who are allowed to continue androgen deprivation therapy.			
9. The patient has had major surgery within 14 days prior to randomization.			
10. The patient has received an experimental treatment in a clinical trial within the last 30 days of 5 half-lives, whichever is longer, prior to randomization, or is currently enrolled in any other type of medical research (for example: medical device) judged by the sponsor not to be scientifically or medically compatible with this study.			
11. Patient is pregnant or nursing.			
12. Symptomatic progressive brain metastases, either parenchymal or leptomeningeal. An exception is made for patients with asymptomatic brain metastasis, or those who have stable symptoms and did not require an increased dose of corticosteroids in the past 7 days prior to study treatment.			
a. <u>For patients with a primary brain tumor</u>: (I) Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). EIAED are prohibited. Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization. (II) No radiotherapy within the three months prior to the diagnosis of progression. (III) No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.			
13. Patients with a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.			
14. Patients with known left ventricular ejection fraction (LVEF) < 40% are not eligible.			
15. Patients with stroke (including TIA) or acute myocardial infarction within 2 months before the first dose of study treatment are not eligible.			

Exclusion criteria	Yes	No	n.a.
16. Patients with serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).			
17. Patients with active systemic bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]. Screening is not required for enrollment.			

NB Please note that official prescription instructions, as outlined in the Summary of Product Characteristics (SPC, most recent version can be downloaded from https://www.ema.europa.eu/en/medicines) and / or any other official documents concerning this drug, will always take precedence over this manual. This manual is provided for practical support; treatment can be performed according to local standard-of-care protocols.

2. Treatment schedule

	Screening (≤28 days before treatment start)	After screening, before start	D1 of every treatment cycle (1 cycle = 28 days)	D15 of the first 2 cycles (1 cycle = 28 days)	At the end of every 2nd treatment cycle	After end of treatment (≤ 30 days after stop)
Concurrent meds	x		x			
Adverse events			x			
Physical exam	x		x[1]			
Vital signs	x		x[1]			
Performance Status	x		x[1]			
Hb, Complete Blood Count	x[2]		x[2]	x[2]		
Serum chemistry	x		x[1]			
ALT, AST, bilirubin, amylase and lipase	x[3]		x[3]	x[3]		
Serum pregnancy test	x[4]					
Radiological imaging	x[5]					
Abemaciclib			x (continuous dosing)			
Tumor biopsy		x[6]				x[6]
Response evaluation	x[7]				x[7]	

1. According to local standard clinical practice, or as clinically indicated.
2. Before initiation of treatment with abemaciclib, every 2 weeks for the first 2 months. After cycle 4 according to standard of local care or if clinically indicated.
3. Prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.
4. During screening, a serum test should be performed within 7 days before the first dose of abemaciclib for all female participants of childbearing potential.
5. This should include a chest CT-scan to confirm no pre-existing pulmonary conditions are present.
6. Tumor biopsy: after screening is positive, a mandatory DRUP pre-treatment biopsy should be taken. After termination of DRUP treatment, a post-treatment biopsy can be obtained. The post-treatment biopsy is optional.
7. A baseline scan should be performed <28 days before start of treatment. Tumor assessments will initially be repeated every 8 weeks after treatment initiation. If the patient continues study treatment beyond 3 response evaluations (i.e., 24 weeks), response evaluation will thereafter be performed at the end of every 3rd treatment cycle (i.e., every 12 weeks).

3. Administration and starting dosage

The recommended dose of abemaciclib is 200 mg taken orally twice daily for continuous 28-day cycles. The dose can be taken with or without food. Abemaciclib should not be taken with grapefruit or grapefruit juice. The capsules should be swallowed whole. Do not chew, break, crush or open the capsule prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact.
Patients should be encouraged to take their dose at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.
Continue treatment until disease progression or unacceptable toxicity.

4. How supplied

Abemaciclib is supplied as 50 mg tablets. Drugs can be (re-)ordered by filling in the required fields in the eCRF. Drugs will be shipped to the site's pharmacy. Per shipment, sufficient drug can be ordered to treat the patient until the next response evaluation (and 1 cycle beyond for the first order, to cover the period in between response evaluation and re-supply).
Abemaciclib must be stored at room temperature. For specific storage instructions, please refer to the product label.

5. Dose modifications for toxicity

Please refer to the SPC, or to section 6 Warnings and precautions below.

6. Warnings and precautions

Management of some adverse reactions may require temporary dose interruptions/delays, and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided below.

