ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Copiktra 15 mg hard capsules
Copiktra 25 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Copiktra 15 mg hard capsules

Each hard capsule contains 15 mg duvelisib (as monohydrate)

Copiktra 25 mg hard capsules

Each hard capsule contains 25 mg duvelisib (as monohydrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Copiktra 15 mg hard capsules

Opaque, pink, size no. 2, hard gelatin capsules marked “duv 15 mg” in black ink. Dimensions: approx. 18 mm x 6 mm (length and diameter).

Copiktra 25 mg hard capsules

Opaque, white to off-white and orange, size no. 2, hard gelatin capsules marked “duv 25 mg” in black ink. Dimensions: approx. 18 mm x 6 mm (length and diameter).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Copiktra monotherapy is indicated for the treatment of adult patients with:

- Relapsed or refractory chronic lymphocytic leukaemia (CLL) after at least two prior therapies. (see section 4.4.and 5.1).
- Follicular lymphoma (FL) that is refractory to at least two prior systemic therapies. (see section 4.4.and 5.1).

4.2 Posology and method of administration

Treatment with Copiktra should be conducted by a physician experienced in the use of anti-cancer therapies.

Posology

The recommended dose is 25 mg duvelisib twice daily. A cycle consists of 28 days. Treatment should be continued until disease progression or unacceptable toxicity.

Delayed or missed doses
Patients should be advised that if a dose is missed by less than 6 hours, the missed dose should be taken right away and the next dose should be taken as usual. If a dose is missed by more than 6 hours, patients should be advised to wait and to take the next dose at the usual time.

Dose modification for concomitant use with CYP3A4 inhibitors
The dose of Copiktra should be reduced to 15 mg twice daily when co-administered with strong CYP3A4 inhibitors (e.g. ketoconazole) [see section 4.5]. No dose adjustment is necessary when co-administered with moderate CYP3A4 inhibitors (e.g. fluconazole) but potential adverse reactions of duvelisib should be closely monitored.

Dose modifications for adverse reactions
Toxicities should be managed as per Table 1 with dose reduction, treatment hold, or discontinuation of Copiktra.

Table 1: Copiktra dose modifications and toxicity management

Toxicity	**Adverse reaction grade**	**Recommended management**
Nonhematologic adverse reactions		
Infections	Grade 3 or higher infection	• Withhold Copiktra until resolved • Resume at the same or reduced dose (25 mg or 15 mg twice daily)
	Clinical CMV infection or viremia (positive PCR or antigen test)	• Withhold Copiktra until resolved • Resume at the same or reduced dose (25 mg or 15 mg twice daily) • If Copiktra is resumed, monitor patients for CMV reactivation (by PCR or antigen test) at least monthly. In clinical studies iNHL, FL (IPI-145-06) and CLL/SLL (IPI-145-07 the outcome of starting at same dose or reduction are comparable
	PJP	• For suspected PJP, withhold Copiktra until evaluated • For confirmed PJP, discontinue Copiktra
Non-infectious diarrhoea or colitis	Mild/moderate diarrhoea (Grade 1-2, up to 6 stools per day over baseline) and responsive to anti-diarrhoeal agents, OR Asymptomatic (Grade 1) colitis	• No change in dose • Initiate supportive therapy with anti-diarrhoeal agents as appropriate • Monitor at least weekly until resolved
	Mild/moderate diarrhoea (Grade 1-2, up to 6 stools per day over baseline) and unresponsive to anti-diarrhoeal agents	• Withhold Copiktra until resolved • Initiate supportive therapy with enteric acting steroids (e.g., budesonide) • Monitor at least weekly until resolved • Resume at a reduced dose (15 mg twice daily)

Table 1: Copiktra dose modifications and toxicity management

Toxicity	Adverse reaction grade	Recommended management
	Abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs, OR Severe diarrhoea (Grade 3, >6 stools per day over baseline)	• Withhold Copiktra until resolved • Initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids • Monitor at least weekly until resolved • Resume at a reduced dose (15 mg twice daily) • For recurrent Grade 3 diarrhoea or recurrent colitis of any grade, discontinue Copiktra
	Life-threatening	• Discontinue Copiktra
Cutaneous reactions	Grade 1-2	• No change in dose • Initiate supportive care with emollients, anti-histamines (for pruritus), or topical steroids • Monitor closely
	Grade 3	• Withhold Copiktra until resolved • Review all concomitant medications and discontinue any medication potentially contributing to the event • Initiate supportive care with steroids (topical or systemic) and antihistamines for pruritus • Monitor at least weekly until resolved • Resume at reduced dose (15 mg twice daily) • If severe cutaneous reaction does not improve, worsens, or recurs, discontinue Copiktra
	Life-threatening	• Discontinue Copiktra
	SJS, TEN, DRESS (any grade)	• Discontinue Copiktra for any grade
Pneumonitis without suspected infectious cause	Moderate (Grade 2) symptomatic pneumonitis	• Withhold Copiktra • Treat with systemic steroid therapy • If pneumonitis recovers to Grade 0 or 1, Copiktra may be resumed at reduced dose (15 mg twice daily) • If non-infectious pneumonitis recurs or patient does not respond to steroid therapy, discontinue Copiktra
	Severe (Grade 3) or life-threatening pneumonitis	• Discontinue Copiktra • Treat with systemic steroid therapy
ALT/AST elevation	3 to 5 × upper limit of normal (ULN) (Grade 2)	• Maintain Copiktra dose • Monitor at least weekly until return to < 3 × ULN
	> 5 to 20 × ULN (Grade 3)	• Withhold Copiktra and monitor at least weekly until return to < 3 × ULN • Resume Copiktra at same dose (25 mg twice daily) for first occurrence or at a reduced dose (15 mg twice daily) for subsequent occurrence
	> 20 × ULN (Grade 4)	• Discontinue Copiktra

Table 1: Copiktra dose modifications and toxicity management

Toxicity	Adverse reaction grade	Recommended management
Haematologic adverse reactions		
Neutropenia	Absolute neutrophil count (ANC) 0.5 to 1.0 × 10^9 /L	• Maintain Copiktra dose • Monitor ANC at least weekly
	ANC less than 0.5 × 10^9 /L	• Withhold Copiktra. • Monitor ANC until > 0.5 × 10^9 /L • Resume Copiktra at same dose (25 mg twice daily) for first occurrence or at a reduced dose (15 mg twice daily) for subsequent occurrence
Thrombocytopenia	Platelet count 25 to < 50 × 10^9 /L (Grade 3) with Grade 1 bleeding	• No change in dose • Monitor platelet counts at least weekly
	Platelet count 25 to < 50 × 10^9 /L (Grade 3) with Grade 2 bleeding or Platelet count < 25 × 10^9 /L (Grade 4)	• Withhold Copiktra • Monitor platelet counts until ≥ 25 × 10^9 /L and resolution of bleeding (if applicable) • Resume Copiktra at the same dose (25 mg twice daily) for first occurrence or resume at a reduced dose (15 mg twice daily) for subsequent occurrence

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CMV = cytomegalovirus; DRESS = drug reaction with eosinophilia and systemic systems; PCR = polymerase chain reaction; PJP = *Pneumocystis jirovecii* pneumonia; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal
Note: Doses withheld for > 42 days due to treatment-related toxicity will result in permanent discontinuation from treatment

Special populations

Elderly
No specific dose adjustment is required for elderly patients (aged ≥ 65 years) (see section 5.2).

