# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

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

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 10 mg film-coated tablets
Venclyxto 50 mg film-coated tablets
Venclyxto 100 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Venclyxto 10 mg film-coated tablets
Each film-coated tablet contains 10 mg of venetoclax.

Venclyxto 50 mg film-coated tablets
Each film-coated tablet contains 50 mg of venetoclax.

Venclyxto 100 mg film-coated tablets
Each film-coated tablet contains 100 mg of venetoclax.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Venclyxto 10 mg film-coated tablet
Pale yellow, round biconvex shaped tablet 6 mm diameter debossed with V on one side and 10 on the other.

Venclyxto 50 mg film-coated tablet
Beige, oblong biconvex shaped tablet 14 mm long, 8 mm wide debossed with V on one side and 50 on the other.

Venclyxto 100 mg film-coated tablet
Pale yellow, oblong biconvex shaped tablet 17.2 mm long, 9.5 mm wide debossed with V on one side and 100 on the other.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

Venclyxto in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

Venclyxto monotherapy is indicated for the treatment of 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
- in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

## 4.2 Posology and method of administration

Treatment with venetoclax should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

*Dose-titration schedule*

The starting dose is 20 mg of venetoclax once daily for 7 days. The dose must be gradually increased over a period of 5 weeks up to the daily dose of 400 mg as shown in Table 1.

Table 1: Dose increase schedule

| Week | Venetoclax daily dose |
|---|---|
| 1 | 20 mg |
| 2 | 50 mg |
| 3 | 100 mg |
| 4 | 200 mg |
| 5 | 400 mg |

The 5-week dose-titration schedule is designed to gradually reduce tumour burden (debulk) and decrease the risk of tumour lysis syndrome.

*Venetoclax in combination with obinutuzumab*

Venetoclax is given for a total of 12 cycles, each cycle consisting of 28 days: 6 cycles in combination with obinutuzumab, followed by 6 cycles of venetoclax as a single agent.

Administer obinutuzumab 100 mg on Cycle 1 Day 1, followed by 900 mg which may be administered on Day 1 or Day 2. Administer 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle, for a total of 6 cycles.

Start the 5-week venetoclax dose-titration schedule (see Table 1) on Cycle 1 Day 22 and continue through Cycle 2 Day 28.

After completing the dose-titration schedule, the recommended dose of venetoclax is 400 mg once daily from Cycle 3 Day 1 of obinutuzumab to the last day of Cycle 12.

*Post-titration dose for venetoclax in combination with rituximab*

The recommended dose of venetoclax in combination with rituximab is 400 mg once daily (see section 5.1 for details of the combination regimen).

Administer rituximab after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days.

Venetoclax is taken for 24 months from Cycle 1 Day 1 of rituximab (see section 5.1).

*Post-titration dose for venetoclax monotherapy*

The recommended dose of venetoclax is 400 mg once daily. Treatment is continued until disease progression or no longer tolerated by the patient.

*Prevention of tumour lysis syndrome (TLS)*
Venetoclax can cause rapid reduction in tumour, and thus poses a risk for TLS in the initial 5-week dose-titration phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including comorbidities. Patients with high tumour burden (e.g., any lymph node with a diameter ≥5 cm or high absolute lymphocyte count [ALC ≥25 x $10^9$/l]) are at greater risk of TLS when initiating venetoclax. Reduced renal function (creatinine clearance [CrCl] <80 ml/min) further increases the risk. The risk may decrease as tumour burden decreases with venetoclax treatment (see section 4.4).

Prior to initiating venetoclax, tumour burden assessment, including radiographic evaluation (e.g., CT scan), must be performed for all patients. Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) should be assessed and pre-existing abnormalities corrected. The prophylaxis measures listed below should be followed. More intensive measures should be employed as overall risk increases.

*Hydration*
Patients should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink plenty of water daily starting 2 days before and throughout the dose-titration phase. Patients should be particularly instructed to drink 1.5 to 2.0 L of water daily, 2 days prior to and the days of dosing at initiation and each subsequent dose increase. Intravenous fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration.

*Anti-hyperuricaemic agents*
Anti-hyperuricaemic agents should be administered 2 to 3 days prior to starting treatment with venetoclax in patients with high uric acid levels or at risk of TLS and may be continued through the titration phase.

*Laboratory assessments*
Pre-dose: For all patients, blood chemistries should be assessed prior to the initial dose to evaluate kidney function and correct pre-existing abnormalities. Blood chemistries should be reassessed prior to each subsequent dose increase during the titration phase.

Post-dose: For patients at risk of TLS, blood chemistries should be monitored at 6 to 8 hours and at 24 hours after the first dose of venetoclax. Electrolyte abnormalities should be corrected promptly. The next venetoclax dose should not be administered until the 24-hour blood chemistry results have been evaluated. The same monitoring schedule should be followed at the start of the 50 mg dose and then for patients who continue to be at risk, at subsequent dose increases.

*Hospitalisation*
Based on physician assessment, some patients, especially those at greater risk of TLS, may require hospitalisation on the day of the first dose of venetoclax for more intensive prophylaxis and monitoring during the first 24 hours (see section 4.8). Hospitalisation should be considered for subsequent dose increases based on reassessment of risk.

*Dose modifications for tumour lysis syndrome*
If a patient experiences blood chemistry changes suggestive of TLS, the following day's venetoclax dose should be withheld. If resolved within 24 to 48 hours of last dose, treatment with venetoclax can be resumed at the same dose. For events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve, treatment should be resumed at a reduced dose (see Table 2). When resuming treatment after interruption due to TLS, the instructions for prevention of TLS should be followed (see "Prevention of tumour lysis syndrome" above).

*Dose modifications for other toxicities*
Treatment with Venclyxto should be withheld for any grade 3 or 4 non-haematological toxicities, grade 3 or 4 neutropenia with infection or fever, or grade 4 haematological toxicities, except lymphopenia. Once the toxicity has resolved to grade 1 or baseline level (recovery), therapy with venetoclax may be restarted at the same dose. If the toxicity recurs, and for any subsequent occurrences, the dose reduction guidelines in

Table 2 should be followed when resuming treatment with venetoclax following resolution. A larger dose reduction may occur at the discretion of the physician. For patients who require dose reductions to less than 100 mg for more than 2 weeks, discontinuation of venetoclax should be considered.

Table 2: Dose modification for TLS and other toxicities

| **Dose at interruption (mg)** | **Restart dose (mg[a])** |
|---|---|
| 400 | 300 |
| 300 | 200 |
| 200 | 100 |
| 100 | 50 |
| 50 | 20 |
| 20 | 10 |
| [a]The modified dose should be continued for 1 week before increasing the dose. | |

For patients who have had a dosing interruption lasting more than 1 week during the first 5 weeks of dose titration or more than 2 weeks after completing the dose-titration phase, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g., all or some levels of the dose titration; see Table 2).

*Dose modifications for use with CYP3A inhibitors*
Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase and for other toxicities (see section 4.5).

Table 3 describes Venclyxto contraindication or dosage modification based on concomitant use with a strong or moderate CYP3A inhibitor. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor (see sections 4.3, 4.4 and 4.5).