Abemaciclib recommended dose modifications for adverse reactions

Dose level	*Dose*
Recommended dose	200 mg twice daily
First dose reduction	150 mg twice daily
Second dose reduction	100 mg twice daily
Third dose reduction	50 mg twice daily*

*If further dose reduction below 50 mg/day is required, discontinue the treatment

Dose modification and management – Haematological toxicities[b]:

CTCAE grade[a]	*Action to be taken*
Grade 1 or 2	No dose adjustment is required.
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
Grade 3, recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose.

CTCAE grade[a]	*Action to be taken*
Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

[a] Grading according to CTCAE v4.03

[b] Hematologic toxicities including neutropenia, leukopenia, anemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Patients should be monitored closely for signs of infection, anemia, and bleeding.

Guidelines for Diarrhea Management

At enrollment, patients should receive instructions on the prompt management of diarrhea. In the event of diarrhea, supportive care measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy (e.g. loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- For additional information for diarrhea management and dose modification, use the following table:

Dose modification and management – Diarrhea[a]

CTCAE grade	*Dose modifications*
Grade 1	No dose adjustment is required.
Grade 2	If toxicity does not resolve within 24 hours to ≤Grade 1, 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. Resume at next lower dose.
Grade 3 or 4 or requires hospitalization	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose.

[a] Grading according to CTCAE v4.03

General Guidance for Hepatic Monitoring

Dose Modification and Management — Increased ALT/AST[a]

CTCAE grade	*Dose modifications*
Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN)	No dose adjustment is required.

CTCAE grade	*Dose modifications*
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN) that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1 without increase in total bilirubin above 2 x ULN	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade ≥ 2 (>3.0 x ULN) with total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue abemaciclib.
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.

[a] Grading according to CTCAE v4.03

Hepatic monitoring should be performed in all study participants. Monitor ALT prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. Liver testing including ALT, AST, alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin, gamma-glutamyltransferase (GGT), and creatine kinase (CK) should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of …	**Develops the following elevations:**
ALT or AST <1.5 x ULN	ALT or AST ≥ 5 x ULN or ALT or AST ≥ 3 x ULN concurrent with TBL ≥ 2 x ULN
ALT or AST ≥1.5 x ULN	ALT or AST ≥ 3 x baseline or ALT or AST ≥ 21x baseline concurrent with TBL ≥ 2x ULN

If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests below.

Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [c]	Anti-actin antibody [b]
Hepatis C virus (HCV) testing:	*Epstein-Barr virus (EBV) testing:*
HCV antibody	EBV antibody
HCV RNA [c]	EBV DNA [c]
Hepatitis D virus (HDV) testing:	*Cytomegalovirus (CMV) testing:*
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [c]
HEV IgG antibody	*Herpes simplex virus (HSV) testing:*
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [c]	HSV (Type 1 and 2) DNA [c]
Microbiology	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	

Blood
Urine

[a] Not required if anti-actin antibody is tested.
[b] Not required if anti-smooth muscle antibody (ASMA) is tested.
[c] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

General Guidance for Increases in Serum Creatinine and Assessment of Renal Insufficiency

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). 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.

General Guidance for Interstitial lung disease (ILD)/Pneumonitis events
Interstitial lung disease (ILD) / pneumonitis has been identified as an adverse drug reaction for abemaciclib. Adverse events reported included events such as interstitial lung disease, pneumonitis, obliterative bronchiolitis, organizing pneumonia, pulmonary fibrosis. The majority of events were Grade 1 or Grade 2 with serious cases and fatal events reported.

Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis and please ask patients to report any new or worsening pulmonary symptoms. Symptoms may include hypoxia, cough, dyspnea, or interstitial inflltrates on radiologic exams.; these symptoms should be investigated and treated as per local clinical practice and/or guidelines (including corticosteroids as appropriate). Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Investigations may include imaging such as high resolution computer tomography (HRCT), broncheoalveolar lavage (BAL), and biopsy as clinically indicated (see also Table 7: *refer to dose adjustment table for interstitial lung disease/pneumonitis*).

<u>Dose modification and management – Interstitial Lung Disease/Pneumonitis</u>

CTCAE grade	*Dose modifications*
Grade 1 or 2	No dose adjustment 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 ≤Grade 1. Resume at next lower dose.
Grade 3 or 4	Discontinue abemaciclib

[a] Grading according to CTCAE v4.03

General Guidance for Concomitant Therapy

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites.