Renal impairment
No dose adjustment is required for patients with mild and moderate renal impairment. No data are available for severe and end-stage renal impairment with or without dialysis, (see sections 5.2).

Hepatic impairment
No dose adjustment of the starting dose is required for patients with hepatic impairment Child Pugh Class A, B, and C (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of duvelisib in children aged 0 to 18 years has not been established. No data are available.
There is no relevant use of duvelisib in the paediatric population for the indication of CLL and FL.

Method of administration

Copiktra is for oral use and can be taken with or without food. The capsules should be swallowed whole. Patients should be advised not to open, break, or chew the capsules.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

General

The safety and efficacy of duvelisib after prior idelalisib use has not been established.

Infections

Serious, including fatal infections have occurred in patients receiving duvelisib. The most common serious infections were pneumonia, sepsis, and lower respiratory infections. Median time to onset of any grade infection was 3 months with 75% of cases occurring within 6 months (see section 4.8).

Any infections should be treated prior to initiation of duvelisib. Patients should be monitored for infection, including respiratory signs and symptoms, throughout treatment. Patients should be advised to report any new or worsening infections promptly (see Table 1 for management).

Serious, including fatal, PJP pneumonia occurred in patients taking duvelisib. Prophylaxis for PJP should, therefore, be administered to all patients (see Table 1). CMV reactivation/infection occurred in patients taking duvelisib. Prophylactic antivirals should be considered during treatment to prevent CMV infection including CMV reactivation (see Table 1).

Recommended prophylaxis
Any infections should be treated prior to initiation of duvelisib . Patients should be monitored for infection, including respiratory signs and symptoms, throughout treatment. Patients should be advised to report any new or worsening infections promptly (see Table 1 for management).

Prophylaxis for PJP should be provided during treatment with duvelisib. Following completion of duvelisib treatment, PJP prophylaxis should be continued until the absolute CD4+ T cell count is greater than 200 cells/μL.

Duvelisib should be withheld in patients with suspected PJP of any grade and discontinued if PJP is confirmed.

Prophylactic antivirals should be considered during duvelisib treatment to prevent CMV infection including CMV reactivation.

Diarrhoea or colitis

Serious, including fatal diarrhoea or colitis occurred in patients receiving duvelisib. The median time to onset of any grade diarrhoea or colitis was 4 months, with 75% of cases occurring by 8 months. The median event duration was 0.5 months. Patients should be advised to report any new or worsening diarrhoea (see Table 1 for management) (see section 4.8).

Cutaneous reactions

Serious, including fatal cutaneous reactions occurred in patients receiving duvelisib. Fatal cases included drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN). Median time to onset of any grade cutaneous reaction was 3 months, with a median event duration of 1 month (see section 4.8).

Presenting features for the serious cutaneous events were primarily described as pruritic, erythematous, or maculo-papular. Less common presenting features include exanthem, desquamation, erythroderma, skin exfoliation, keratinocyte necrosis, and papular rash. Patients should be advised to report any new or worsening cutaneous reactions (see Table 1 for management). All concomitant medicinal products should be reviewed and any medicinal products potentially contributing to the event should be discontinued.

Pneumonitis

Serious, including fatal, pneumonitis without an apparent infectious cause occurred in patients receiving duvelisib. Median time to onset of any grade pneumonitis was 4 months with 75% of cases occurring within 9 months (see section 4.8). The median event duration was 1 month, with 75% of cases resolving by 2 months (see Table 1 for management).

Hepatotoxicity

Grade 3 and 4 ALT and/or AST elevation developed in patients receiving duvelisib. Two percent of patients had both an ALT or AST greater than 3 x ULN and total bilirubin greater than 2 x ULN. Median time to onset of any grade transaminase elevation was 2 months with a median event duration of 1 month. Hepatic function should be monitored during treatment with duvelisib especially during the first three months of therapy on a monthly basis. This guideline applies for the patients who have only ALT and AST elevation.

Neutropenia

Grade 3 or 4 neutropenia occurred in patients receiving duvelisib. The median time to onset of Grade ≥ 3 neutropenia was 2 months with 75% of cases occurring within 4 months. Neutrophil counts should be monitored at least every 2 weeks for the first 2 months of duvelisib.

CYP3A4 inducers

Duvelisib exposure may be reduced when co-administered with strong CYP3A inducers. Since a reduction in duvelisib plasma concentrations may result in decreased efficacy, co-administration of duvelisib with strong CYP3A inducers should be avoided (see section 4.5).

CYP3A substrates

Duvelisib and its major metabolite, IPI-656, are strong CYP3A4 inhibitors. Thus, duvelisib has the potential to interact with medicinal products that are metabolised by CYP3A, which may lead to increased serum concentrations of the other product (see section 4.5). When duvelisib is co-administered with other medicinal products, the Summary of Product Characteristics (SmPC) for the other medicinal product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors. Concomitant treatment of duvelisib with sensitive CYP3A substrates should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on duvelisib pharmacokinetics

Strong and moderate CYP3A4 inducers
Co-administration of 600 mg once daily rifampin, a strong CYP3A inducer, for 7 days with a single oral 25 mg duvelisib dose in healthy adults (N = 13) decreased duvelisib C_{max} by 66% and AUC by 82%. Co-administration with a strong CYP3A inducer decreases duvelisib area under the curve (AUC) (see section 5.2), which may reduce duvelisib efficacy. Co-administration of duvelisib with strong CYP3A4 inducers (e.g., apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort) should be avoided.

Co-administration of 200 mg twice daily etravirine, a moderate CYP3A inducer, for 10 days with a single oral 25 mg duvelisib dose in healthy adults (N = 20) decreased duvelisib C_{max} by 16% and AUC by 35%. Co-administration of duvelisib with moderate CYP3A inducers decreases AUC of duvelisib to less than 1.5-fold and dose reduction is not recommended. Examples of moderate CYP3A4 inducers are bosentan, efavirenz, etravirine, phenobarbital, primidone. If a moderate CYP3A4 inducer must be

used, the patient should be closely monitored for potential lack of efficacy. Examples: bosentan, efavirenz, etravirine, phenobarbital, primidone.

Strong and moderate CYP3A inhibitors
Co-administration of a strong CYP3A inhibitor ketoconazole (at 200 mg twice daily (BID) for 5 days), with a single oral 10 mg dose of duvelisib in healthy adults (n= 16) increased duvelisib C_{max} by 1.7-fold and AUC by 4-fold. Due to time-dependent CYP3A4 auto-inhibition, duvelisib susceptibility to moderate and strong CYP3A4 inhibitors is decreased under steady-state conditions. Based on physiologically-based pharmacokinetic (PBPK) modelling and simulation , the increase in exposure to duvelisib is estimated to be ~1.6-fold at steady state in cancer patients when concomitantly used with strong CYP3A4 inhibitors such as ketoconazole and itraconazole.