Table 3: Management of potential Venclyxto interactions with CYP3A inhibitors

| **Inhibitors** | **Initiation and titration phase** [a] | **Steady daily dose (After titration phase)** |
|---|---|---|
| Strong CYP3A inhibitor | Contraindicated | Reduce the Venclyxto dose by at least 75% |
| Moderate CYP3A inhibitor | Reduce the Venclyxto dose by at least 50% | |
| [a]Avoid concomitant use of Venclyxto with moderate CYP3A inhibitors at initiation and during the dose titration phase. Consider alternative medications or reduce the Venclyxto dose as described in this table. | | |

*Missed dose*
If a patient misses a dose of venetoclax within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible on the same day. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the following day.

If a patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day.

*Special populations*

*Elderly*

No specific dose adjustment is required for elderly patients (aged ≥65 years) (see section 5.1).

*Renal impairment*
No dose adjustment is needed for patients with mild or moderate renal impairment (CrCl ≥30 ml/min and <90 ml/min) (see section 5.2). Patients with reduced renal function (CrCl <80 ml/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS at initiation and during the dose-titration phase (see "Prevention of tumour lysis syndrome" above). Safety in patients with severe renal impairment (CrCl <30 ml/min) or on dialysis has not been established, and a recommended dose for these patients has not been determined. Venetoclax should be administered to patients with severe renal impairment only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity due to increased risk of TLS (see section 4.4).

*Hepatic impairment*
No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Patients with moderate hepatic impairment should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase (see section 4.8).

A dose reduction of at least 50% throughout treatment is recommended for patients with severe hepatic impairment (see section 5.2). These patients should be monitored more closely for signs of toxicity (see section 4.8).

*Paediatric population*
The safety and efficacy of venetoclax in children aged less than 18 years have not been established. No data are available.

Method of administration

Venclyxto film-coated tablets are for oral use. Patients should be instructed to swallow the tablets whole with water at approximately the same time each day. The tablets should be taken with a meal in order to avoid a risk for lack of efficacy (see section 5.2). The tablets should not be chewed, crushed, or broken before swallowing.

During the dose-titration phase, venetoclax should be taken in the morning to facilitate laboratory monitoring.

Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax (see section 4.5).

## 4.3 Contraindications

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

Concomitant use of strong CYP3A inhibitors at initiation and during the dose-titration phase (see sections 4.2 and 4.5).

Concomitant use of preparations containing St. John's wort (see sections 4.4 and 4.5).

## 4.4 Special warnings and precautions for use

Tumour lysis syndrome

Tumour lysis syndrome, including fatal events, has occurred in patients with CLL with high tumour burden when treated with venetoclax (see section 4.8).

Venetoclax can cause rapid reduction in tumour, and thus poses a risk for TLS in the initial 5-week dose-titration phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including comorbidities. Patients with high tumour burden (e.g., any lymph node with a diameter ≥5 cm or high ALC ≥25 x $10^9$/l) are at greater risk of TLS when initiating venetoclax. Reduced renal function (CrCl <80 ml/min) further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricaemics. Blood chemistries should be monitored and abnormalities managed promptly. Dosing should be interrupted if needed (see section 4.2). More intensive measures (intravenous hydration, frequent monitoring, hospitalisation) should be employed as overall risk increases. The instructions for "Prevention of tumour lysis syndrome" should be followed (see section 4.2).

Concomitant use of this medicinal product with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase (see sections 4.2 and 4.3). Also, inhibitors of P-gp or BCRP may increase venetoclax exposure (see section 4.5).

Neutropenia and infections

Grade 3 or 4 neutropenia has been reported in patients treated with venetoclax in combination studies with rituximab or obinutuzumab and in monotherapy studies (see section 4.8). Complete blood counts should be monitored throughout the treatment period. Dose interruptions or reductions are recommended for patients with severe neutropenia (see section 4.2).

Serious infections, including sepsis with fatal outcome, have been reported (see section 4.8). Monitoring of any signs and symptoms of infection is required. Suspected infections are to receive prompt treatment, including antimicrobials and dose interruption or reduction as appropriate (see section 4.2).

Immunisation

The safety and efficacy of immunisation with live attenuated vaccines during or following venetoclax therapy have not been studied. Live vaccines should not be administered during treatment and thereafter until B-cell recovery.

CYP3A inducers

Co-administration of CYP3A4 inducers may lead to decreased venetoclax exposure and consequently a risk for lack of efficacy. Concomitant use of venetoclax with strong or moderate CYP3A4 inducers should be avoided (see sections 4.3 and 4.5).

Women of childbearing potential

Women of childbearing potential must use a highly effective method of contraception while taking venetoclax (see section 4.6).

## 4.5 Interaction with other medicinal products and other forms of interaction

Venetoclax is predominantly metabolised by CYP3A.

Agents that may alter venetoclax plasma concentrations

*CYP3A inhibitors*

Co-administration of 400 mg once daily ketoconazole, a strong CYP3A, P-gp and BCRP inhibitor, for 7 days in 11 previously treated patients with NHL increased venetoclax $C_{max}$ by 2.3-fold and $AUC_{\infty}$ by 6.4-fold. Co-administration of 50 mg once daily ritonavir, a strong CYP3A and P-gp inhibitor, for 14 days in 6 healthy subjects increased venetoclax $C_{max}$ by 2.4-fold and AUC by 7.9-fold. Co-administration of venetoclax with other strong CYP3A4 inhibitors is predicted to increase venetoclax AUC by on average 5.8- to 7.8-fold.

Concomitant use of venetoclax with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir) at initiation and during the dose-titration phase is contraindicated due to increased risk for TLS (see section 4.3).

At initiation and during the dose-titration phase, concomitant use of venetoclax with moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil) should be avoided. Alternative treatments should be considered. If a moderate CYP3A inhibitor must be used, the initiation dose of venetoclax and the doses for the titration phase (see section 4.2) should be reduced by at least 50%. Patients should be monitored more closely for signs and symptoms of TLS.

For patients who have completed the dose-titration phase and are on a steady daily dose of venetoclax, the venetoclax dose should be reduced by 50% when used concomitantly with moderate CYP3A inhibitors and by 75% when used concomitantly with strong CYP3A inhibitors. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor (see section 4.2).

Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax as they contain inhibitors of CYP3A.

*P-gp and BCRP inhibitors*
Venetoclax is a substrate for P-gp and BCRP. Co-administration of a 600 mg single dose of rifampin, a P-gp inhibitor, in 11 healthy subjects increased venetoclax $C_{max}$ by 106% and $AUC_{\infty}$ by 78%. Concomitant use of venetoclax with P-gp and BCRP inhibitors at initiation and during the dose-titration phase should be avoided; if a P-gp and BCRP inhibitor must be used, patients should be monitored closely for signs of toxicities (see section 4.4).

*CYP3A inducers*
Co-administration of 600 mg once daily rifampin, a strong CYP3A inducer, for 13 days in 10 healthy subjects decreased venetoclax $C_{max}$ by 42% and $AUC_{\infty}$ by 71%. Concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered. Preparations containing St. John's wort are contraindicated during treatment with venetoclax, as efficacy may be reduced (see section 4.3).

*Azithromycin*
In a drug-drug interaction study in 12 healthy subjects, co-administration of 500 mg of azithromycin on the first day followed by 250 mg of azithromycin once daily for 4 days decreased venetoclax $C_{max}$ by 25% and $AUC_{\infty}$ by 35%. No dose adjustment is needed during short-term use of azithromycin when administered concomitantly with venetoclax.

