IBRELYN
(Palbociclib Capsules 75mg, 100mg and 125mg)

DESCRIPTION:
IBRELYN 75: Yellow colored granular powder filled in size '2' hard gelatin capsule of light orange color cap imprinted with 'NAT' and light orange colour body imprinted with '75'.
IBRELYN 100: Yellow colored granular powder filled in size '1' hard gelatin capsule of caramel color cap imprinted with 'NAT' and light orange colour body imprinted with '100'.
IBRELYN 125: Yellow colored granular powder filled in size '0' hard gelatin capsule of caramel color cap imprinted with 'NAT' and caramel colour body imprinted with '125'.

COMPOSITION: *Capsule source: Bovine*
IBRELYN 75: Each hard gelatin capsule contains 75mg of Palbociclib.
IBRELYN 100: Each hard gelatin capsule contains 100mg of Palbociclib.
IBRELYN 125: Each hard gelatin capsule contains 125mg of Palbociclib.

PHARMACODYNAMICS:
Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE33.

Mechanism of action
Palbociclib is a highly selective, reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signalling pathways which lead to cellular proliferation.

Pharmacodynamic effects
Through inhibition of CDK4/6, palbociclib reduced cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high activity against luminal breast cancers, particularly ER-positive breast cancers. In the cell lines tested, the loss of retinoblastoma (Rb) was associated with loss of palbociclib activity. However, in a follow-up study with fresh tumour samples, no relation between RB1 expression and tumour response was observed. Similarly, no relation was observed when studying the response to palbociclib in *in vivo* models with patient-derived xenografts (PDX models).

Cardiac Electrophysiology
The effect of palbociclib on the QT interval corrected for heart rate (QTc) interval was evaluated using time matched electrocardiogram (ECG) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with advanced breast cancer. Palbociclib did not prolong the QTc to any clinically relevant extent at the recommended dose of 125 mg daily (Schedule 3/1).

PHARMACOKINETICS:
The pharmacokinetics of palbociclib were characterized in patients with solid tumours including advanced breast cancer and in healthy subjects.

Absorption
The mean Cmax of palbociclib is generally observed between 6 to 12 hours following oral administration. The mean absolute bioavailability of palbociclib capsules after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the area under the curve (AUC) and Cmax increase proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. With repeated once daily administration, palbociclib accumulates with a median accumulation ratio of 2.4 (range 1.5 to 4.2).

Food effect: Palbociclib absorption and exposure were very low in approximately 13% of the population under the fasted condition. Food intake increased the palbociclib exposure in this small subset of the population, but did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Compared to palbociclib capsules given under overnight fasted conditions, the AUC_{INF} and Cmax of palbociclib increased by 21% and 38%, respectively, when given with high-fat food by 12% and 27%, respectively, when given with low-fat food, and by 13% and 24%, respectively, when moderate-fat food was given 1 hour before and 2 hours after palbociclib dosing. In addition, food intake significantly reduced the intersubject and intrasubject variability of palbociclib exposure. Based on these results, palbociclib should be taken with food.

Distribution
Binding of palbociclib to human plasma proteins *in vitro* was approximately 85%, with no concentration dependence. The mean fraction unbound (f_u) of palbociclib in human plasma *in vivo* increased incrementally with worsening hepatic function. There was no obvious trend in the mean palbociclib f_u in human plasma *in vivo* with worsening renal function. *In vitro*, the uptake of palbociclib into human hepatocytes occurred mainly via passive diffusion. Palbociclib is not a substrate of OATP1B1 or OATP1B3.

Biotransformation
In vitro and *in vivo* studies indicated that palbociclib undergoes hepatic metabolism in humans. Following oral administration of a single 125 mg dose of [^{14}C]palbociclib to humans, the major primary metabolic pathways for palbociclib involved oxidation and sulfonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma. The majority of the material was excreted as metabolites. In faeces, the sulfamic acid conjugate of palbociclib was the major drug-related component, accounting for 25.8% of the administered dose. *In vitro* studies with human hepatocytes, liver cytosolic and S9 fractions, and recombinant sulphotransferase (SULT) enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

Elimination
The geometric mean apparent oral clearance (CL/F) of palbociclib was 63 L/h, and the mean plasma elimination half-life was 28.8 hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [^{14}C]palbociclib, a median of 92% of the total administered radioactive dose was recovered in 15 days; faeces (74% of dose) was the major route of excretion, with 17% of the dose recovered in urine. Excretion of unchanged palbociclib in faeces and urine was 2% and 7% of the administered dose, respectively.