Duvelisib dose should be reduced to 15 mg twice daily when co-administered with a strong CYP3A4 inhibitor (see section 4.2) (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodon, cobicistat, voriconazole and posaconazole, and grapefruit juice).

PBPK modelling and simulation estimated no clinically significant effect on duvelisib exposures from concomitantly used moderate CYP3A4 inhibitors. Dose reduction of duvelisib is not necessary when co-administered with moderate CYP3A4 inhibitors (see section 4.2) (e.g., aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil)

<u>Effect of duvelisib on the pharmacokinetics of other medicinal products</u>

CYP3A4 substrates
Co-administration of multiple doses of duvelisib 25 mg BID for 5 days with single oral 2 mg midazolam, a sensitive CYP3A4 substrate, in healthy adults (N = 14), increased in the midazolam AUC by 4.3-fold and C_{max} by 2.2-fold. PBPK simulations in cancer patients under steady state conditions have shown that the C_{max} and AUC of midazolam would increase by approximately 2.5-fold and ≥5- fold respectively. Co-administration of midazolam with duvelisib should be avoided.

Duvelisib and its major metabolite, IPI-656, are strong CYP3A4 inhibitors. Dose reduction of CYP3A4 substrate should be considered when co-administered with duvelisib,especially for medicinal products with narrow therapeutic index. Patients should be monitored for signs of toxicities of the co-administered sensitive CYP3A substrate. Examples of sensitive substrates include: alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan. Examples of moderately sensitive substrsates include: alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil. This list is not exhaustive and is intended to serve as guidance only. The SmPC for the other product should be consulted for recommendations regarding co-administration with CYP3A4 inhibitors (see section 4.4).

Hormonal contraceptives
It is unknown whether duvelisib reduces the effectiveness of hormonal contraceptives. Therefore, women using hormonal contraceptives should be advised to add a barrier method as a second form of contraception (see section 4.6).

Proton pump inhibitors
Population Pharmacokinetic (POPPK) analysis has shown that proton pump inhibitors (PPI) do not affect the exposure of COPIKTRA. PPI may be co-administered with duvelisib

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

There are no data on the use of duvelisib in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposures (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Copiktra during pregnancy.

Breast-feeding

It is not known whether duvelisib and its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Breast-feeding should be discontinued during treatment with Copiktra and for at least 1 month after the last dose.

Fertility

No human data on the effect of duvelisib on fertility are available. In rats, but not in monkeys, effects on testes were observed.

4.7 Effects on ability to drive and use machines

Copiktra has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions (incidence ≥ 20%) are diarrhoea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anaemia.

The most frequently reported serious adverse reactions were pneumonia, colitis and diarrhoea.

Tabulated list of adverse reactions

The adverse reactions reported with duvelisib treatment are listed by system organ class and frequency in Table 2. Frequencies are defined as 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) and 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 2: Adverse drug reactions reported in patients with haematologic malignancies receiving duvelisib (N=442)

System organ class / preferred term or adverse reaction	All grades	Grade 3 or more
Infections and infestations		
Lower respiratory tract infection[1]	Very common	Common
Sepsis	Common	Common
Upper respiratory tract infection[1]	Very common	Uncommon
Blood and lymphatic system disorders		
Neutropenia[1]	Very common	Very common
Anaemia[1]	Very common	Very common
Thrombocytopenia[1]	Very common	Very common
Metabolism and nutrition disorders		
Decreased appetite	Very common	Uncommon
Nervous system disorders		
Headache[1]	Very common	Uncommon
Respiratory, thoracic and mediastinal disorders		

System organ class / preferred term or adverse reaction	All grades	Grade 3 or more
Dyspnoea[1]	Very common	Common
Pneumonitis[2]	Common	Common
Cough[1]	Very common	Uncommon
Gastrointestinal disorders		
Diarrhoea/Colitis[3]	Very common	Very common
Nausea[1]	Very common	Uncommon
Vomiting	Very common	Common
Abdominal pain[1]	Very common	Common
Constipation	Very common	Uncommon
Skin and subcutaneous tissue disorders		
Rash[4]	Very common	Common
Pruritus[1]	Common	Uncommon
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[1]	Very common	Common
Arthralgia	Very common	Uncommon
General disorders and administration site conditions		
Pyrexia	Very common	Common
Fatigue[1]	Very common	Common
Investigations		
Lipase increased	Common	Common
Transaminases increased[5]	Very common	Common

[1] Grouped term for reactions with multiple preferred terms

[2] Pneumonitis includes the preferred terms: pneumonitis, interstitial lung disease, lung infiltration

[3] Diarrhoea or colitis includes the preferred terms: colitis, enterocolitis, colitis microscopic, colitis ulcerative, diarrhoea, diarrhoea haemorrhagic

[4] Rash includes the preferred terms: dermatitis (including allergic, exfoliative, perivascular), erythema (including multiforme), rash (including exfoliative, erythematous, follicular, generalized, macular & papular, pruritic, pustular), toxic epidermal necrolysis and toxic skin eruption, drug reaction with eosinophilia and systemic symptoms, drug eruption, Stevens-Johnson syndrome.

[5] Transaminase elevation includes the preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, hypertransaminasaemia, hepatocellular injury, hepatotoxicity

Note: Doses withheld for > 42 days due to treatment-related toxicity will result in permanent discontinuation from treatment

Description of selected adverse reactions

Infections

The most common serious infections were pneumonia, sepsis, and lower respiratory infections. Median time to onset of any grade infection was 3 months (range: 1 day to 32 months), with 75% of cases occurring within 6 months. Infections should be treated prior to initiation of duvelisib. Patients should be advised to report any new or worsening signs and symptoms of infection.

For management of infections see sections 4.2 (Table 1) and 4.4.

Diarrhoea and colitis

The median time to onset of any grade diarrhoea or colitis was 4 months (range: 1 day to 33 months), with 75% of cases occurring by 8 months. The median event duration was 0.5 months (range: 1 day to 29 months; 75th percentile: 1 month). Patients should be advised to report any new or worsening diarrhea.

Non-infectious pneumonitis

Median time to onset of any grade pneumonitis was 4 months (range: 9 days to 27 months), with 75% of cases occurring within 9 months. The median event duration was 1 month, with 75% of cases resolving by 2 months.

Duvelisib should be withheld in patients who present with new or progressive pulmonary signs and symptoms such as cough, dyspnoea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation and evaluate for etiology. If the pneumonitis is infectious, patients may be restarted on duvelisib at the previous dose once the infection, pulmonary signs and symptoms resolve.