*Gastric acid reducing agents*
Based on population pharmacokinetic analysis, gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) do not affect venetoclax bioavailability.

*Bile acid sequestrants*
Co-administration of bile acid sequestrants with venetoclax is not recommended as this may reduce the absorption of venetoclax. If a bile acid sequestrant is to be co-administered with venetoclax, the SmPC for the bile acid sequestrant should be followed to reduce the risk for an interaction, and venetoclax should be administered at least 4-6 hours after the sequestrant.

Agents that may have their plasma concentrations altered by venetoclax

*Warfarin*
In a drug-drug interaction study in three healthy volunteers, administration of a single dose of 400 mg venetoclax with 5 mg warfarin resulted in an 18% to 28% increase in $C_{max}$ and $AUC_{\infty}$ of R-warfarin and

S-warfarin. Because venetoclax was not dosed to steady state, it is recommended that the international normalized ratio (INR) be monitored closely in patients receiving warfarin.

*Substrates of P-gp, BCRP, and OATP1B1*
Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor *in vitro*. In a drug-drug interaction study, administration of a single 100 mg dose of venetoclax with 0.5 mg digoxin, a P-gp substrate, resulted in a 35% increase in digoxin $C_{max}$ and a 9% increase in digoxin $AUC_{\infty}$. Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g., digoxin, dabigatran, everolimus, sirolimus) with venetoclax should be avoided.

If a narrow therapeutic index P-gp or BCRP substrate must be used, it should be used with caution. For an orally administered P-gp or BCRP substrate sensitive to inhibition in the gastrointestinal tract (e.g., dabigatran exetilate), its administration should be separated from venetoclax administration as much as possible to minimise a potential interaction.

If a statin (OATP substrate) is used concomitantly with venetoclax, close monitoring of statin-related toxicity is recommended.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women should avoid becoming pregnant while taking Venclyxto and for at least 30 days after ending treatment. Therefore, women of childbearing potential must use highly effective contraceptive measures while taking venetoclax and for 30 days after stopping treatment. It is currently unknown whether venetoclax may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method.

Pregnancy

Based on embryo-foetal toxicity studies in animals (see section 5.3), venetoclax may harm the foetus when administered to pregnant women.

There are no adequate and well-controlled data from the use of venetoclax in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Venetoclax is not recommended during pregnancy and in women of childbearing potential not using highly effective contraception.

Breast-feeding

It is unknown whether venetoclax or its metabolites are excreted in human milk.

A risk to the breast-feeding child cannot be excluded.

Breast-feeding should be discontinued during treatment with Venclyxto.

Fertility

No human data on the effect of venetoclax on fertility are available. Based on testicular toxicity in dogs at clinically relevant exposures, male fertility may be compromised by treatment with venetoclax (see section 5.3). Before starting treatment, counselling on sperm storage may be considered in some male patients.

## 4.7 Effects on ability to drive and use machines

Venclyxto has no or negligible influence on the ability to drive and use machines. Fatigue has been reported in some patients taking venetoclax and should be considered when assessing a patient's ability to drive or operate machines.

## 4.8 Undesirable effects

Summary of safety profile

The overall safety profile of Venclyxto is based on data from 758 patients with CLL treated in clinical trials with venetoclax in combination with obinutuzumab or rituximab or as monotherapy. The safety analysis included patients from two phase 3 studies (CLL14 and MURANO), two phase 2 studies (M13-982 and M14-032), and one phase 1 study (M12-175). CLL14 was a randomised, controlled trial in which 212 patients with previously untreated CLL and comorbidities received venetoclax in combination with obinutuzumab. MURANO was a randomised, controlled trial in which 194 patients with previously treated CLL received venetoclax in combination with rituximab. In the phase 2 and phase 1 studies, 352 patients with previously treated CLL, which included 212 patients with 17p deletion and 146 patients who had failed a B-cell receptor pathway inhibitor were treated with venetoclax monotherapy (see section 5.1).

The most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in the combination studies with obinutuzumab or rituximab were neutropenia, diarrhoea, and upper respiratory tract infection. In the monotherapy studies, the most common adverse reactions were neutropenia/neutrophil count decreased, diarrhoea, nausea, anaemia, fatigue, and upper respiratory tract infection.

The most frequently reported serious adverse reactions (≥2%) in patients receiving venetoclax in combination with obinutuzumab or rituximab were pneumonia, sepsis, febrile neutropenia, and TLS. In the monotherapy studies, the most frequently reported serious adverse reactions (≥2%) were pneumonia and febrile neutropenia.

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Venclyxto, either in combination with obinutuzumab or rituximab or as monotherapy, are summarised in Table 4. Adverse reactions are listed below by MedDRA body system organ class and by frequency. 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), very rare (<1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Adverse drug reactions reported in patients with CLL treated with venetoclax

| System organ class | Frequency (all grades)[a] | Adverse reactions | Grade ≥3[a] |
|---|---|---|---|
| **Infections and infestations** | Very common | Pneumonia<br>Upper respiratory tract infection | |
| | Common | Sepsis<br>Urinary tract infection | Sepsis<br>Pneumonia<br>Urinary tract infection<br>Upper respiratory tract infection |
| **Blood and lymphatic system disorders** | Very common | Neutropenia<br>Anaemia<br>Lymphopenia | Neutropenia<br>Anaemia |
| | Common | Febrile neutropenia | Febrile neutropenia<br>Lymphopenia |
| **Metabolism and nutrition disorders** | Very common | Hyperkalaemia<br>Hyperphosphataemia<br>Hypocalcaemia | |
| | Common | Tumour lysis syndrome<br>Hyperuricaemia | Tumour lysis syndrome<br>Hyperkalaemia<br>Hyperphosphataemia<br>Hypocalcaemia<br>Hyperuricaemia |
| **Gastrointestinal disorders** | Very common | Diarrhoea<br>Vomiting<br>Nausea<br>Constipation | |
| | Common | | Diarrhoea<br>Vomiting<br>Nausea |
| | Uncommon | | Constipation |
| **General disorders and administration site conditions** | Very common | Fatigue | |
| | Common | | Fatigue |
| **Investigations** | Common | Blood creatinine increased | |
| | Uncommon | | Blood creatinine increased |

[a]Only the highest frequency observed in the trials is reported (based on studies CLL14, MURANO, M13-982, M14-032, and M12-175).

*Discontinuation and dose reductions due to adverse reactions*

Discontinuations due to adverse reactions occurred in 16% of patients treated with venetoclax in combination with obinutuzumab or rituximab in the CLL14 and MURANO studies, respectively. In the monotherapy studies with venetoclax, 11% of patients discontinued due to adverse reactions.

Dosage reductions due to adverse reactions occurred in 21% of patients treated with the combination of venetoclax and obinutuzumab in the CLL14 study, in 15% of patients treated with the combination of

venetoclax and rituximab in the MURANO study and 14% of patients treated with venetoclax in the monotherapy studies.