In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations.

In vitro evaluations indicate that palbociclib has low potential to inhibit the activities of organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, and bile salt export pump (BSEP) at clinically relevant concentrations.

Special Populations
Age, Gender, and Body Weight
Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age range from 22 to 89 years, and body weight range from 38 to 123 kg), gender had no effect on the exposure of palbociclib, and age and body weight had no clinically important effect on the exposure of palbociclib.

Paediatric Population
Pharmacokinetics of palbociclib capsules have not been evaluated in patients <18 years of age.

Hepatic Impairment
Data from a pharmacokinetic trial in subjects with varying degrees of hepatic impairment indicate that palbociclib unbound exposure (unbound AUC_{INF}) decreased 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child- Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function.
Peak palbociclib unbound exposure (unbound Cmax) was increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function. In addition, based on a population pharmacokinetic analysis that included 183 patients with advanced cancer, where 40 patients had mild hepatic impairment based on National Cancer Institute (NCI) classification (total bilirubin ≤ Upper Limit of Normal (ULN) and Aspartate Aminotransferase (AST) > ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the pharmacokinetics of palbociclib.

Renal Impairment
Data from a pharmacokinetic trial in subjects with varying degrees of renal impairment indicate that total palbociclib exposure (AUC_{INF}) increased by 39%, 42%, and 31% with mild (60 mL/min ≤CrCl <90 mL/min), moderate (30 mL/min ≤CrCl <60 mL/min), and severe (CrCl <30 mL/min) renal impairment, respectively, relative to subjects with normal (CrCl≥90 mL/min) renal function. Peak palbociclib exposure (Cmax) increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. In addition, based on a population pharmacokinetic analysis that included 183 patients with advanced cancer, where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the pharmacokinetics of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

Ethnicity
In a pharmacokinetic study in healthy volunteers, palbociclib AUC_{inf} and Cmax values were 30% and 35% higher, respectively, in Japanese subjects compared with non-Asian subjects after a single oral dose. However, this finding was not reproduced consistently in subsequent studies in Japanese or Asian breast cancer patients after multiple dosing. Based on an analysis of the cumulative pharmacokinetic, safety and efficacy data across Asian and non-Asian populations, no dose adjustment based on Asian race is considered necessary.

INDICATION:

Palbociclib capsules are indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women, or
- fulvestrant in women who have received prior endocrine therapy.

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

RECOMMENDED DOSAGE:

Recommended Dose and Schedule:
The recommended dose of palbociclib capsules is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib capsules should be taken with food [see Pharmacodynamics].

Administer the recommended dose of an aromatase inhibitor when given with palbociclib capsules. Please refer to the full prescribing information for the aromatase inhibitor being used.

When given with palbociclib capsules, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter. Please refer to the full prescribing information of fulvestrant.

Patients should be encouraged to take their dose of palbociclib capsules at approximately the same time each day.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Palbociclib capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). Capsules should not be ingested if they are broken, cracked, or otherwise not intact.

Pre/perimenopausal women treated with the combination palbociclib capsules plus fulvestrant therapy should also be treated with luteinizing hormone releasing hormone (LHRH) agonists according to current clinical practice standards.

Dose Modification:
The recommended dose modifications for adverse reactions are listed in Tables 1, 2 and 3.

Table 1. Recommended Dose Modification for Adverse Reactions

Dose Level	Dose
Recommended starting dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day*
* If further dose reduction below 75 mg/day is required, discontinue the treatment	

Table 2. Dose Modification and Management[a] – Hematologic Toxicities

Monitor complete blood counts prior to the start of palbociclib capsules therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.	
CTCAE Grade	**Dose Modifications**
Grade 1 or 2	No dose adjustment is required.
Grade 3	Day 1 of cycle: Withhold palbociclib capsules, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the same dose. Day 15 of first 2 cycles: If Grade 3 on Day 15, continue palbociclib capsules at current dose to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.
Grade 3 neutropenia[b] with fever ≥38.5°C and/or infection	At any time: Withhold palbociclib capsules until recovery to Grade ≤2. Resume at the *next lower dose.*
Grade 4	At any time: Withhold palbociclib capsules until recovery to Grade ≤2. Resume at the *next lower dose.*
Grading according to CTCAE 4.0. CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal. [a] Table applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections). [b] Absolute neutrophil count (ANC): Grade 1: ANC <LLN - 1500/mm3; Grade 2: ANC 1000 - <1500/mm3; Grade 3: ANC 500 - <1000/mm3; Grade 4: ANC <500/mm3	