Severe cutaneous reactions
Median time to onset of any grade cutaneous reaction was 3 months (range: 1 day to 29 months, 75th percentile: 6 months), with a median event duration of 1 month (range: 1 day to 37 months, 75th percentile: 2 months). Severe cutaneous reactions include rash, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrosis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

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

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8). In case of overdose, general supportive measures and treatment should be provided. The patient should be monitored for signs and symptoms, laboratory parameters, and vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, phosphatidylinositol-3-kinase (Pi3K) inhibitors, ATC code: L01EM04

Mechanism of action

Duvelisib is a dual inhibitor of phosphatidylinositol 3-kinase p110δ (PI3K-δ) and PI3K-γ. PI3K-δ inhibition directly reduces proliferation and survival of malignant B-cell lines and primary CLL tumour cells, while PI3K-γ inhibition reduces the activity of CD4+ T cells and macrophages in the tumor microenvironment to support the malignant B cells. At 25 mg BID, the plasma levels of duvelisib may not be high enough to cause sustained inhibition of PI3K-γ, and the contribution of PI3K-γ inhibition to the efficacy may be limited.

Cardiac electrophysiology

The effect of multiple doses of duvelisib 25 and 75 mg BID on the corrected QT (QTc) interval was evaluated in patients with previously treated hematologic malignancies. Increases of > 20 ms in the QTc interval were not observed.

Clinical efficacy in relapsed or refractory CLL/SLL

IPI-145-07
A randomised, multicenter, open-label trial (Study IPI-145-07) compared duvelisib versus ofatumumab in 319 adult patients with CLL (N = 312) or SLL (N = 7) after at least one prior therapy. Patients were not appropriate for treatment with a purine-based analogue regimen (per National Comprehensive Cancer Network or European Society for Medical Oncology guidelines), including

relapse ≤ 36 month from a purine-based chemoimmunotherapy regimen or relapse ≤ 24 months from a purine-based monotherapy regimen. Patients who received prior BTK- or PI3K-inhibitors were excluded from the trial. None of the patients enrolled received prior BCL-2 inhibitor therapy. The study randomised patients with a 1:1 ratio to receive either duvelisib 25 mg BID until disease progression or unacceptable toxicity or ofatumumab for 7 cycles. Ofatumumab was administered intravenously at an initial dose of 300 mg, followed one week later by 2000 mg once weekly for 7 doses, and then 2000 mg once every 4 weeks for 4 additional doses. Treatment with ofatumumab beyond 7 cycles was not permitted, and no patients received more than 7 cycles of ofatumumab.

In the overall study population, (160 randomised to duvelisib, 159 to ofatumumab), the median patient age was 69 years (range: 39 to 90 years) with 68% of patients over 65 years, 60% were male, and 92% has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 61% of patients had Rai stage of ≥ I, and 39% had Binet stage ≥ B. The percentage of patients with unmutated IGHV (Ig heavy chain V-111) was 71%. Thirty-eight percent (38%) received 1 prior line of therapy, and 62% received 2 or more prior lines. Ninety-four percent (94%) of patients received prior alkylator therapy, with 38% of patients receiving prior bendamustine therapy; 80% of patients received prior rituximab therapy. 60% in the duvelisib arm and 71% in the ofatumumab arm had prior purine analogue treatment (but were not refractory as defined by IwCLL). At baseline, 46% of patients had at least one tumour ≥ 5 cm, 24% of patients had a documented 17p deletion, 32% of patients had a documented 17p deletion and/or *TP53* mutation, and 23% had a documented 11q deletion. The median time from initial diagnosis was 7 years (range: 0.3 to 34.7 years). The median time from most recent relapse/refractory diagnosis was 2.4 months (range: 0.2 to 80.2 months). The median time from most recent systemic therapy was 19.5 months (range: 0.5 to 148.8 months).

During randomised treatment, the median duration of exposure to duvelisib was 12 months (range: 0.2 to 37), with 72% of patients receiving at least 6 months and 49% receiving at least 12 months of duvelisib. The median duration of exposure to ofatumumab was 5 months (range: < 0.1 to 6).

The approval of Copiktra is based on efficacy and safety analysis of patients with at least 2 prior lines of therapy, where the benefit:risk appeared greater in this more heavily pretreated population compared to the overall trial population.

In this subset of patients with at least 2 prior lines of therapy, (95 randomised to duvelisib, 101 to ofatumumab), the median patient age was 69 years (range: 40 to 90 years) with 70% of patients over 65 years, 59% were male, and 88% had an ECOG performance status of 0 or 1. 62% of the patients had Rai stage of ≥ I, and 38% had Binet stage ≥ B. The percentage of patients with unmutated IGHV (Ig heavy chain V-111) was 69%. Forty-six percent (46%) received 2 prior lines of therapy, and 54% received 3 or more prior lines. Ninety-six percent (96%) of patients received prior alkylator therapy, with 51% of patients receiving prior bendamustine therapy; 86% of patients received prior rituximab therapy. 70% in the duvelisib arm and 77% in the ofatumumab arm had prior purine analogue treatment (but were not refractory as defined by IwCLL). At baseline, 52% of patients had at least one tumour ≥ 5 cm, 22% of patients had a documented 17p deletion, 31% of patients had a documented 17p deletion and/or *TP53* mutation, and 27% of patients had a documented 11q deletion. The median time from initial diagnosis was 8 years (range: 0.9 to 34.7 years). The median time from most recent relapse/refractory diagnosis was 2.6 months (range: 0.2 to 69 months). The median time from most recent systemic therapy was 15.5 months (range: 0.5 to 107.2 months).

During randomised treatment, the median duration of exposure to duvelisib was 13 months (range: 0.2 to 37), with 80% of patients receiving at least 6 months and 52% receiving at least 12 months of duvelisib. The median duration of exposure to ofatumumab was 5 months (range: < 0.1 to 6).

Efficacy was based on the primary endpoint progression-free survival (PFS) as assessed by an Independent Review Committee (IRC). Patients on both arms were to continue to be followed for disease progression after discontinuation of randomized treatment until initiation of subsequent anticancer therapy. Other efficacy measures included overall response rate. The efficacy endpoints of overall response rate and overall survival were designated as key secondary efficacy endpoints and were to be tested sequentially only if the primary endpoint of PFS was significant.

Results are presented in Table 3 and Figure 1 for the subset of patients with at least two prior therapies.

Table 3: Efficacy in CLL after at least two prior therapies (IPI-145-07)

Outcome	**Duvelisib N = 95**	**Ofatumumab N = 101**
PFS per IRC		
Median PFS (95% CI), months [a]	16.4 (12.0, 20.5)	9.1 (7.9, 10.7)
Hazard Ratio (95% CI), [b] Duvelisib/ofatumumab	0.4 (0.27, 0.59)	
p-value	<0.0001	
Response rate per IRC		
ORR, n (%)[c] (95% CI)	75 (78.9) (70.7, 87.1)	39 (38.6) (29.1, 48.1)
CR, n (%)	0	0
PR, n (%)	75 (78.9)	39 (38.6)
p-value	<0.0001	
Overall Survival (OS[d])		
Median OS (95% CI), months [a]	45.2 (35.9, 59.7)	46.9 (33.3, 75.0)
Hazard Ratio (95% CI), [b] Duvelisib/ofatumumab p-value	1.1 (0.7, 1.6) 0.6065	

Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; PFS = progression-free survival; PR = partial response

[a] Kaplan-Meier estimate

[b] Stratified Cox proportional hazards model using randomization strata as used for randomization

[c] IWCLL or revised IWG response criteria, with modification for treatment-related lymphocytosis

[d] OS analysis includes data from subjects who received ofatumumab on Study and subsequently received duvelisib in an extension study, based on intent-to-treat analysis. Subjects in both arms continued to be followed for OS after discontinuation of randomised treatment, regardless of subsequent therapies received. OS has been updated per the final analysis, with all subjects off study.