Dose interruptions due to adverse reactions occurred in 74% of patients treated with the combination of venetoclax and obinutuzumab in the CLL14 study and in 71% of patients treated with the combination of venetoclax and rituximab in the MURANO study; the most common adverse reaction that led to dose interruption of venetoclax was neutropenia (41% and 43% in the CLL14 and MURANO studies, respectively). In the monotherapy studies with venetoclax, dose interruptions due to adverse reactions occurred in 40% of patients; the most common adverse reaction leading to dose interruption was neutropenia (5%).

Description of selected adverse reactions

*Tumour lysis syndrome*
Tumour lysis syndrome is an important identified risk when initiating venetoclax. In the initial Phase 1 dose-finding studies, which had a shorter (2 to 3 week) titration phase and higher starting dose, the incidence of TLS was 13% (10/77; 5 laboratory TLS; 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis.

The risk of TLS was reduced after revision of the dosing regimen and modification to prophylaxis and monitoring measures. In venetoclax clinical studies, patients with any measurable lymph node ≥10 cm or those with both an ALC ≥25 x $10^9$/l and any measurable lymph node ≥5 cm were hospitalised to enable more intensive hydration and monitoring for the first day of dosing at 20 mg and 50 mg during the titration phase (see section 4.2).

In 168 patients with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg in studies M13-982 and M14-032, the rate of TLS was 2%. All events were laboratory TLS (laboratory abnormalities that met ≥2 of the following criteria within 24 hours of each other: potassium >6 mmol/l, uric acid >476 µmol/l, calcium <1.75 mmol/l, or phosphorus >1.5 mmol/l; or were reported as TLS events) and occurred in patients who had a lymph node(s) ≥5 cm or ALC ≥25 x $10^9$/l. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden death and/or seizures was observed in these patients. All patients had CrCl ≥50 ml/min.

In the open-label, randomised phase 3 study (MURANO), the incidence of TLS was 3% (6/194) in patients treated with venetoclax + rituximab. After 77/389 patients were enrolled in the study, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures described in Posology (see section 4.2). All events of TLS occurred during the venetoclax dose-titration phase and resolved within two days. All six patients completed the dose titration and reached the recommended daily dose of 400 mg of venetoclax. No clinical TLS was observed in patients who followed the current 5-week dose-titration schedule and TLS prophylaxis and monitoring measures (see section 4.2). The rates of grade ≥3 laboratory abnormalities relevant to TLS were hyperkalaemia 1%, hyperphosphataemia 1%, and hyperuricaemia 1%.

In the open-label, randomised phase 3 study (CLL14), the incidence of TLS was 1.4% (3/212) in patients treated with venetoclax + obinutuzumab. All three events of TLS resolved and did not lead to withdrawal from the study. Obinutuzumab administration was delayed in two cases in response to the TLS events.

*Neutropenia and infections*
Neutropenia is an identified risk with Venclyxto treatment. In the CLL14 study, neutropenia (all grades) was reported in 58% of patients in the venetoclax + obinutuzumab arm; 41% of patients treated with venetoclax + obinutuzumab experienced dose interruption and 2% of patients discontinued venetoclax due to neutropenia. Grade 3 neutropenia was reported in 25% of patients and grade 4 neutropenia in 28% of patients. The median duration of grade 3 or 4 neutropenia was 22 days (range: 2 to 363 days). Febrile neutropenia was reported in 6% of patients, grade ≥3 infections in 19%, and serious infections in 19% of patients. Deaths due to infection occurred in 1.9% of patients while on treatment and 1.9% of patients following treatment discontinuation.
In the MURANO study, neutropenia (all grades) was reported in 61% of patients in the venetoclax + rituximab arm. Forty-three percent of patients treated with venetoclax + rituximab experienced

dose interruption and 3% of patients discontinued venetoclax due to neutropenia. Grade 3 neutropenia was reported in 32% of patients and grade 4 neutropenia in 26% of patients. The median duration of grade 3 or 4 neutropenia was 8 days (range: 1 to 712 days). With venetoclax + rituximab treatment, febrile neutropenia was reported in 4% of patients, grade ≥3 infections in 18%, and serious infections in 21% of patients.

Reporting of suspected adverse reactions

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

### 4.9 Overdose

There is no specific antidote for venetoclax. Patients who experience overdose should be closely monitored and appropriate supportive treatment provided. During dose-titration phase, treatment should be interrupted and patients should be monitored carefully for signs and symptoms of TLS (fever, chills, nausea, vomiting, confusion, shortness of breath, seizures, irregular heartbeat, dark or cloudy urine, unusual tiredness, muscle or joint pain, abdominal pain and distension) along with other toxicities (see section 4.2). Based on venetoclax large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, ATC code: L01XX52

Mechanism of action

Venetoclax is a potent, selective inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumour cell survival and has been associated with resistance to chemotherapeutics. Venetoclax binds directly to the BH3-binding groove of BCL-2, displacing BH3 motif-containing pro-apoptotic proteins like BIM, to initiate mitochondrial outer membrane permeabilization (MOMP), caspase activation, and programmed cell death. In non-clinical studies, venetoclax has demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.

Pharmacodynamic effects

*Cardiac electrophysiology*
The effect of multiple doses of venetoclax up to 1200 mg once daily on the QTc interval was evaluated in an open-label, single-arm study in 176 patients. Venetoclax had no effect on QTc interval and there was no relationship between venetoclax exposure and change in QTc interval.

Clinical efficacy and safety

*Venetoclax in combination with obinutuzumab for the treatment of patients with previously untreated CLL – study BO25323 (CLL14)*
A randomised (1:1), multicenter, open-label phase 3 study evaluated the efficacy and safety of venetoclax + obinutuzumab versus obinutuzumab + chlorambucil in patients with previously untreated CLL and comorbidities (total Cumulative Illness Rating Scale [CIRS] score >6 or creatinine clearance [CrCl] <70 ml/min). Patients in the study were assessed for risk of TLS and received prophylaxis accordingly prior to obinutuzumab administration. All patients received obinutuzumab at 100 mg on Cycle 1 Day 1, followed by 900 mg which could have been administered on Day 1 or Day 2, then 1000 mg doses on Days 8 and 15 of Cycle 1, and on Day 1 of each subsequent cycle, for a total of 6 cycles. On Day 22 of Cycle 1, patients in the venetoclax + obinutuzumab arm began the 5-week venetoclax dose-titration schedule, continuing through Cycle 2 Day 28. Upon completion of the dose-titration schedule, patients continued venetoclax 400 mg once

daily from Cycle 3 Day 1 until the last day of Cycle 12. Each cycle was 28 days. Patients randomised to the obinutuzumab + chlorambucil arm received 0.5 mg/kg oral chlorambucil on Day 1 and Day 15 of Cycles 1-12. Patients continued to be followed for disease progression and overall survival after completing therapy.

Baseline demographic and disease characteristics were similar between the study arms. The median age was 72 years (range: 41 to 89 years), 89% were white, and 67% were male; 36% and 43% were Binet stage B and C, respectively. The median CIRS score was 8.0 (range: 0 to 28) and 58% of patients had CrCl <70 ml/min. A 17p deletion was detected in 8% of patients, *TP53* mutations in 10%, 11q deletion in 19%, and unmutated *IgVH* in 57%. The median follow-up at the time of the primary analysis was 28 months (range: 0 to 36 months).

