Swiss Public Summary of the Risk Management Plan (RMP)

for

Zydelig®, Film-coated tablets

(idelalisib)
100 mg & 150 mg

Version 2.0 (October 2021)
Based on EU RMP version 6.1 (October 2021)

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SUMMARY OF RISK MANAGEMENT PLAN FOR ZYDELIG® (IDELALISIB)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Zydelig is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the „Arzneimittelinformation / Information sur le médicament“ approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Zydelig in Switzerland is the „Arzneimittelinformation / Information sur le médicament“ (see www.swissmedic.ch) approved authorized by Swissmedic. Gilead Sciences Switzerland Sàrl is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Zydelig.

I. The Medicine and What is it Used for

Zydelig is authorized for the treatment of certain patients with chronic lymphocytic leukemia (CLL) or follicular lymphoma (FL) (see SmPC for the full indication). It contains idelalisib as the active substance and it is given by mouth.

Further information about the evaluation of Zydelig’s benefits can be found in Zydelig’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003843/human_med_001803.jsp&mid=WC0b01ac058001d124

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterize the Risks

Important risks of Zydelig, together with measures to minimize such risks and the proposed studies for learning more about Zydelig’s risks, are outlined below.

Measures to minimize 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 authorized 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 public (e.g. with or without prescription) can help to minimizes its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including PSUR assessment 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 Zydelig is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of Zydelig are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Zydelig. 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);

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	Hepatotoxicity including transaminase elevation and hepatocellular injury
	Severe diarrhoea/colitis
	Pneumonitis
	Serious infections (including opportunistic infections such as Pneumocystis jirovecii pneumonia [PJP] and cytomegalovirus [CMV] and in off-label use[a] [first line CLL therapy in patients without 17p deletion/TP53 mutation, early line indolent non-Hodgkin lymphoma [iNHL] therapy])
	Severe toxic skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
Important Potential Risks	Reproductive toxicity including teratogenicity
	Progressive multifocal leukoencephalopathy (PML)
Missing Information	Long-term safety
	Safety in patients with severe hepatic impairment

a Off-label use refers to use in conditions not approved by the EMA

II.B. Summary of Important Risks

Zydelig has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy should be initiated by a doctor experienced in the management of anticancer therapies (as described in section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Important Identified Risk	**Hepatotoxicity including Transaminase Elevation and Hepatocellular Injury**
Evidence for linking the risk to the medicine	High grade transaminase elevations have been observed in clinical studies of Zydelig. Increases in liver transaminases were generally observed within the first 12 weeks of treatment and were reversible with dose interruption. There have also been reports of hepatocellular injury, including hepatic failure, some of which were associated with a fatal outcome. The relationship of these events of hepatocellular injury to Zydelig is unclear.
Risk factors and risk groups	Known history of drug-induced liver injury, chronic active HCV, chronic active HBV, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension, elevated liver function tests.
Risk Minimization Measure(s)	*Routine risk communication:* SmPC sections 4.4 and 4.8 PL sections 2 and 4 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Recommendations on dose modification in the event of Grade 3 or 4 transaminase elevation are included in SmPC sections 4.2 and 4.4. Recommendations for liver function monitoring are included in SmPC section 4.4. *Additional risk minimization measures:* **None**
Important Identified Risk	**Severe Diarrhoea/colitis**
Evidence for linking the risk to the medicine	Cases of severe diarrhoea/colitis (≥ Grade 3) associated with idelalisib have occurred relatively late (months) after the start of therapy with idelalisib. Most cases resolved within a few weeks with drug interruption and additional treatment (eg, antidiarrheal and anti-inflammatory agents such as enteric budesonide), but some have been associated with a fatal outcome.
Risk factors and risk groups	Unknown
Risk Minimization Measure(s)	*Routine risk communication:* SmPC sections 4.4 and 4.8 PL sections 2 and 4 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Recommendations on dose modification in the event of Grade 3 or 4 diarrhoea/colitis are included in SmPC sections 4.2 and 4.4.