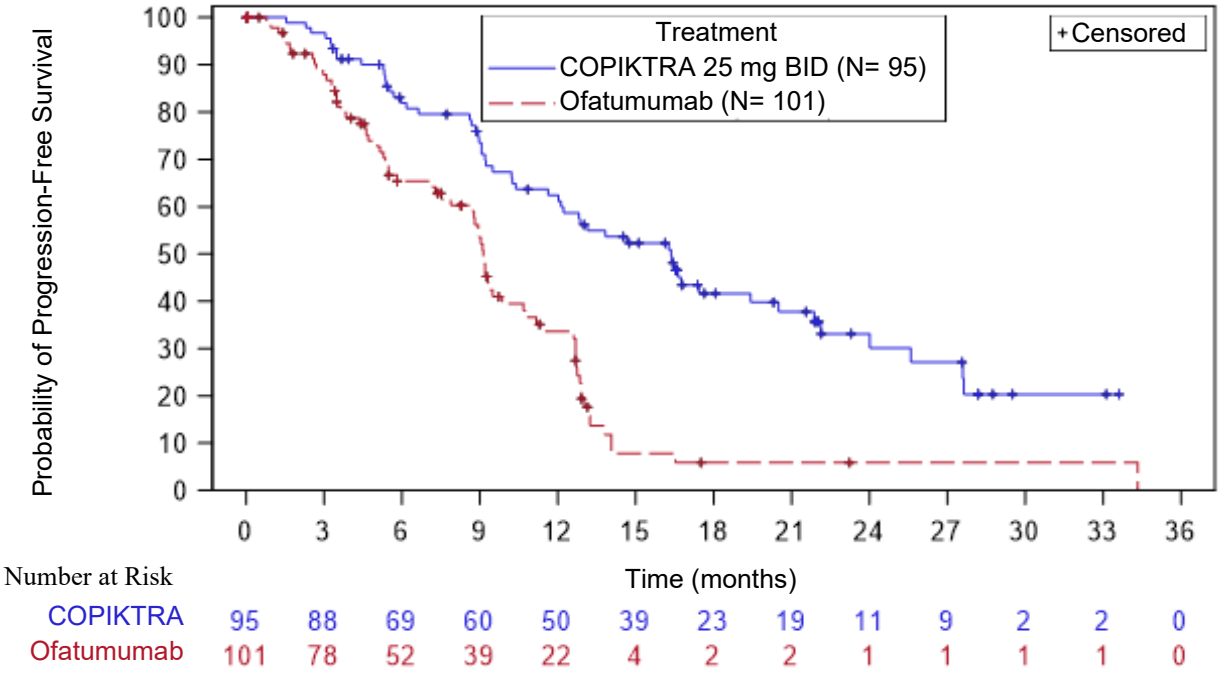
Table 4: Summary of PFS and response rates in subgroups therapy in patients with at least two prior therapies – (IPI-145-07)

Outcome per IRC	**Duvelisib**	**Ofatumumab**
17p deletion/*TP53* mutation	**N=29**	**N=30**
Median PFS (95% CI), months [a]	12.8 (8.9, 22.1)	8.7 (5.3, 12.6)
Hazard Ratio (95% CI), [b] Duvelisib/ofatumumab	0.36 (0.18, 0.72)	
ORR, (95% CI)[c]	72.4 (56.1, 88.7)	36.7 (19.4, 53.9)
Age ≥65	**N=68**	**N=69**
Median PFS (95% CI), months [a]	16.4 (10.4, 24.0)	9.2 (8.7, 10.8)
Hazard Ratio (95% CI), [b] Duvelisib/ofatumumab	0.38 (0.24, 0.61)	
ORR, (95% CI)[c]	77.9 (68.1, 87.8)	39.1 (27.6, 50.6)
Unmutated IGHV	**N=65**	**N=70**
Median PFS (95% CI), months [a]	17.4 (12.0, 24.0)	9.0 (7.3, 10.7)
Hazard Ratio (95% CI), [b] Duvelisib/ofatumumab	0.27 (0.17, 0.45)	
ORR, (95% CI)[c]	86.2 (77.8, 94.6)	40 (28.5, 51.5)

Abbreviations: CI = confidence interval; IRC = Independent Review Committee; PFS = progression-free survival

[a] Kaplan-Meier estimate
[b] Cox proportional hazards model
[c] IWCLL or revised IWG response criteria, with modification for treatment-related lymphocytosis

Figure 1: Kaplan-Meier curve of PFS per IRC in patients with at least two prior therapies (IPI-145-07)



Number at Risk

COPIKTRA	95	88	69	60	50	39	23	19	11	9	2	2	0
Ofatumumab	101	78	52	39	22	4	2	2	1	1	1	1	0

Clinical efficacy in relapsed or refractory Follicular Lymphoma (FL)

IPI-145-06

Efficacy of duvelisib in patients with previously treated FL is based on a single-arm, multicenter trial (Study IPI-145-06). In this study, duvelisib 25 mg BID was administered in 129 patients with indolent B-cell non-Hodgkin lymphoma (iNHL, including: FL, n = 83; SLL, n=28; and marginal zone lymphoma [MZL], n=18) who were refractory to rituximab and to either chemotherapy or radioimmunotherapy. Refractory disease was defined as less than a partial remission or relapse within 6 months after the last dose. The trial excluded patients with Grade 3b FL, large cell transformation, prior allogeneic transplant, and prior exposure to a PI3K inhibitor or to a Bruton's tyrosine kinase inhibitor.

The median age was 65 years (range: 30 to 90 years) with 50% of subjects over 65 years and 14% of subjects age 75 or older, 68% were male, and 40% had bulky disease assessed at baseline (target lesion ≥ 5 cm). Patients had a median of 3 prior lines of therapy (range: 1 to 18), with 96% being refractory to their last therapy and 77% being refractory to 2 or more prior lines of therapy. Ninety-eight percent (98%) of patients were refractory to rituximab, and 91% were refractory to an alkylating agent. Most patients (approximately 75%) experienced early relapse (no response on treatment or progressive disease [PD] or time to next treatment less than 2 years) after their first treatment regimen. The median time from initial diagnosis was 4.5 years (range 4 months to 27 years). Most patients (95%) had an ECOG performance status of 0 or 1.

The median duration of exposure to duvelisib was 7 months (range: 0.4 to 45.5), with 53% of patients receiving at least 6 months and 26% receiving at least 12 months of duvelisib.

Efficacy was based on the primary endpoint of overall response rate. Secondary endpoints were progression-free survival, duration of response as assessed by an IRC and overall survival (Table 5).

