Swiss Summary of the Risk Management Plan (RMP)

Venclyxto®

(Venetoclax)

10 mg, 50 mg, 100 mg

Film-coated tablets

Version 4 (03 February 2022)

Based on RMP, version 6.3, dated June 2021

AbbVie AG, Cham

Disclaimer

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 Venclyxto® 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 Venclyxto® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. AbbVie AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Venclyxto®.

Part VI: Summary of the Risk Management Plan

I. The Medicine and What it Is Used For

Venclyxto is authorized for the treatment of

CLL:

- Patients with previously untreated CLL in combination with obinutuzumab.
- CLL in combination with rituximab in adult patients who have received at least one prior therapy.
- CLL in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor; or
- CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.
- (See SmPC for the full indication)

AML

- Adult patients with newly-diagnosed AML in combination with a hypomethylating agent or low dose cytarabine who are ineligible for intensive chemotherapy.

It contains venetoclax as the active substance and it is given by mouth.

Further information about the evaluation of Venclyxto's benefits can be found in Venclyxto's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

[http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/004106/WC500218803.pdf].

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

Important risks of Venclyxto, together with measures to minimize such risks and the proposed studies for learning more about Venclyxto'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 patient (e.g., with or without prescription) can help to minimize 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 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 Venclyxto is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of Venclyxto are risks that need risk management activities to further investigate or minimize 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 Venclyxto. 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	• Tumor lysis syndrome • Neutropenia • Serious infection
Important potential risks	• Embryofetal toxicity • Medication error • Richter's transformation (for CLL only) • Second primary malignancy • Toxicity in patients with severe hepatic impairment
Missing information	• Safety in severe renal impairment • Safety in long-term exposure (> 12 months) (for CLL only)

II.B Summary of Important Risks

The SmPC was used for the CLL and AML indications.

The table contains safety information from the SmPC for CLL and AML (Venclyxto + HMA) indications and additional information for the Venclyxto + LDAC in AML indication from the CCDS.

Important identified risk: Tumor lysis syndrome	
Evidence for linking the risk to the medicine	Because CLL cells are essentially 'addicted' to BCL-2 for survival and are exquisitely sensitive to venetoclax, an on-target pharmacological effect can cause rapid reduction in size of tumor (debulk) and may pose a risk of TLS. TLS could also be a risk in AML, as primary AML cells have also been shown in preclinical studies to be highly sensitive to venetoclax, either alone or in combination with azacitidine or cytarabine.
Risk factors and risk groups	The risk is more among subjects who have high tumor burden. Also, subjects with renal dysfunction or splenomegaly may be at added risk. These risk factors are not unique to venetoclax. They are consistent with that reported in literature, e.g., patients with bulky disease (including elevated white blood cell [WBC] count in patients with CLL), renal dysfunction, and baseline elevations in uricacid are at higher risk (Blum 2011). In a study involving 772 chemotherapy treated patients with AML, factors significantly associated with increased risk of clinical and laboratory TLS included elevated WBC (≥ 25 - 75 × 10^9/L), uric acid (> 7.5 mg/dL), lactate dehydrogenase (≥ 1 - 4 × ULN) and creatinine (> 1.4 mg/dL) (Montesinos 2008).
Risk minimization measures	Routine risk minimization measures: Posology and method of administration, including prophylactic measures for TLS, are described in section 4.2 of the SmPC (CLL and venetoclax + HMAs in AML) and section 3.1.2 and section 3.4.2of the CCDS (venetoclax + LDAC in AML). Warnings and precautions for TLS are listed in section 4.4 of theSmPC (CLL and AML). Interaction with other medicinal products is described in section 4.5of the SmPC (CLL and AML). TLS is described in section 4.8 of the SmPC (CLL and venetoclax +HMAs in AML) and section 9.2 and section 9.3 of the CCDS (venetoclax + LDAC in AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Packaging design and language to facilitate adherence to the dose titration schedule • Pack size and package leaflet