Table 3. Dose Modification and Management – Non-Hematologic Toxicities

CTCAE Grade	**Dose Modifications**
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 non-hematologic toxicity (if persisting despite optimal medical treatment)	Withhold until symptoms resolve to: • Grade ≤1; • Grade ≤2 (if not considered a safety risk for the patient) Resume at the next lower dose.
Grading according to CTCAE 4.0. CTCAE=Common Terminology Criteria for Adverse Events.	

Permanently discontinue palbociclib capsules in patients with severe interstitial lung disease (ILD)/pneumonitis.

Refer to the full prescribing information for co-administered endocrine therapy dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications.

Dose Modifications for Use with Strong CYP3A Inhibitors:
Avoid concomitant use of strong CYP3A inhibitors and consider an alternative concomitant medication with no or minimal CYP3A inhibition. If patients must be co-administered a strong CYP3A inhibitor, reduce the palbociclib capsules dose to 75 mg once daily. If the strong inhibitor is discontinued, increase the palbociclib capsules dose (after 3 to 5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor [see Interactions with other medicaments and Pharmacokinetics].

Dose Modifications for Hepatic Impairment:
No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of palbociclib capsules is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days [see Pharmacokinetics].

ROUTE OF ADMINISTRATION: Oral

CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any of the excipients.
Use of preparations containing St. John's Wort.

WARNINGS & PRECAUTIONS:

Pre/Perimenopausal Women

Ovarian ablation or suppression with an LHRH agonist is mandatory when pre/perimenopausal women are administered Palbociclib Capsule in combination with an aromatase inhibitor, due to the mechanism of action of aromatase inhibitors. Palbociclib in combination with fulvestrant in pre/perimenopausal women has only been studied in combination with an LHRH agonist.

Critical Visceral Disease

The efficacy and safety of palbociclib have not been studied in patients with critical visceral disease.

Haematological Disorders

Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia. Appropriate monitoring should be performed.

Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with Palbociclib Capsule when taken in combination with endocrine therapy.
Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.
Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspnoea). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, interrupt Palbociclib Capsule immediately and evaluate the patient. Permanently discontinue Palbociclib Capsule in patients with severe ILD or pneumonitis.

Infections

Since Palbociclib Capsule has myelosuppressive properties, it may predispose patients to infections.
Infections have been reported at a higher rate in patients treated with Palbociclib Capsule in randomised clinical studies compared to patients treated in the respective comparator arm. Grade 3 and Grade 4 infections occurred in patients treated with Palbociclib Capsule in any combination.
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.

Hepatic Impairment

Administer Palbociclib Capsule with caution to patients with moderate or severe hepatic impairment, with close monitoring of signs of toxicity.

Renal Impairment

Administer Palbociclib Capsule with caution to patients with moderate or severe renal impairment, with close monitoring of signs of toxicity.

Concomitant Treatment with Inhibitors or Inducers of CYP3A4

Strong inhibitors of CYP3A4 may lead to increased toxicity. Concomitant use of strong CYP3A inhibitors during treatment with palbociclib should be avoided. Coadministration should only be considered after careful evaluation of the potential benefits and risks. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the Palbociclib Capsule dose to 75 mg once daily. When the strong inhibitor is discontinued, increase the Palbociclib Capsule dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.
Coadministration of CYP3A inducers may lead to decreased palbociclib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of palbociclib with strong CYP3A4 inducers should be avoided. No dose adjustments are required for coadministration of palbociclib with moderate CYP3A inducers.

Women of Childbearing Potential or Their Partners

Women of childbearing potential or their male partners must use a highly effective method of contraception while taking Palbociclib Capsule.

Lactose

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

Sodium

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

Effects on Ability to Drive and Use Machine

Palbociclib has minor influence on the ability to drive and use machines. However, Palbociclib may cause fatigue and patients should exercise caution when driving or using machines.

INTERACTION WITH OTHER MEDICAMENTS:

Palbociclib is primarily metabolised by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. *In vivo*, Palbociclib is a weak, time dependent inhibitor of CYP3A.