	Additional risk minimization measures: **None**
Important Identified Risk	**Pneumonitis**
Evidence for linking the risk to the medicine	Cases of pneumonitis, including organising pneumonia, some with fatal outcome, have occurred with idelalisib. The spectrum of clinical course severity of pneumonitis in the clinical trials was broad, and the range included resolution with oral steroid treatment in ambulatory care, serious pulmonary events requiring hospitalization without ventilation, respiratory failure requiring intensive care with eventual resolution, or rapid clinical deterioration leading to death despite high-dose systemic steroids.
Risk factors and risk groups	Co-exposure to a known pulmonary toxic agent**.**
Risk Minimization Measure(s)	*Routine risk communication:* SmPC sections 4.4 and 4.8 PL sections 2 and 4 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Recommendations on dose modification in the event of pneumonitis are included in SmPC sections 4.2 and 4.4. *Additional risk minimization measures:* **None**
Important Identified Risk	**Serious Infections (including opportunistic infections such as Pneumocystis jirovecii pneumonia [PJP] and cytomegalovirus [CMV] and in off-label use [first line CLL therapy in patients without 17p deletion/TP53 mutation, early line indolent non-Hodgkin lymphoma [iNHL] therapy])**
Evidence for linking the risk to the medicine	Serious and fatal infections have occurred with idelalisib, including opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV) and in first line treatment for CLL without 17p deletion/TP53 mutation and early line iNHL.
Risk factors and risk groups	Use of Zydelig in first line treatment for CLL without 17p deletion/TP53 mutation and early line iNHL. Exposure to prior chemotherapies, immunotherapies, and /or advanced haematological disease. The advanced age of the population treated with Zydelig and the frequent presence of comorbidities (eg, diabetes, COPD, heart disease).
Risk Minimization Measure(s)	*Routine risk communication:* SmPC sections 4.1, 4.4 and 4.8 PL sections 1, 2 and 4 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Recommendations on dose modification in the event of neutropenia are included in SmPC sections 4.2 and 4.4. Recommendations for monitoring absolute neutrophil count are included in SmPC section 4.4. How to detect early signs and symptoms of serious infections and recommendations on PJP prophylaxis/CMV monitoring are included in SmPC section 4.4.

	Additional risk minimization measures: **None**
Additional Pharmacovigilance activities	See Part VI Section II.C of this summary for an overview of the post-authorization development plan.
Important Identified Risk	**Severe Toxic Skin Reactions, including SJS and TEN**
Evidence for linking the risk to the medicine	Cases of SJS and TEN with fatal outcomes have been reported when Zydelig was administered concomitantly with other medications associated with these syndromes.
Risk factors and risk groups	Unknown
Risk Minimization Measure(s)	*Routine risk communication:* SmPC sections 4.4 and 4.8 PL sections 2 and 4 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Recommendations on dose modification in the event of Grade 3 or 4 rash are included in SmPC section 4.2. Recommendations on interrupting Zydelig in the event of suspected SJS or TEN are included in SmPC section 4.4. *Additional risk minimization measures:* **None**
Important Potential Risk	**Reproductive Toxicity including Teratogenicity**
Evidence for linking the risk to the medicine	Embryo-fetal death and malformation were observed in a study on the effect of Zydelig on embryo-fetal development in rats. Effects on embryo-foetal development were not investigated in a second species. No cases of reproductive toxicity or pregnancy associated with Zydelig use in women have been reported to date.
Risk factors and risk groups	Pregnant women and women of reproductive potential.
Risk Minimization Measure(s)	*Routine risk communication:* SmPC sections 4.6 and 5.3 PL sections 2 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Recommendations on contraceptive measures to be taken by women of childbearing potential are included in SmPC sections 4.4 and 4.6. *Additional risk minimization measures:* **None**
Important Potential Risk	**Progressive Multifocal Leukoencephalopathy (PML)**
Evidence for linking the risk to the medicine	Cases of progressive multifocal leukoencephalopathy (PML) have been reported following the use of idelalisib within the context of prior- or concomitant immunosuppressive therapies that have been associated with PML. Fatal cases have been reported.

Risk factors and risk groups	Co-exposure to immunochemotherapeutic medications, including fludarabine and select anti-CD20 monoclonal antibodies (eg, rituximab).
Risk Minimization Measure(s)	*Routine risk communication:* SmPC sections 4.4 PL section 2 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Recommendations on measures to facilitate the diagnosis of PML are included in SmPC section 4.4 *Additional risk minimization measures:* **None**
Missing information	**Long-term Safety**
Risk Minimization Measure(s)	No risk minimization measures.
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: GS-EU-313-4172 (Non-interventional study to assess the safety profile of Zydelig in patients with refractory FL) See Part VI Section II.C of this summary for an overview of the post-authorization development plan.
Missing information	**Safety in Patients with Severe Hepatic Impairment**
Risk Minimization Measure(s)	*Routine risk communication:* SmPC sections 4.2, 4.4, and 5.2 PL sections 2 *Routine risk minimization activities recommending specific clinical measures to address the risk:* Intensified monitoring of adverse reactions in patients with severe hepatic impairment is recommended in SmPC sections 4.2 and 4.4. *Additional risk minimization measures:* **None**

II.C. Post-authorization Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorization

None

II.C.2. Other Studies in Post-Authorization Development Plan

Table Part VI.3. Other Studies in Post-Authorization Development Plan

Short Study Name	Purpose of the Study
GS-EU-313-4172 Non-interventional study to assess the safety profile of Zydelig in patients with refractory FL	To assess the overall safety profile and effectiveness of idelalisib monotherapy in patients with refractory FL