At baseline, the median lymphocyte count was 55 x $10^9$ cells/l in both study arms. On Cycle 1 Day 15, the median count had decreased to 1.03 x $10^9$ cells/l (range: 0.2 to 43.4 x $10^9$ cells/l) in the obinutuzumab + chlorambucil arm and 1.27 x $10^9$ cells/l (range: 0.2 to 83.7 x $10^9$ cells/l) in the venetoclax + obinutuzumab arm.

Progression-free survival (PFS) was assessed by investigators and by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

Efficacy results for investigator-assessed PFS at the time of the primary analysis (data cut-off date 17 August 2018) are shown in Table 5.

Table 5: Investigator-assessed progression-free survival in patients with previously untreated CLL in CLL14 (primary analysis)

| | Venetoclax + obinutuzumab (N = 216 ) | Obinutuzumab + chlorambucil (N = 216) |
|---|---|---|
| Number of events (%) | 30 (14) | 77 (36) |
| Median, months (95% CI) | NR | NR |
| Hazard ratio (95% CI) | 0.35 (0.23, 0.53) | |
| P-value[a] | <0.0001 | |
| 12-month PFS estimate (95% CI) | 94.6 (91.5, 97.7) | 92.2 (88.4, 95.8) |
| 24-month PFS estimate (95% CI) | 88.2 (83.7, 95.1) | 64.1 (57.4, 70.8) |
| CI = confidence interval; NR = not reached<br>[a]Stratified P-value. | | |

At an updated efficacy analysis (data cut-off date 23 August 2019 and median follow-up of 40 months), the median PFS had not been reached in the venetoclax + obinutuzumab arm and was 35.6 months [95% CI: 33.7,40.7] in the obinutuzumab + chlorambucil arm with a HR of 0.31 [95% CI: 0.22, 0.44]. The 36-month PFS estimate in the venetoclax + obinutuzumab arm was 81.9% [95% CI: 76.5, 87.3] and in the obinutuzumab + chlorambucil arm was 49.5% [95% CI: 42.4, 56.6]. The updated Kaplan-Meier curve for PFS is shown in Figure 1.

Figure 1: Kaplan-Meier curve of investigator-assessed progression-free survival (ITT population) in CLL14 with 40 months follow-up

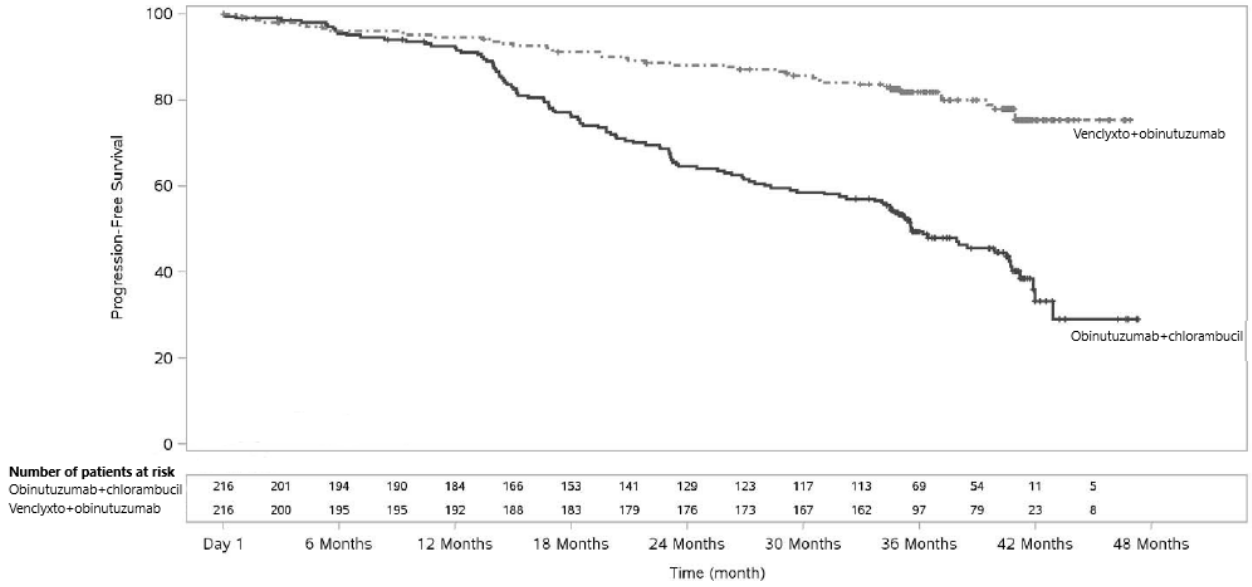



Table 6: Additional efficacy results in CLL14 (primary analysis)

| Endpoint | Venetoclax + obinutuzumab (N = 216) | Obinutuzumab + chlorambucil (N = 216) |
|---|---|---|
| IRC-assessed PFS | | |
| Number of events (%) | 29 (13) | 79 (37) |
| Median, months | NR | NR |
| Hazard ratio (95% CI) | 0.33 (0.22, 0.51) | |
| P-value[a] | <0.0001 | |
| 12-month PFS estimate (95% CI) | 94.6 (91.5, 97.7) | 91.1 (87.3, 95.1) |
| 24-month PFS estimate (95% CI) | 88.6 (84.2, 93) | 63.7 (57, 70.4) |
| Response rate | | |
| ORR[b], % (95% CI) | 85 (79.2, 89.2) | 71 (64.8, 77.2) |
| CR+CRi[b], (%) | 50 | 23 |
| MRD negativity rate[c] at end of treatment | | |
| Peripheral blood, % (95% CI) | 76 (69.17, 81.05) | 35 (28.83, 41.95) |
| P-value | <0.0001 | |
| Bone marrow[d], % (95% CI) | 57 (50.05, 63.64) | 17 (12.36, 22.83) |
| P-value | <0.0001 | |

CR = complete remission; CRi = complete remission with incomplete marrow recovery; IRC = independent review committee; MRD = minimal residual disease; NR = not reached; ORR = overall response rate (CR + CRi + PR).
[a]Stratified P-value.
[b]P-values based on Cochran-Mantel-Haenszel test; P=0.0007 for ORR; P<0.0001 for CR+CRi.
[c]Minimal residual disease was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The cut-off for a negative status was <1 CLL cell per $10^4$ leukocytes.
[d]Per protocol, MRD in bone marrow was to be assessed only in responding patients (CR/CRi and PR).

The PFS benefit with venetoclax + obinutuzumab versus obinutuzumab + chlorambucil treatment was observed across the following subgroups: sex; age; Binet stage at screening; estimated CrCL; del(17p)/*TP53* mutation; *IgVH* mutational status.

*Venetoclax in combination with rituximab for the treatment of patients with CLL who have received at least one prior therapy – study GO28667 (MURANO)*
A randomised (1:1), multicenter, open-label phase 3 study evaluated the efficacy and safety of Venclyxto + rituximab versus BR in patients with previously treated CLL. Patients in the Venclyxto + rituximab arm completed the Venclyxto 5-week dose-titration schedule and then received 400 mg once daily for 24 months from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity. Rituximab was initiated after the 5-week dose-titration schedule at 375 mg/m$^2$ for Cycle 1 and 500 mg/m$^2$ for Cycles 2-6. Each cycle was 28 days. Patients randomised to BR received bendamustine at 70 mg/m$^2$ on Days 1 and 2 for 6 cycles and rituximab as described above.