Effects of Other Medicinal Products on the Pharmacokinetics of Palbociclib

Effect of CYP3A Inhibitors

Coadministration of multiple 200 mg doses of itraconazole with a single 125 mg palbociclib dose increased palbociclib total exposure (AUC_{inf}) and the peak concentration (Cmax)

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 CYP3A inhibitors.

Effect of CYP3A Inducers
Coadministration of multiple 600 mg doses of rifampin with a single 125 mg palbociclib dose decreased palbociclib AUC_{inf} and Cmax.
The concomitant use of strong CYP3A inducers including, but not limited to: carbamazepine, enzalutamide, phenytoin, rifampin, and St. John's Wort should be avoided.
Coadministration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg Palbociclib Capsule dose decreased palbociclib AUC_{inf} and Cmax. No dose adjustments are required for moderate CYP3A inducers.

Effect of Acid Reducing Agents
Under fed conditions (intake of a moderate-fat meal), coadministration of multiple doses of the proton pump inhibitor (PPI) rabeprazole with a single dose of 125 mg Palbociclib Capsule decreased palbociclib Cmax, but had limited impact on AUC_{inf} (decrease) compared with a single dose of 125 mg Palbociclib Capsule administered alone.
Under fasting conditions, the coadministration of multiple doses of the proton pump inhibitor (PPI) rabeprazole with a single dose of 125 mg Palbociclib Capsule decreased palbociclib AUC_{inf} and Cmax. Therefore, Palbociclib Capsule should be taken with food, preferably a meal.
Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, no clinically relevant effect of H2-receptor antagonists or local antacids on palbociclib exposure is expected when palbociclib is taken with food.

Effects of Palbociclib on the Pharmacokinetics of Other Medicinal Products
Palbociclib is a weak, time-dependent inhibitor of CYP3A following daily 125 mg dosing at steady state. Coadministration of multiple doses of palbociclib with midazolam increased the midazolam AUC_{inf} and Cmax values.
The dose of sensitive CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) may need to be reduced when coadministered with Palbociclib Capsule as Palbociclib Capsule may increase their exposure.

Drug-drug Interaction between Palbociclib and Letrozole
Data shows that there was no drug interaction between palbociclib and letrozole when the 2 medicinal products were coadministered.

Effect of Tamoxifen on Palbociclib Exposure
Data indicates that palbociclib exposures were comparable when a single dose of palbociclib was coadministered with multiple doses of tamoxifen and when palbociclib was given alone.

Drug-drug Interaction between Palbociclib and Fulvestrant
Data shows that there was no clinically relevant drug interaction between palbociclib and fulvestrant when the two medicinal products were coadministered.

Drug-drug Interaction between Palbociclib and Oral Contraceptives
There is no data available for use of palbociclib with oral contraceptives

Data with Transporters
Based on data, palbociclib is predicted to inhibit intestinal P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) mediated transport. Therefore, administration of palbociclib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine) or BCRP (e.g., pravastatin, rosuvastatin, sulfasalazine) may increase their therapeutic effect and adverse reactions.

Based on data, palbociclib may inhibit the uptake transporter organic cationic transporter OCT1 and then may increase the exposure of medical product substrates of this transporter (e.g., metformin).

USE IN PREGNANCY & LACTATION:

Women of Childbearing Potential/Contraception
Females of childbearing potential who are receiving this medicinal product, or their male partners should use adequate contraceptive methods (e.g., double-barrier contraception) during therapy and for at least 3 weeks or 14 weeks after completing therapy for females and males, respectively.

Pregnancy
There are no or limited amount of data from the use of palbociclib in pregnant women. Studies in animals have shown reproductive toxicity. Palbociclib is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
No studies have been conducted in humans or animals to assess the effect of palbociclib on milk production, its presence in breast milk, or its effects on the breast-fed child. It is unknown whether palbociclib is excreted in human milk. Patients receiving palbociclib should not breast feed.

Fertility
There were no effects on oestrous cycle (female rats) or mating and fertility in rats (male or female) in nonclinical reproductive studies. However, no clinical data have been obtained on fertility in humans. Based on male reproductive organ findings (seminiferous tubule degeneration in testis, epididymal hypospermia, lower sperm motility and density, and decreased prostate secretion) in nonclinical safety studies, male fertility may be compromised by treatment with palbociclib. Thus, men may consider sperm preservation prior to beginning therapy with Palbociclib.

