Summary of risk management plan for Copiktra (duvelisib)

This is a summary of the risk management plan (RMP) for COPIKTRA. The RMP details important risks of COPIKTRA, how these risks can be minimised, and how more information will be obtained about COPIKTRA's risks and uncertainties (missing information).

COPIKTRA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how COPIKTRA should be used.

This summary of the RMP for COPIKTRA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (https://www.ema.europa.eu/en/medicines/human/EPAR/copiktra).

Important new concerns or changes to the current ones will be included in updates of COPIKTRA's RMP.

I. The medicine and what it is used for

COPIKTRA monotherapy is authorised for adult patients with relapsed or refractory CLL after at least two prior therapies and FL that is refractory to at least two prior systemic therapies (see SmPC for the full indication). It contains duvelisib as the active substance and it is given by oral administration.

Further information about the evaluation of COPIKTRA’s benefits can be found in COPIKTRA’s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of COPIKTRA, together with measures to minimise such risks and the proposed studies for learning more about COPIKTRA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of COPIKTRA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of COPIKTRA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of COPIKTRA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Serious infections Serious diarrhoea/colitis Severe cutaneous reactions Pneumonitis
Important potential risks	Hepatotoxicity Embryo-foetal toxicity Drug-drug interaction with CYP3A substrates
Missing information	Safety in patients with severe hepatic impairment Long term safety follow-up

II.B Summary of important risks

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	**Non-clinical**: Toxicology studies showed lymphoid depletion (both in the peripheral blood and lymphoid tissues) with a functional impact like occurrence of secondary infections. **Clinical studies**: High frequency of infections was observed. Most infections were either upper or lower respiratory infections, the latter being more predominant and specifically represented by Pneumonia. **Post-marketing data**: Cases were reported post-marketing. **Class effect**: ***Zydelig***: High frequency of infections was observed. Most frequently observed were infections in the respiratory system and septic events.
Risk factors and risk groups	Infections remain a common complication in patients with haematological malignancies. These patients are at increased risk of infections not only because of the malignancy itself but also because of neutropenia induced by intensive chemotherapeutic treatment that may be followed by haematopoietic stem cell transplantation, and the cytotoxic effect on the cells that line the alimentary tract. There are often multiple factors that predispose patients with haematological diseases to infections such as neutropenia induced therapy or bone marrow involvement, hypogammaglobulinemia, T-cell dysfunction, asplenia and mucosal damage.

Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section 4.2, 4.4, 4.8* *PL section 2, 4* *Advice regarding dose modifications in included in section 4.2. Advice regarding counselling, monitoring and prophylactic treatment is included in section 4.4.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*

Important identified risk: Serious diarrhoea/colitis	
Evidence for linking the risk to the medicine	**Clinical studies**: High frequency of diarrhoea and colitis was observed. **Post-marketing data**: Cases were reported post-marketing. **Class effect**: ***Zydelig***: Cases of severe drug-related colitis occurred.
Risk factors and risk groups	Patients with haematologic disease are susceptible to CDAD because of their frequent antibiotic use, prolonged duration of hospital stay, and chemotherapy-induced disruption of the intestinal mucosa. Prophylactic and empirical use of broad spectrum antibiotics is the common treatment for neutropenic fever patients with haematologic disease. A higher incidence of Grade ≥3 toxicities was found in younger patients with higher absolute lymphocyte counts. Preliminary data from ongoing studies suggest that patients with severe toxicities had lower baseline levels of T_{reg} functional markers and decreased T_{reg} effector markers (granzyme β, HLA-D related, and programmed cell death-1) after treatment relative to those who do not. Although these observations require confirmation, baseline T_{reg} profiling may be a potential method for prospectively identifying patients at greatest risk for toxicity.
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section 4.2, 4.4, 4.8* *PL section 2, 4* Advice regarding dose modifications in *included in section 4.2. Advice on how to counsel patients is included in section 4.4.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*

Important identified risk: Severe cutaneous reactions	
Evidence for linking the risk to the medicine	**Clinical studies**: High frequency of cutaneous reactions was observed. **Post-marketing data**: Cases were reported post-marketing. **Class effect**: ***Zydelig***: Rash was generally mild to moderate and typically resolved with treatment (e.g., topical and/or oral steroids, diphenhydramine) and dose interruption for severe cases. Rarely, cases of SJS and TEN have occurred when idelalisib was administered concomitantly with other medicinal products associated with these syndromes (bendamustine, rituximab, allopurinol, and amoxicillin). SJS or TEN occurred within one month of the medicinal combination and fatal outcomes have resulted.
Risk factors and risk groups	A genetic disposition to cutaneous adverse drug reactions has long been assumed. Nevertheless, specific reaction types in relation to certain drugs could only recently be determined for patients with specific HLA patterns, which vary according to ethnicity. For example, HLA-A*3101 was shown to be present in European patients with carbamazepine-induced adverse reactions, particularly maculopapular rash, but not in severe reactions like SJS/TEN. A very strong association between carbamazepine-induced SJS/TEN in Han-Chinese patients and HLA-B*1502 was observed which could not be confirmed in Europeans. HLA-B*5801 was found in Han-Chinese patients with SJS/TEN and DRESS after allupurinol intake (100%), as well as in Europeans with SJS/TEN