Median age was 65 years (range: 22 to 85); 74% were male, and 97% were white. Median time since diagnosis was 6.7 years (range: 0.3 to 29.5). Median prior lines of therapy was 1 (range: 1 to 5); and included alkylating agents (94%), anti-CD20 antibodies (77%), B-cell receptor pathway inhibitors (2%) and prior purine analogs (81%, including 55% FCR). At baseline, 46.6% of patients had one or more nodes ≥5 cm, and 67.6% had ALC ≥25 x 10$^9$/l. A 17p deletion was detected in 26.9% of patients, *TP53* mutations in 26.3%, 11q deletion in 36.5%, and unmutated *IgVH* gene in 68.3%. Median follow-up time for primary analysis was 23.8 months (range: 0.0 to 37.4 months).

Progression-free survival (PFS) was assessed by investigators using the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

Efficacy results for PFS at the time of pre-specified primary analysis (data cut-off date 8 May 2017) are shown in Table 7.

Table 7: Investigator-assessed progression-free survival in patients with previously treated CLL in MURANO

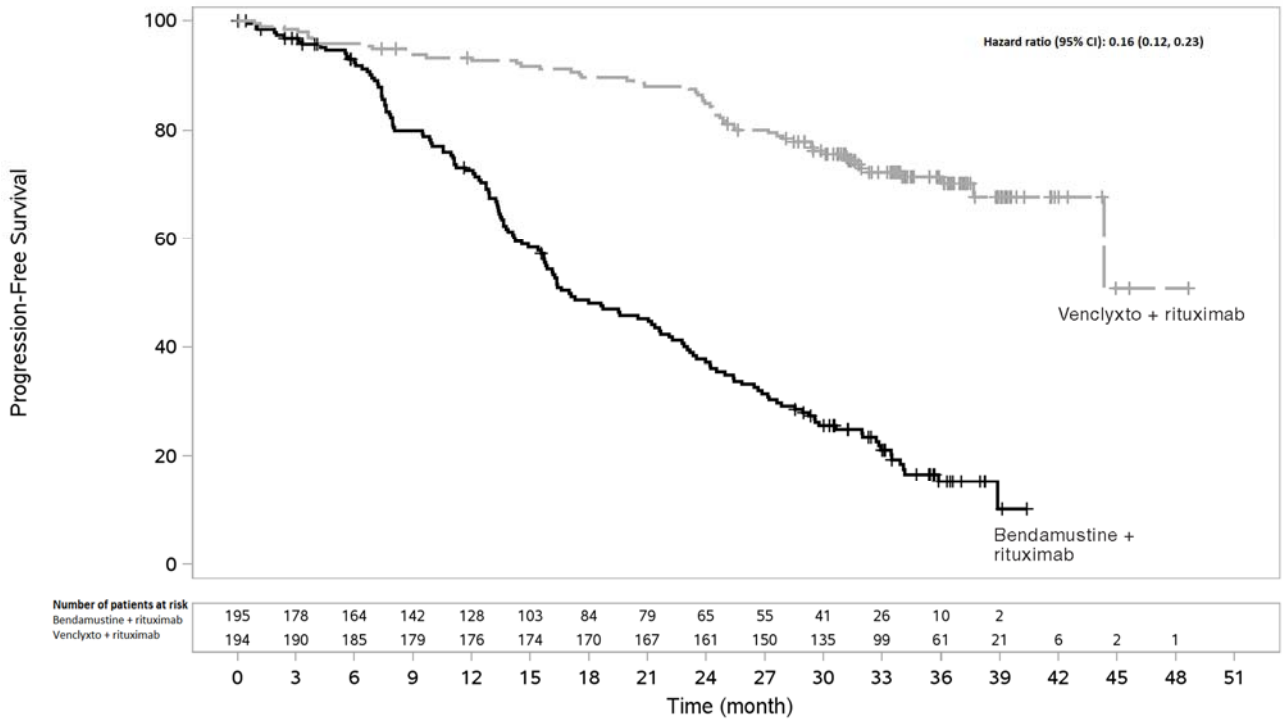
| | Venetoclax + rituximab N = 194 | Bendamustine + rituximab N = 195 |
|---|---|---|
| Number of events (%) | 32 (16.5) | 114 (58.5) |
| Disease progression | 21 | 98 |
| Death events | 11 | 16 |
| Median, months (95% CI) | NR | 17.0 (15.5, 21.6) |
| Hazard ratio (95% CI) | 0.17 (0.11, 0.25) | |
| P-value[a] | <0.0001 | |
| 12-month PFS estimate (95% CI) | 92.7 (89.1, 96.4) | 72.5 (65.9, 79.1) |
| 24-month PFS estimate (95% CI) | 84.9 (79.1, 90.6) | 36.3 (28.5, 44.0) |

CI = confidence interval; NR = not reached
[a]Stratified P-value.

At an updated efficacy analysis with all patients off treatment (data cut-off date 8 May 2018 and median follow-up of 36 months) the 36-month PFS estimate in the venetoclax + rituximab arm was 71.4% [95% CI: 64.8, 78.1] and in the bendamustine + rituximab arm was 15.2% [95% CI: 9.1, 21]. Kaplan-Meier curves of investigator-assessed PFS from the updated efficacy analysis are shown in Figure 2.

In total, 130 patients in the venetoclax + rituximab arm completed 2 years of venetoclax treatment without progression. Of the 130 patients, 92 patients completed the 6-month post treatment follow-up visit. The estimated PFS rate at 6 months post treatment was 92%.

Figure 2: Kaplan-Meier curves of investigator-assessed progression-free survival (intent-to-treat population) in MURANO (data cut-off date 8 May 2018)




Efficacy results for the pre-specified primary analysis (data cut-off date 8 May 2017) were also assessed by an Independent Review Committee (IRC) demonstrating a statistically significant 81% reduction in the risk of progression or death for patients treated with venetoclax + rituximab (hazard ratio: 0.19 [95% CI: 0.13, 0.28]; P<0.0001). Additional efficacy results for the pre-specified primary analysis are shown in Table 8 and Figure 3 and Figure 4.