SIDE EFFECTS:

Summary of the Safety Profile

The most common adverse reactions of any grade reported in patients receiving palbociclib were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anaemia, diarrhoea, alopecia and thrombocytopenia. The most common Grade ≥ 3 adverse reactions of palbociclib were neutropenia, leukopenia, infections, anaemia, aspartate aminotransferase (AST) increased, fatigue, and alanine aminotransferase (ALT) increased.

Tabulated List of Adverse Reactions

Table 4 reports the adverse reactions. The median duration of palbociclib treatment across at the time of the final overall survival (OS) analysis was 14.8 months.

The adverse reactions are listed by system organ class and frequency category. Frequency categories are defined as: very common, common, and uncommon. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4: Adverse Reactions:

System organ class **Frequency** **Preferred term**[a]
Infections and infestations
Very common
Infections[b]
Blood and lymphatic system disorders
Very common
Neutropenia[c]
Leukopenia[d]
Anaemia[e]
Thrombocytopenia[f]
Common
Febrile neutropenia
Metabolism and nutrition disorders
Very common
Decreased appetite
Nervous system disorders
Common
Dysgeusia
Eye disorders
Common
Vision blurred
Lacrimation increased
Dry eye
Respiratory, thoracic, and mediastinal disorders
Common
Epistaxis
ILD/pneumonitis*,[i]
Gastrointestinal disorders
Very common
Stomatitis[g]
Nausea
Diarrhoea
Vomiting
Skin and subcutaneous tissue disorders
Very common
Rash[h]
Alopecia
Dry skin
Uncommon
Cutaneous lupus erythematosus*
General disorders and administration site conditions
Very common
Fatigue
Asthenia
Pyrexia
Investigations
Very common
ALT increased
AST increased
ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; ILD = Interstitial lung disease. * Adverse Drug Reaction (ADR) [a] Preferred Terms (PTs) are listed according to MedDRA 17.1. [b] Infections includes all PTs that are part of the System Organ Class Infections and Infestations. [c] Neutropenia includes the following PTs: Neutropenia, Neutrophil count decreased.

[d] Leukopenia includes the following PTs: Leukopenia, White blood cell count decreased.
[e] Anaemia includes the following PTs: Anaemia, Haemoglobin decreased, Haematocrit decreased.
[f] Thrombocytopenia includes the following PTs: Thrombocytopenia, Platelet count decreased.
[g] Stomatitis includes the following PTs: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.
[h] Rash includes the following PTs: Rash, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash papular, Dermatitis, Dermatitis acneiform, Toxic skin eruption.
[I] ILD/pneumonitis includes any reported PTs that are part of the Standardised MedDRA Query Interstitial Lung Disease (narrow).

Description of Selected Adverse Reactions
Overall, neutropenia of any grade was reported in patients receiving Palbociclib Capsule regardless of the combination, with Grade 3 neutropenia being reported, and Grade 4 neutropenia being reported. The median time to first episode of any grade neutropenia was 15 days and the median duration of Grade ≥ 3 neutropenia was 7 days.
Febrile neutropenia has been reported in patients receiving Palbociclib Capsule in combination with fulvestrant and in patients receiving palbociclib in combination with letrozole.
Febrile neutropenia has been reported in patients exposed to Palbociclib Capsule across the overall clinical programme.

SYMPTOMS AND TREATMENT OF OVERDOSE:
In the event of a palbociclib overdose, both gastrointestinal (e.g., nausea, vomiting) and haematological (e.g., neutropenia) toxicity may occur and general supportive care should be provided.

INCOMPATIBILITIES: Not Applicable

STORAGE CONDITIONS: Store below 30˚C.

SHELF LIFE: 48 months

PACK SIZE:
Palbociclib capsules is packed in the following package configurations:
- One HDPE Bottle of 21 Capsules
- 10 capsules in blister such 3 blisters packed in outer carton
- 7 capsules in blister such 1 blister packed in outer carton

MANUFACTURER:
Natco Pharma Limited (Pharma-Division)
Kothur – 509228, Rangareddy District, Telangana, India.

PRODUCT REGISTRATION HOLDER:
Duopharma HAPI Sdn Bhd.
No.2 Jalan Saudagar U1/16, Zon Perindustrian Hicom Glenmarie,
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