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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Copiktra 15 mg hard capsules

Each hard capsule contains 15 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).

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-	• No change in dose • Initiate supportive therapy with anti-diarrhoeal agents as appropriate

Table 1: Copiktra dose modifications and toxicity management

Toxicity	**Adverse reaction grade**	**Recommended management**
	diarrhoeal agents, OR Asymptomatic (Grade 1) colitis	• 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)
	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

Table 1: Copiktra dose modifications and toxicity management

Toxicity	**Adverse reaction grade**	**Recommended management**
	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
Haematologic adverse reactions		

Table 1: Copiktra dose modifications and toxicity management

Toxicity	**Adverse reaction grade**	**Recommended management**
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

Pregnancy

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: Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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

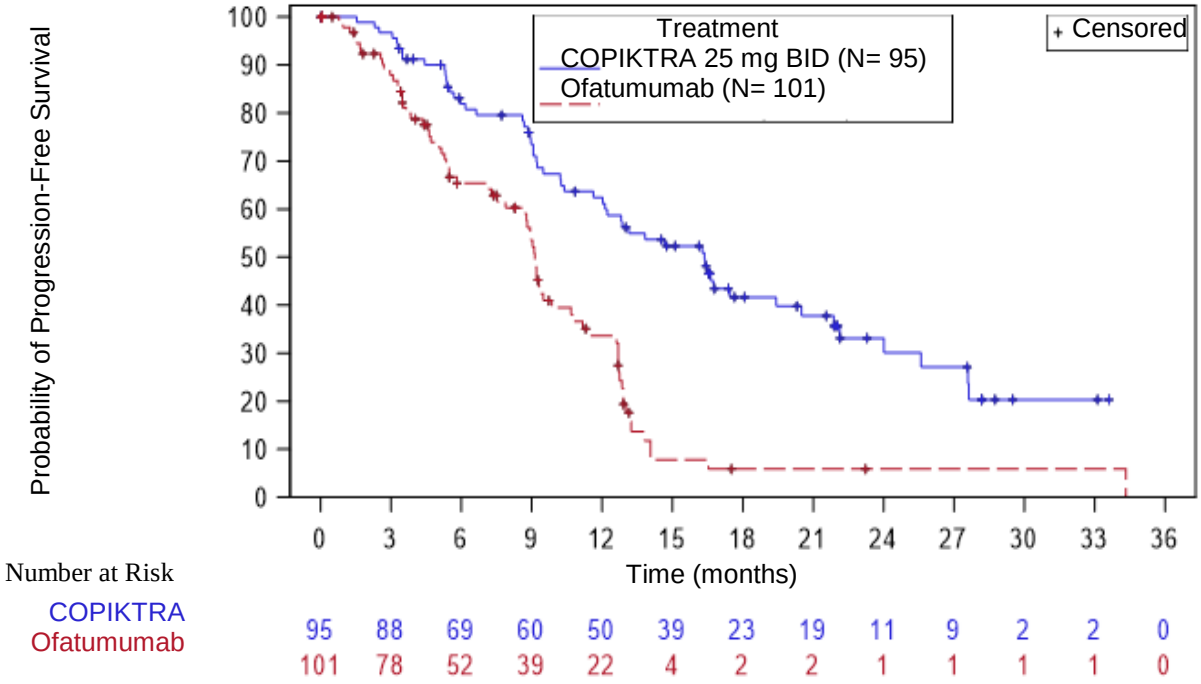
[d] OS analysis includes data from subjects who received ofatumumab on Study and subsequently received duvelisib in an extension study, based on intent-to-treat analysis. Subjects in both arms continued to be followed for OS after discontinuation of randomised treatment, regardless of subsequent therapies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



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 licensing authority 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

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

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)

PL 53958/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/05/2021

10 DATE OF REVISION OF THE TEXT

30/08/2023