Table 5: Efficacy in patients with at least two prior therapies, relapsed or refractory FL (IPI-145-06)

Endpoint	
FL	**N=73**
ORR, n (%) [a]	29 (40)
95% CI	(31, 54)
CR, n (%)	0
PR, n (%)	29 (40)
Duration of response	
Range, months	0.0+ to 41.9
Median DOR (95% CI), months[b]	10.01 (6.3, NE)

Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; ORR = overall response rate; PR = partial response

[a] Per IRC according to Revised International Working Group criteria

[b] Kaplan-Meier estimate

+ Denotes censored observation

Elderly

Clinical trials of duvelisib included 270 patients (61%) that were 65 years of age and older and 104 (24%) that were 75 years of age and older. No major differences in efficacy or safety were observed between patients less than 65 years of age and patients 65 years of age and older. No specific dose adjustment is required for elderly patients (aged ≥ 65 years) (see section 5.2).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with duvelisib for the treatment of mature B cell malignancies for all subsets of the paediatric population from birth to less than 18 years of age (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Duvelisib exposure increased in a dose-proportional manner over a dose range of 8 mg to 75 mg (0.3 to 3 times the recommended dose) following a single dose. Dose proportionality was not estabilished after multiple doses.

At steady state following 25 mg BID administration of duvelisib in patients, the geometric mean (CV%) maximum concentration (C_{max}) was 1.5 (64%) µg/mL and AUC was 7.9 (77%) µg•h/mL.

Absorption

The absolute bioavailability of 25 mg duvelisib after a single oral dose in healthy volunteers was 42%. The median time to peak concentration (T_{max}) was observed at 1 to 2 hours in patients.

Effect of food
Duvelisib may be administered without regard to food. The administration of a single dose of duvelisib with a high-fat meal (fat accounted for approximately 50% of the total caloric content of the meal) decreased C_{max} by approximately 37% and decreased the AUC by approximately 6%, relative to fasting conditions.

Distribution

Protein binding of duvelisib is greater than 95%. The mean blood-to-plasma ratio was 0.5. The geometric mean (CV%) apparent volume of distribution at steady state (V_{ss}/F) is 28.5 L (62%).

Biotransformation

Duvelisib is primarily metabolized by cytochrome P450 CYP3A4. The major metabolite is IPI-656, which is pharmacologically inactive at clinically observed exposure levels.

Elimination

The geometric mean (CV%) apparent systemic clearance at steady-state is 4.2 L/hr (56%) in patients with lymphoma or leukaemia. The geometric mean (CV%) elimination half-life of duvelisib is 4.7 hours (57%) during 0-8 hours postdose.

Excretion
Following a single 25 mg oral dose of radiolabeled duvelisib, 79% of the radioactivity was excreted in feces (11% unchanged) and 14% was excreted in the urine (1% unchanged). These data have been determined in healthy subjects.

In vitro drug interaction studies

Duvelisib is a substrate of P-glycoprotein (P-gp) and breast cancer-resistant protein (BCRP). Duvelisib is highly absorbed following an oral dose and therefore no clinically relevant effect of P-gp and BCRP inhibitors is expected.

In vitro studies combined with human *in vivo* Pharmacokinetic (PK) data suggested that clinically relevant drug-drug interactions of duvelisib and its main metabolite IPI-656 with substrates of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BCRP, or P-gp are unlikely. Therefore, interaction studies with Pgp, BCRP and CYP2C8 are considered not necessary.

Both duvelisib and IPI-656 were determined as direct inhibitors of CYP2C8 and CYP3A4 as well as metabolism-dependent inhibitors of CYP3A4 (Please refer to section 4.5).). Simulations indicated that at supratherapeutic doses duvelisib can be a mild inhibitor of CYP2C8, which is considered unlikely to result in clinically relevant interactions.

Special populations

Age (18 to 90 years), sex, race, renal impairment (creatinine clearance 23 to 80 mL/ min), hepatic impairment (Child Pugh Class A, B, and C) and body weight (40 to 154 kg) had no clinically significant effect on the exposure of duvelisib.

Duvelisib pharmacokinetics were highly variable in subjects with moderate and severe hepatic impairment.Geometric mean duvelisib $AUC_{0-\infty}$ in mild, moderate, and severely hepatically impaired subjects were lower (within 20%) compared to the exposure observed in healthy subjects and was 89%, 94%, and 81% of the exposure observed in healthy subjects and is not considered clinically significant. The exposures in moderately and severely impaired subjects were highly variable (CV% 46 – 67%) and these patients should be carefully monitored for adverse events (see section 4.4). Exposures obtained in cancer patients were approximately 2-fold higher than the exposures observed in healthy subjects.

5.3 Preclinical safety data

In repeat-dose toxicity studies in rat and cynomolgus monkey, adverse effects were mainly related to expected exaggarated pharmacology, including adverse effects on lymphoid tissues, bone marrow and haematology parameters at exposures of free duvelisib at 8 to 16 fold, corresponding to total duvelisib at 2 to 11 fold Maximum Recommended Human Dose (MRHD) of 25 mg BID in human.

Duvelisib did not cause genetic damage in *in vitro* or *in vivo* assays.

In dose range finding and pivotal embryo-fetal developmental toxicity studies in rat and rabbit, duvelisib (free fraction) induced embryo-fetal developmental toxicity only at free plasma exposures

margins of >25 fold of 25 mg BID in human (MRHD), corresponding to 4 to 5 fold total plasma concentrations.

Fertility studies with duvelisib were not conducted. Histological findings in male and female rats were observed in the repeat dose toxicity studies and included testis (seminiferous epithelial atrophy, decreased weight, soft testes), and epididymis (small size, oligo/aspermia) in males and ovary (decreased weight) and uterus (atrophy) in females.

Carcinogenicity studies have not been conducted with duvelisib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Colloidal silicon dioxide
Crospovidone
Magnesium stearate
Microcrystalline cellulose

Capsule shell
Gelatin
Titanium dioxide (E 171)
Iron oxide red (E 172)

Printing black ink
Shellac glaze
Iron oxide black (E 172)
Propylene glycol
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Copiktra 15 mg hard capsules

5 years

Copiktra 25 mg hard capsules

5 years

6.4 Special precautions for storage

Store below 30°C.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Copiktra 15 mg hard capsules

Child-resistant PVC-PE-PCTFE / Aluminium blisters.

Pack size: 28 days carton containing 56 capsules (2 blisters with 28 capsules each).

Copiktra 25 mg hard capsules

Child-resistant PVC-PE-PCTFE / Aluminium blisters.
Pack size: 28 days carton containing 56 capsules (2 blisters with 28 capsules each).

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Secura Bio Limited
32 Molesworth Street
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1542/001
EU/1/21/1542/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 May 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Millmount Healthcare Limited (trading as PCI Pharma Services)
Block-7, City North Business Campus
Stamullen, Co. Meath, K32 YD60
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Copiktra 15 mg hard capsules
duvelisib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 15 mg duvelisib (as monohydrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules (2 blisters of 28 capsules each)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Secura Bio Limited
32 Molesworth Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1542/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Copiktra 15 mg capsules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER SLEEVE CONTAINING THE BLISTER

OUTER SLEEVE

1. NAME OF THE MEDICINAL PRODUCT

Copiktra 15 mg hard capsules
duvelisib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 15 mg duvelisib (as monohydrate).