Table 8: Additional efficacy results in MURANO

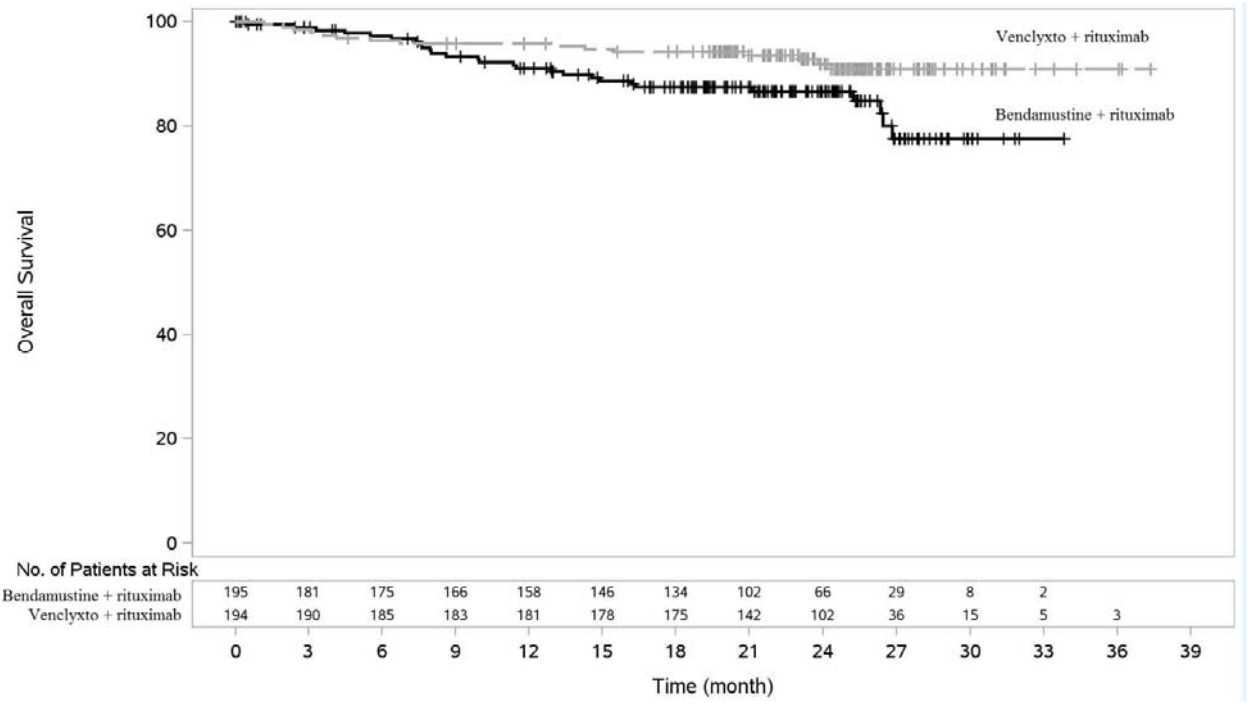
| | Investigator assessed | | IRC assessed | |
|---|---|---|---|---|
| Endpoint | Venetoclax + rituximab N = 194 | Bendamustine + rituximab N = 195 | Venetoclax + rituximab N = 194 | Bendamustine + rituximab N = 195 |
| Response rate | | | | |
| ORR, % (95% CI) | 93.3 (88.8, 96.4) | 67.7 (60.6, 74.2) | 92.3 (87.6, 95.6) | 72.3 (65.5, 78.5) |
| CR+CRi, (%) | 26.8 | 8.2 | 8.2 | 3.6 |
| nPR, (%) | 3.1 | 6.2 | 1.5 | 0.5 |
| PR, (%) | 63.4 | 53.3 | 82.5[a] | 68.2[a] |
| MRD negativity rate at end of combination treatment[b] | | | | |
| Peripheral blood, % (95% CI)[c] | 62.4 (55.2, 69.2) | 13.3 (8.9, 18.9) | NA | NA |
| Bone marrow, % (95% CI)[d] | 15.5 (10.7, 21.3) | 1.0 (0.1, 3.7) | NA | NA |
| Overall Survival[e] | | | | |
| Number of events (%) | 15 (7.7) | 27 (13.8) | | |
| Hazard ratio (95% CI) | 0.48 (0.25, 0.90) | | | |
| Time to next anti-leukaemic therapy | | | | |
| Number of events (%) | 23 (11.9) | 83 (42.6) | NA | NA |
| Median, months (95% CI) | NR | 26.4 | NA | NA |
| Hazard ratio | 0.19 (0.12, 0.31) | | NA | |

CR = complete remission; CRi = complete remission with incomplete marrow recovery; IRC = independent review committee; MRD = minimal residual disease; nPR = nodular partial remission; NA = not available; NR = not reached; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.

[a]The discrepancy between IRC- and investigator-assessed CR rate was due to interpretation of residual adenopathy on CT scans. Eighteen patients in the venetoclax + rituximab arm and 3 patients in the bendamustine + rituximab arm had negative bone marrow and lymph nodes <2 cm.
[b]Minimal residual disease was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and/or flow cytometry. The cut-off for a negative status was one CLL cell per $10^4$ leukocytes.
[c]Of those with MRD assay results available in peripheral blood, 72.5% (121/167) in the venetoclax + rituximab arm and 20% (26/128) in the bendamustine + rituximab arm were found to be MRD negative.
[d]Of those with MRD assay results available in bone marrow, 76.9% (30/39) in the venetoclax + rituximab arm and 6.7% (2/30) in the bendamustine + rituximab arm were found to be MRD negative.
[e]Overall survival data are not yet mature.

Median DOR was not reached with median follow-up of approximately 23.8 months.

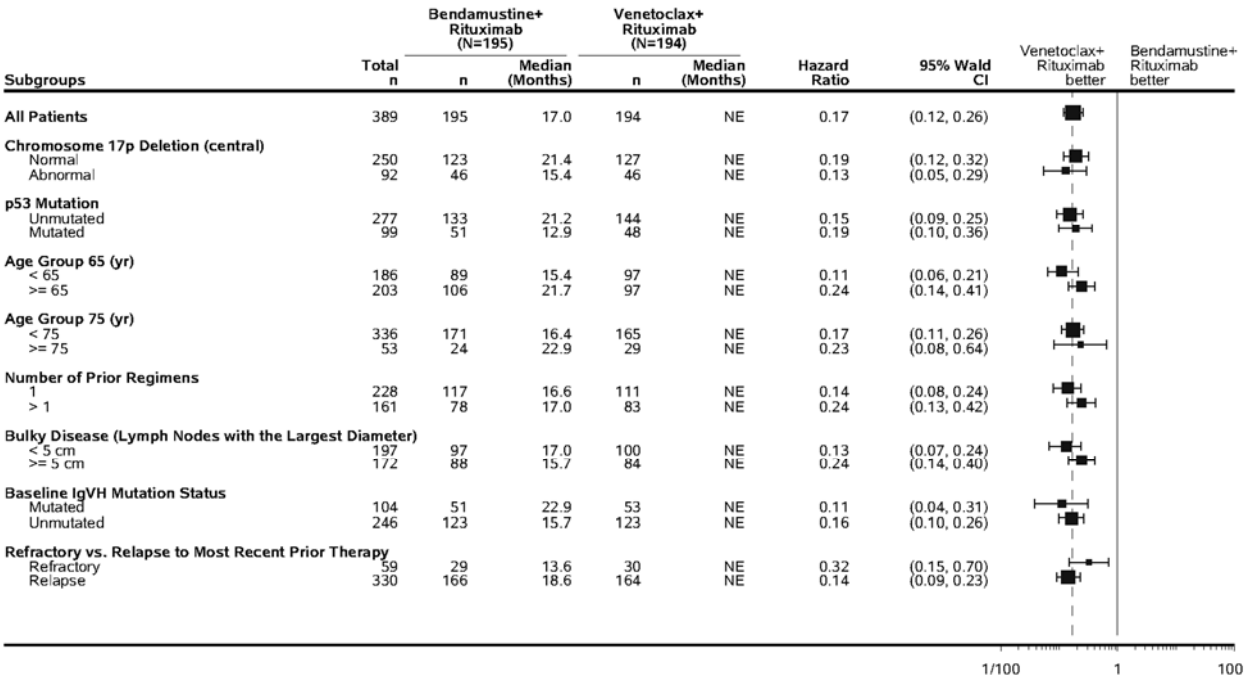
Figure 3: Kaplan-Meier curves of overall survival (intent-to-treat population) in MURANO




Results of subgroup analyses

The observed PFS benefit of venetoclax + rituximab compared with bendamustine + rituximab was consistently observed across all subgroups of patients evaluated, including age (< 65, ≥ 65 years and < 75, ≥ 75 years), prior lines of therapy (1, >1), bulky disease (< 5 cm, ≥ 5 cm), 17p deletion, 11q deletion, *TP53* mutation, *IgVH* mutation, and refractory versus relapse to most recent therapy (Figure 4).