	(55%). These results clearly show that first, the genetic predisposition for the development of severe cutaneous adverse reactions is highly associated with specific drugs, and that second, ethnicity plays a more important role than expected. HIV individuals are at an increased risk of hypersensitivity reaction to certain drugs such as sulfonamides and nevirapine. Furthermore, hypersensitivity reaction to nevirapine reaction is CD4 dependent and is abrogated by a CD4 count of <250.
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section 4.2, 4.4, 4.8* *PL section 2, 4* *Advice regarding dose modifications in included in section 4.2. Advice on how to counsel patients is included in section 4.4.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*

Important identified risk: Pneumonitis	
Evidence for linking the risk to the medicine	**Clinical studies**: Non-Infectious Pneumonitis cases were observed. **Post-marketing data**: Cases were reported post-marketing. **Class effect**: ***Zydelig***: Cases of pneumonitis and organising pneumonia (some with fatal outcome), have been reported with idelalisib.
Risk factors and risk groups	Preliminary data from ongoing studies suggest that patients with severe toxicities had lower baseline levels of T_{reg} functional markers and decreased T_{reg} effector markers (granzyme β, HLA-D related, and programmed cell death-1) after treatment relative to those who do not. Although these observations require confirmation, baseline T_{reg} profiling may be a potential method for prospectively identifying patients at greatest risk for toxicity. In addition, patients exposed to harsh chemicals or irritants, moulds and bacteria, as well as radiation treatment, may be more susceptible.
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section 4.2, 4.4, 4.8* *PL section 2, 4* Advice regarding dose modifications in included in section 4.2. *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*

Important potential risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	**Non-clinical**: Toxicology studies showed hepatic changes (inflammation) in some studies. **Clinical studies**: There were a few cases of hepatoxicity and none were serious. **Post-marketing data**: Cases were reported post-marketing. **Class effect**: ***Zydelig***: There have been reports of hepatocellular injury including hepatic failure.
Risk factors and risk groups	Preliminary data from ongoing studies suggest that patients with severe toxicities had lower baseline levels of T_{reg} functional markers and decreased T_{reg} effector markers (granzyme β, HLA-D related, and programmed cell death-1) after treatment relative to those who do not. Although these observations require confirmation, baseline T_{reg} profiling may be a potential method for prospectively identifying patients at greatest risk for toxicity. Hepatotoxicity was more prevalent in younger, previously untreated patients. In addition, risk factors for drug-induced liver injury include race, age, sex, alcohol ingestion, pre-existing liver disease, genetic factors, other comorbidities, drug formulation and host factors.

Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section 4.2, 4.4, 4.8* *PL section 2, 4* *Advice regarding dose modifications in included in section 4.2.* *Monitoring of hepatic function during treatment with COPIKTRA is included in section 4.4.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*

Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	**Non-clinical**: Toxicology studies showed maternal toxicity (mortality, body weight loss, decreased food consumption) as well as reduced foetal weights or litter resorption. **Clinical studies**: None reported. **Post-marketing data**: None reported. **Class effect**: ***Zydelig***: Toxicology studies showed maternal toxicity and litter resorption.
Risk factors and risk groups	Women of child-bearing potential, as well as their partners.
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section 4.4, 4.6* *PL section 2* *Advice regarding the use of contraception in included in section 4.4 and advice that it is preferable to avoid the use of COPIKTRA during pregnancy is included in section 4.6.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*

Important potential risk: Drug-drug interaction with CYP3A substrates	
Evidence for linking the risk to the medicine	**Non-clinical**: Duvelisib and its metabolite are strong inhibitors of CYP3A4. **Clinical studies**: Co-administration of duvelisib and midazolam, a sensitive CYP3A4 substrate, in healthy adults, increased the midazolam AUC by 4.3-fold and C_{max} by 2.2-fold. Pharmacokinetic simulations in cancer patients under steady state conditions have shown that the C_{max} and AUC of midazolam would increase by 2.5-fold and 5.9-fold respectively. **Class effect**: Zydelig is a strong CYP3A inhibitor that can increase the AUC of a sensitive CYP3A substrates.
Risk factors and risk groups	None
Risk minimisation measures	**Routine risk minimisation measures**: *SmPC section 4.4, 4.5, 5.2* *PL section 2* *Advice regarding the need to avoid co-administration of midazolam with COPIKTRA and the need to avoid concomitant treatment of duvelisib with sensitive CYP3A substrates and use of alternative medicinal products that are less sensitive to CYP3A4 inhibition is included in section 4.4.* *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*

Missing information: Safety in patients with severe hepatic impairment	
Risk minimisation measures	**Routine risk minimisation measures**: *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*

Missing information: Long term safety follow-up	
Risk minimisation measures	**Routine risk minimisation measures**: *Prescription only medicine* **Additional risk minimisation measures**: *No risk minimisation measures*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Copiktra.

II.C.2 Other studies in post-authorisation development plan

None