CYP3A inducers

Avoid concomitant use of CYP3A inducers and consider alternative agents.

CYP3A inhibitors

Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with coadministered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the abemaciclib dose to 100 mg twice daily or, in the case of ketoconazole, reduce the abemaciclib dose to 50 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily. Avoid grapefruit or grapefruit juice. If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

General Guidance for use of Radiotherapy in Combination with Abemaciclib

Limited data are available with abemaciclib and radiotherapy or alternate dosing schedules (e.g. induction phase). Thus, caution should be exercised with coadministering abemaciclib with radiotherapy.

General Guidance for Venous Thromboembolic Events

VTE has been identified as an ADR for abemaciclib in combination with endocrine therapy. However, in studies with single-agent abemaciclib use in the metastatic breast cancer or other tumor types, including NSCLC, no increased rates of VTEs were observed as compared to the incidence of VTEs for these particular patient populations who were treated with other anticancer agents. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. Venous thromboembolic events have been reported with other CDK4 and 6 inhibitors, and ET is known to be associated with the occurrence of VTEs. Monitor patients for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate.

Dose Modification and Management — Venous Thromboembolic Events

CTCAE Grade	Abemaciclib Dose Modifications
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.

Dose Modification and Management — Nonhematologic Toxicities Excluding Diarrhea, ALT/AST Increased, and ILD/Pneumonitis

CTCAE Grade	Abemaciclib 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

Special populations:
Elderly: no dose adjustment of abemaciclib is required based on age.

Hepatic impairment: no dose adjustments of abemaciclib are required for patients with mild hepatic impairment (total bilirubin ≤1 × upper limit of normal [ULN] and aspartate aminotransferase [AST] >1 × ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST). Insufficient data are available in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) to provide any dose adjustment recommendation. Administer abemaciclib to patients with moderate and severe hepatic impairment only after careful consideration of the potential benefits and risks and with close monitoring of signs of toxicity.

Renal impairment: no dose adjustments of abemacicilib are required for patients with mild to moderate renal impairment (creatinine clearance [CrCl] ≥30 mL/min). Insufficient data are available in patients with severe renal impairment (CrCl <30 mL/min) or requiring haemodialysis to provide any dose adjustment recommendation. Administer abemaciclib to patients with severe renal impairment only after careful consideration of the potential benefits and risks and with close monitoring of signs of toxicity.

Special warnings and precautions:
Infections: since abemaciclib has myelosuppressive properties, it may predispose patients to infections. Infections have been reported at a higher rate in patients treated with abemaciclib in randomized clinical studies compared to patients treated in the respective comparator arm. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate. Physicians should inform patients to promptly report any episodes of fever.

Interactions:
- It is not recommended to consume grapefruit juice while on abemaciclib therapy.
- The concomitant use of strong CYP3A inhibitors including, but not limited to: clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice, should be avoided. No dose adjustments are needed for mild and moderate CYP3A4 inhibitors.

- The concomitant use of strong CYP3A inducers including, but not limited to: carbamazepine, enzalutamide, phenytoin, rifampin, and St. John's Wort should be avoided. No dose adjustments are needed for moderate CYP3A4 inducers.
- Administration of abemaciclib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin), BCRP (e.g., rosuvastatin, sulfasalazine) or OCT (e.g., metformin) may increase their therapeutic effect and adverse reactions.

Women of Child Bearing Potential and/or Use of Contraceptive Methods

Based on findings in animals, abemaciclib can cause fetal harm when administered to a pregnant woman. In animal studies, abemaciclib was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on the area under the plasma concentration versus time curve (AUC) at the recommended human dose. Therefore, teratogenicity is considered an important potential risk for abemaciclib. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. Additionally, there are no available data on effects of breastfeeding. Advise a nursing woman to discontinue breastfeeding during treatment with abemaciclib.

- A female of childbearing potential, must have a negative serum pregnancy test within 7 days of the first dose of abemaciclib and agree to use a highly effective contraception method during the treatment period and for 3 weeks following the last dose of abemaciclib.
- Contraceptive methods may include an intrauterine device [IUD] or barrier method. If condoms are used as a barrier method, a spermicidal agent should be added as a double barrier protection.
- Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported. If a patient or spouse/partner is determined to be pregnant following abemaciclib initiation, she must discontinue treatment immediately. Data on fetal outcome and breast-feeding are to be collected for regulatory reporting and drug safety evaluation.