Important identified risk: Neutropenia	
Evidence for linking the risk to the medicine	Risk is based on suspected BCL-2 mechanism-based toxicity with a BCL-2 inhibitor (venetoclax) (Leverson 2015).
Risk factors and risk groups	In CLL, risk factors for neutropenia include older age, poor performance status, advanced disease, low baseline blood cell counts, low nutritional status, and prior treatment with myelosuppressive chemotherapies (Lyman 2005). The population included in venetoclax studies has risk factors consistent with that described in literature. In AML, the target population, in general, has a high risk for neutropenia. In AML studies, the average age of patients are above 70 years of age. In these patients, there are no particular risk factors or groups that contribute further to the risk of neutropenia.
Risk minimization measures	Routine risk minimization measures: Posology and method of administration are described in section 4.2 of the SmPC (CLL and venetoclax + HMAs in AML). Dose modifications are described in section 3.5 of the CCDS (venetoclax + LDAC in AML). Warnings and precautions for neutropenia are listed in section 4.4 of the SmPC (CLL and AML). Neutropenia is listed as a very common adverse reaction in section 4.8 of the SmPC (CLL and venetoclax + HMAs in AML) and sections 9.2 and 9.3 of the CCDS (venetoclax + LDAC in AML). Other routine risk minimization measures: • Prescription only medicine. • Use of treatment should be initiated and supervised by specialist • Package leaflet

Important identified risk: Serious infection	
Evidence for linking the risk to the medicine	CLL: Lymphopenia and neutropenia are on-target effects of venetoclax. Although their role in the pathogenesis of serious infections cannot be ruled out, to date attribution of serious infections to cytopenia has not been established. AML: AML patients have a high background rate of neutropenia and are more susceptible to infections.
Risk factors and risk groups	Risk factors for the development of serious infection in CLL patients include age, decreased immunoglobulin levels, neutropenia, treatment with more than one line of chemotherapy, clinical stage at diagnosis, IgVH mutation status, high serum creatinine concentration, advanced disease stage, previous anti-neoplastic therapy, refractoriness to fludarabine-based therapy, high serum β2-microglobulin level, low serum albumin level and a low granulocyte count (Anaissie 1998, Molteni 2005, Francis 2006). All patients with AML are at risk of infection and patients with poor-prognosis cytogenetics and low hemoglobin (< 10) and platelet count (< 20,000 cells/µL) at presentation have been reported to amongst the most high risk (Merkel 2013). The population studied in the venetoclax development programme is consistent with that described in literature.
Risk minimization measures	Routine risk minimization measures: Posology and method of administration are described in section 4.2 of the SmPC (CLL and AML). Supportive measures for infections associated with neutropenia are described in section 4.4 of the SmPC (CLL and AML). Observed infections and infestations are tabulated in section 4.8 (CLL and venetoclax + HMA in AML) and section 9.2 and section 9.3 in the CCDS (venetoclax + LDAC in AML).Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist • Package leaflet

Important potential risk: Embryofetal toxicity	
Evidence for linking the risk to the medicine	The pro-apoptotic mechanism of action for venetoclax is consistent with anticipated embryotoxicity. The wide distribution of Bcl-2 in the developing embryo (pre- and post-implantation) suggests that many immature cells require a death repressor protein, and pharmacological perturbation of these anti-apoptotic proteins (with drugs such as venetoclax), can alter embryo development. This is evidenced by studies that have demonstrated that knockout or knock down of Bcl-2 family proteins can adversely affect embryo growth and development (LeBrun 1993, Novack 1994, Boumela 2011).
Risk factors and risk groups	Women of childbearing potential
Risk minimization measures	Routine risk minimization measures: Language concerning embryofetal toxicity is included in section 4.6 and section 5.3 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet

Important potential risk: Medication error	
Evidence for linking the risk to the medicine	CLL Potential intentional errors in the prescribing, dispensing, and administration of venetoclax especially during the gradual dose increase over a period of 5 weeks up to the recommended daily dose of 400 mg. AML Medication errors including prescribing, dispensing or administration of venetoclax may occur during the 3 - 4-day ramp-up phase with a starting dose of 100 mg or at the recommended daily dose
Risk factors and risk groups	CLL: Risk groups include elderly CLL patients. Risk factors include venetoclax having three different tablet strengths and use during the 5-week dose-titration period. AML: Risk groups include elderly AML patients. Risk factors include venetoclax dose ramp-up over 3 - 4 days, during which 100-mg tablets are used (multiple tablets to be administered).
Risk minimization measures	Routine risk minimization measures: Posology and method of administration are described in section 4.2 of the SmPC (CLL and AML). Dose titration is described in section 3.1.2 of the CCDS (venetoclax + LDAC in AML). Description of contents of venetoclax container, including dose strength, shape and color of tablets, in section 3 and section 6.5 of SmPC (CLL). Language concerning overdose is included in section 4.9 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • In CLL, each carton will be dispensed weekly to the patient during the first 4 weeks of the dose titration • In AML, only 100 mg tablets will be dispensed to minimize medication errors • Labeling and packaging layout (immediate and outer packaging) has been designed to minimize medication errors • Pack size and package leaflet

Important potential risk: Richter's transformation (for CLL only)	
Evidence for linking the risk to the medicine	Unknown
Risk factors and risk groups	Risk factors include R/R CLL disease, 17p del, multiple prior cytotoxic therapies, prior fludarabine-based therapy.
Risk minimization measures	Routine risk minimization measures: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Studies GO28667 (MURANO), M14-032, M13-982, and M12-175. See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk: Second primary malignancy	
Evidence for linking the risk to the medicine	Unknown
Risk factors and risk groups	CLL patients with R/R disease, multiple prior cytotoxic therapies, prior fludarabine-based therapy
Risk minimization measures	Routine risk minimization measures: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLL only Studies GO28667 (MURANO), M12-175, M14-032, M13-982, and P16-562

Important potential risk: Toxicity in patients with severe hepatic impairment	
Evidence for linking the risk to the medicine	Patients with severe hepatic impairment may have higher venetoclax systemic exposures due to reduced hepatic elimination.
Risk factors and risk groups	Patients with severe hepatic impairment are at risk
Risk minimization measures	Routine risk minimization measures: Posology and method of administration including dose modification, included in section 4.2 of the SmPC (CLL and AML). PK study results pertaining to hepatic impairment are included in section 5.2 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet

Missing information: Safety in severe renal impairment	
Risk minimization measures	Routine risk minimization measures: Section 4.2 of the SmPC advises that safety and efficacy have not yet been established in certain populations (CLL and AML). Section 5.2 of the SmPC presents PK study results pertaining to renal impairment (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet

Missing information: Safety in long-term exposure (> 12 months) (for CLL only)	
Risk minimization measures	Routine risk minimization measures: Median duration of treatment is included in section 5.1 of the SmPC Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLL: Studies GO28667 (MURANO), M14-032, M13-982, M12-175, and Study P16-562 See Section II.C of this summary for an overview of the post-authorization development plan.

II.C Post-Authorization Development Plan

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

Not applicable.

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

CLL

Study short name: Study M14-032

Purpose of this study: to assess the efficacy and safety of venetoclax monotherapy in subjects with CLL relapsed after or refractory to treatment with ibrutinib or idelalisib.

Study short name: Study GO28667 (MURANO)

Purpose of this study: to evaluate the safety and efficacy of venetoclax and rituximab compared with BR in subjects with R/R CLL.

Study short name: Study M13-982

Purpose of this study: to evaluate the safety and efficacy of venetoclax monotherapy in subjects with R/R CLL in the presence of 17p deletion or TP53 mutations.

Study short name: Study M12-175

Purpose of this study: to assess the safety profile; characterize pharmacokinetics (PK); determine maximum tolerated dose, recommended Phase 2 dose, and lead-in period regimen of venetoclax monotherapy in subjects with R/R CLL (Arm A) or NHL (Arm B).

Study short name: Study P16-562

This is a prospective observational cohort study to assess the safety of venetoclax in the Swedish cohort of CLL patients.

Purpose of this study: to assess the long-term safety of venetoclax using a prospective cohort containing both venetoclax exposed and non-exposed patients.

Study short name: Study M16-185

This is a clinical drug-drug interaction study with an oral contraceptive.

Purpose of study: to assess the effect of venetoclax on the pharmacokinetics of oral contraceptives in patients with a hematologic malignancy.