3. LIST OF EXCIPIENTS

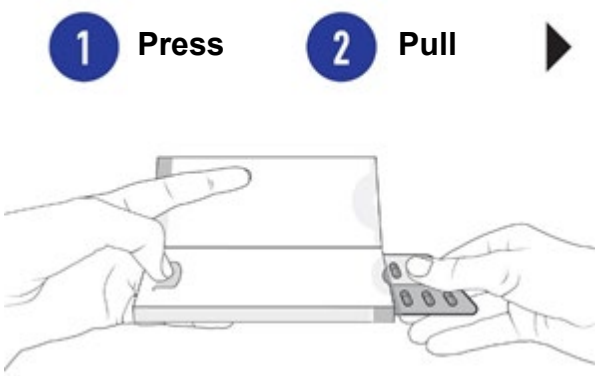
4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

1. Press and hold here



OPENING INSTRUCTIONS
1. Push the button gently with thumbnail and hold it down.
2. Pull out the medication card.
3. Find correct daily pill on the blister card, press out and take pill.
4. To close, slide the blister card back into the package.

2. Pull out here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Secura Bio Limited
32 Molesworth Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1542/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17.	UNIQUE IDENTIFIER – 2D BARCODE

18.	UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Copiktra 15 mg hard capsules
duvelisib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Secura Bio Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Copiktra 25 mg hard capsules
duvelisib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 25 mg duvelisib (as monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules (2 blisters of 28 capsules each)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Secura Bio Limited
32 Molesworth Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1542/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Copiktra 25 mg capsules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER SLEEVE CONTAINING THE BLISTER

OUTER SLEEVE

1. NAME OF THE MEDICINAL PRODUCT

Copiktra 25 mg hard capsules
duvelisib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 25 mg duvelisib (as monohydrate).

3. LIST OF EXCIPIENTS

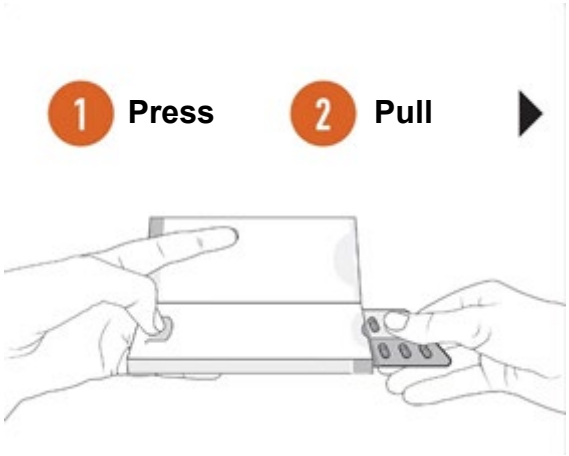
4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

1. Press and hold here



OPENING INSTRUCTIONS
1. Push the button gently with thumbnail and hold it down.
2. Pull out the medication card.
3. Find correct daily pill on the blister card, press out and take pill.
4. To close, slide the blister card back into the package.

2. Pull out here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Secura Bio Limited
32 Molesworth Street
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1542/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Copiktra 25 mg hard capsules
duvelisib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Secura Bio Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Copiktra 15 mg hard capsules
Copiktra 25 mg hard capsules
duvelisib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Copiktra is and what it is used for

Copiktra is a cancer medicine that contains the active substance duvelisib. It works by blocking the effects of enzymes needed for the growth and survival of B-lymphocytes (a type of white blood cell). These enzymes are overactive in certain cancerous white blood cells and by blocking them Copiktra can kill and reduce the number of cancerous B-lymphocytes.

Copiktra is used for the treatment of cancers of B-lymphocytes called
- chronic lymphocytic leukaemia (or small lymphocytic lymphoma)
- follicular leukaemia.

In these diseases the B-lymphocytes multiply too quickly and live too long, so there are too many of them in the blood or lymph nodes. Copiktra is used when patients have previously been given at least 2 other therapies that did not work or are no longer working.

2. What you need to know before you take Copiktra

Do not take Copiktra
- if you are allergic to duvelisib or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor before taking Copiktra.

Warnings and precautions

Talk to your doctor or pharmacist before taking Copiktra,
- if you have an infection. This must be treated before you start taking Copiktra.
- if you have intestinal problems
- if you have lung or breathing problems

Infections
Infections are common during Copiktra treatment, and can be serious and can lead to death. Tell your doctor, pharmacist, or nurse right away if you have fever, chills, or other signs of an infection during treatment with Copiktra. Your doctor may prescribe another medicine while you are taking Copiktra, to prevent certain types of infection.

Diarrhoea or inflammation of your intestine
Diarrhoea or inflammation of your intestine (colitis) is common during Copiktra treatment, and can be serious and can lead to death. Tell your doctor or pharmacist right away if you have any new or worsening diarrhoea, you pass mucus or blood when going to the toilet, or if you have severe abdominal (stomach area) pain. Your doctor or pharmacist should prescribe medicine to help your diarrhoea and check you at least weekly. If your diarrhoea is severe or anti-diarrhoea medicines do not work, you may need treatment with a steroid medicine.

Skin reactions
Copiktra can cause rashes and other skin reactions that can be serious and can lead to death. Tell your doctor or pharmacist right away if you get new or worsening skin rash, or other skin reactions during treatment with Copiktra, including:
- painful sores or ulcers on your skin, lips, or in your mouth
- severe rash with blisters or peeling skin
- rash with itching
- rash with fever

Your doctor may need to prescribe medicines, including a steroid medicine, to treat your skin rash or other skin reactions.

Inflammation of the lungs
Copiktra can cause inflammation of your lungs which can be serious and can lead to death. Tell your doctor or pharmacist right away if you get new or worsening cough or difficulty breathing. Your doctor may do tests to check your lungs if you have breathing problems. Your doctor may treat you with a steroid medicine if you develop inflammation of the lungs that is not due to an infection.

Elevated liver enzymes
Copiktra may cause abnormalities in blood tests for your liver. Your doctor will check for liver problems during your treatment with Copiktra. Tell your doctor right away if you get any symptoms of liver problems, including yellowing of your skin or the white part of your eyes (jaundice), abdominal pain, bruising or bleeding more easily than normal.

Blood counts
Low white blood cell counts (neutropenia) and decrease in red blood cell (anaemia or bloodlessness) can occur in patients treated with Copiktra. Both can be serious. Your doctor will check your blood counts regularly. Tell your doctor right away if you get fever or any signs of infection, if you feel tired or dizzy, or if you have headache.

If you have any of the above serious side effects during treatment with Copiktra, your doctor may pause your treatment, change your dose of Copiktra, or completely stop your treatment with Copiktra.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years of age because it has not been studied in this age group.

Other medicines and Copiktra
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This is because Copiktra can affect the way some other medicines work and some other medicines can affect the way Copiktra works.

Tell your doctor or pharmacist if you are taking any of the following medicines:

- **alfentanil, fentanyl, methadone, buprenorphine/naloxone**, medicines used for pain relief
- **alfuzosin**, a medicine used to treat an enlarged prostate
- **amiodarone, bepridil, disopyramide, lidocaine, quinidine**, medicines used to treat heart problems
- **amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil**, medicines used to treat high blood pressure and heart problems
- **amprenavir, atazanavir, darunavir, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir**, medicines used to treat HIV infections
- **aprepitant**, a medicine used to prevent vomiting
- **boceprevir, telaprevir**, medicines used to treat hepatitis C
- **bosentan**, a medicine used to treat pulmonary hypertension, a lung disease that makes breathing difficult
- **budesonide, fluticasone**, steroid medicines used to treat hayfever and asthma, and **salmeterol**, used to treat asthma
- **buspirone, clorazepate, diazepam, estazolam, flurazepam, zolpidem**, medicines used to treat nervous system disorders
- **carbamazepine, mephenytoin, phenytoin**, medicines used to prevent seizures
- **ciclosporin, sirolimus, tacrolimus**, medicines used to prevent organ rejection' after a transplant
- **ciprofloxacin, clarithromycin, erythromycin, nafcillin, telithromycin**, medicines used to treat bacterial infections
- **cisapride**, a medicine used to relieve certain stomach problems
- **colchicine**, a medicine used to treat gout
- **conivaptan**, a medicine to treat heart problems
- **dabigatran, warfarin**, medicines used to prevent blood clots
- **dasatinib, imatinib, nilotinib, paclitaxel, vinblastine, vincristine**, medicines used to treat cancer
- **dihydroergotamine, ergotamine**, medicines used to treat migraine headache
- **fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole**, medicines used to treat fungal infections
- **midazolam, triazolam**, when taken by mouth to help you sleep or relieve anxiety
- **modafinil**, a medicine used to treat excessive sleepiness
- **oral or implanted hormonal contraceptives**, used to prevent pregnancy
- **pimozide**, a medicine used to treat abnormal thoughts or feelings
- **quetiapine**, a medicine used to treat schizophrenia, bipolar disorder and major depressive disorder
- **rifabutin**, **rifampicin** medicines used to treat bacterial infections including tuberculosis
- **sildenafil, tadalafil**, medicines used to treat impotence and pulmonary hypertension, a lung disease that makes breathing difficult
- **'statin' medicines such as atorvastatin, lovastatin, simvastatin**, used to lower cholesterol
- **St. John's wort** (*Hypericum perforatum*), a herbal remedy used for depression and anxiety
- **trazodone**, a medicine used to treat depression

Copiktra with food and drink
Avoid drinking grapefruit juice. Grapefruit juice can affect the way Copiktra works.

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. A pregnancy test should be conducted before taking Copiktra.

Use of Copiktra should be avoided during pregnancy.

If you become pregnant during treatment with Copiktra, tell your doctor as soon as possible.

Breast-feeding

It is not known if Copiktra passes into breast milk. Do not breast-feed during treatment with Copiktra and for at least 1 month after the last dose.

Contraception
Use effective contraception, which includes two forms of reliable contraception, during treatment and for at least 1 month after receiving the last dose of Copiktra.

Contraceptive pills
It is not known if Copiktra reduces the effectiveness of the contraceptive pill. If you are taking the contraceptive pill while you are being treated with Copiktra you also need to use a barrier method of contraception (such as condoms). Ask your doctor for advice.

Driving and using machines
Copiktra is unlikely to affect your ability to drive and use machines.

3. How to take Copiktra

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose of Copiktra is 25 mg taken by mouth twice a day. However, your doctor may change your dose of Copiktra or ask you to stop taking Copiktra if you get particular side effects. Do not change your dose or stop taking Copiktra without talking to your doctor first.

Swallow Copiktra capsules whole.
Do not open, break, or chew the capsules . You may take Copiktra with food or between meals. Tell your doctor or caregiver if you have problems swallowing these capsules.

If you take more Copiktra than you should
If you take too much Copiktra, call your doctor or pharmacist right away or go to the nearest hospital emergency room. Take the medicine and this leaflet with you so that you can easily describe what you have taken.

If you forget to take Copiktra
Take care not to miss a dose of Copiktra. If you miss a dose of Copiktra by less than 6 hours, take the missed dose right away, and then take the next dose at your usual time. If you miss a dose by more than 6 hours, wait and take the next dose at your usual time. Do not take a double dose to make up for a forgotten capsule.

If you stop taking Copiktra
Do not stop taking this medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious.

Get medical help immediately if you experience any of the following:
- Fever, chills, or other signs of an infection
- New or worsening diarrhoea, stool with mucus or blood, or severe abdominal (stomach area) pain
- New or worsening skin rash, or other skin reactions including

    - painful sores or ulcers on your skin, lips, or in your mouth
    - severe rash with blisters or peeling skin
    - rash with itching and/or fever
- New or worsening cough or difficulty breathing

Other side effects

Very common: may affect more than 1 in 10 people
- Infections of the upper and lower respiratory tract, lung infection (pneumonia)
- Decrease in some white blood cells (neutropenia)
- Decrease in red blood cell (anaemia)
- Decrease in cells in the blood that help the blood to clot (thrombocytopenia)
- Decreased appetite
- Headache
- Shortness of breath (dyspnoea)
- Cough
- Inflammation of the intestines (colitis), diarrhoea (watery, loose or soft stools), vomiting, nausea, stomach pain
- Difficulty passing stools (constipation)
- Skin rash sometimes with blisters
- Pain in the muscles, bones (musculoskeletal pain) and joints (arthralgia)
- Fever
- Feeling tired or weak
- Increased level of a specific protein in blood that measures function of pancreas
- Increased levels of liver enzymes seen in blood tests

Common: may affect up to 1 in 10 people
- Infection can spread to vital organs causing the organs to not function properly (sepsis)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing)

Uncommon: may affect up to 1 in 100 people
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis, Stevens-Johnson syndrome, drug rash with increase in white blood cell counts (eosinophilia) and symptoms affecting the whole body)

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Copiktra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

Store below 30°C.

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Copiktra contains

- The active substance is duvelisib. Each hard capsule contains 15 mg or 25 mg duvelisib (as monohydrate).
- The other ingredients are:
  Capsule content: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose.
  Capsule shell: gelatin, titanium dioxide (E 171), red iron oxide (E 172).
  Printing black ink: shellac glaze, iron oxide black (E 172), propylene glycol, ammonium hydroxide.

What Copiktra looks like and contents of the pack

Copiktra 15 mg hard capsules

- Opaque pink capsule with "duv 15 mg" printed on the body in black ink.
- Pack size: 28 days carton containing 56 capsules (2 blisters with 28 capsules each).

Copiktra 25 mg hard capsules

- Opaque capsule with a white to off-white body and Orange cap with "duv 25 mg" printed on the body in black ink.
- Pack size: 28 days carton containing 56 capsules (2 blisters with 28 capsules each).

Marketing Authorisation Holder
Secura Bio Limited
32 Molesworth Street
Dublin 2
Ireland

Manufacturer
Millmount Healthcare Limited (trading as PCI Pharma Services)
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Stamullen, Co. Meath, K32 YD60
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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.