Figure 4: Forest plot of Investigator-Assessed PFS in Subgroups from MURANO




17p deletion status was determined based on central laboratory test results.
Unstratified hazard ratio is displayed on the X-axis with logarithmic scale.
NE=not evaluable.

*Venetoclax as monotherapy for the treatment of patients with CLL harbouring 17p deletion or TP53 mutation – study M13-982*

The safety and efficacy of venetoclax in 107 patients with previously treated CLL with 17p deletion were evaluated in a single arm, open-label, multi-center study (M13-982). Patients followed a 4- to 5-week dose-titration schedule starting at 20 mg and increasing to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive venetoclax 400 mg once daily until disease progression or unacceptable toxicity was observed. The median age was 67 years (range: 37 to 85 years); 65% were male, and 97% were white. The median time since diagnosis was 6.8 years (range: 0.1 to 32 years; N=106). The median number of prior anti-CLL treatments was 2 (range: 1 to 10 treatments); 49.5% with a prior nucleoside analogue, 38% with prior rituximab, and 94% with a prior alkylator (including 33% with prior bendamustine). At baseline, 53% of patients had one or more nodes ≥5 cm, and 51% had ALC ≥25 x $10^9$/l. Of the patients, 37% (34/91) were fludarabine refractory, 81% (30/37) harboured the unmutated *IgVH* gene, and 72% (60/83) had *TP53* mutation. The median time on treatment at the time of evaluation was 12 months (range: 0 to 22 months).

The primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the IWCLL updated NCI-WG guidelines (2008). Efficacy results are shown in Table 9. Efficacy data are presented for 107 patients with data cutoff date 30 April 2015. An additional 51 patients were enrolled in a safety expansion cohort. Investigator-assessed efficacy results are presented for 158 patients with a later data cutoff date 10 June 2016. The median time on treatment for 158 patients was 17 months (range: 0 to 34 months).

Table 9: Efficacy results in patients with previously treated CLL with 17p deletion (study M13-982)

| Endpoint | IRC assessment (N=107)[a] | Investigator assessment (N=158)[b] |
|---|---|---|
| Data cutoff date | 30 April 2015 | 10 June 2016 |
| ORR, %<br>(95% CI) | 79<br>(70.5, 86.6) | 77<br>(69.9, 83.5) |
| CR + CRi, % | 7 | 18 |
| nPR, % | 3 | 6 |
| PR, % | 69 | 53 |
| DOR, months, median (95% CI) | NR | 27.5 (26.5, NR) |
| PFS, % (95% CI)<br>12-month estimate<br>24-month estimate | <br>72 (61.8, 79.8)<br>NA | <br>77 (69.1, 82.6)<br>52 (43, 61) |
| PFS, months, median<br>(95% CI) | NR | 27.2 (21.9, NR) |
| TTR, months, median (range) | 0.8 (0.1-8.1) | 1.0 (0.5-4.4) |

[a]One patient did not harbour the 17p deletion.
[b]Includes 51 additional patients from the safety expansion cohort.
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery, DOR = duration of response; IRC = independent review committee; nPR = nodular PR; NA = not available; NR = not reached; ORR = overall response rate; PFS = progression-free survival, PR = partial remission; TTR = time to first response.

Minimal residual disease (MRD) was evaluated using flow cytometry in 93 of 158 patients who achieved complete remission (CR), complete remission with incomplete marrow recovery (CRi), or partial remission (PR) with limited remaining disease with venetoclax treatment. MRD negativity was defined as a result below 0.0001 (<1 CLL cell per $10^4$ leukocytes in the sample). Twenty-seven percent (42/158) of patients were MRD negative in the peripheral blood, including 16 patients who were also MRD negative in the bone marrow.

*Venetoclax as monotherapy for the treatment of patients with CLL who have failed a B-cell receptor pathway inhibitor – study M14-032*
The efficacy and safety of venetoclax in patients with CLL who had been previously treated with and failed ibrutinib or idelalisib therapy were evaluated in an open-label, multi-center, non-randomised, phase 2 study (M14-032). Patients received venetoclax via a recommended dose-titration schedule. Patients continued to receive venetoclax 400 mg once daily until disease progression or unacceptable toxicity was observed.

At the time of data cut-off (26 July 2017), 127 patients were enrolled and treated with venetoclax. Of these, 91 patients had received prior ibrutinib therapy (Arm A) and 36 had received prior idelalisib therapy (Arm B). The median age was 66 years (range: 28 to 85 years), 70% were male, and 92% were white. The median time since diagnosis was 8.3 years (range: 0.3 to 18.5 years; N=96). Chromosomal aberrations were 11q deletion (34%, 43/127), 17p deletion (40%, 50/126), *TP53* mutation (38%, 26/68) and unmutated *IgVH* (78%, 72/92). At baseline, 41% of patients had one or more nodes ≥5 cm and 31% had ALC ≥25 x $10^9$/l. The median number of prior oncology treatments was 4 (range: 1 to 15) in ibrutinib-treated patients and 3 (range: 1 to 11) in idelalisib-treated patients. Overall, 65% of patients received prior nucleoside analogue, 86% rituximab, 39% other monoclonal antibodies, and 72% alkylating agent (including 41% with bendamustine). At the time of evaluation, median duration of treatment with venetoclax was 14.3 months (range: 0.1 to 31.4 months).

The primary efficacy endpoint was ORR according to IWCLL updated NCI-WG guidelines. Response assessments were performed at 8 weeks, 24 weeks, and every 12 weeks thereafter.

Table 10: Efficacy results as assessed by investigator in patients who have failed a B-cell receptor pathway inhibitor (study M14-032)

| | Arm A (ibrutinib failures) (N=91) | Arm B (idelalisib failures) (N=36) | Total (N=127) |
|---|---|---|---|
| ORR, % (95% CI) | 65 (54.1, 74.6) | 67 (49.0, 81.4) | 65 (56.4, 73.6) |
| CR + CRi, % | 10 | 11 | 10 |
| nPR, % | 3 | 0 | 2 |
| PR, % | 52 | 56 | 53 |
| PFS, % (95% CI) | | | |
| 12-month estimate | 75 (64.7, 83.2) | 80 (63.1, 90.1) | 77 (68.1, 83.4) |
| 24-month estimate | 51 (36.3, 63.9) | 61 (39.6, 77.4) | 54 (41.8, 64.6) |
| PFS, months, median (95% CI) | 25 (19.2, NR) | NR (16.4, NR) | 25 (19.6, NR) |
| OS, % (95% CI) | | | |
| 12-month estimate | 91 (82.8, 95.4) | 94.2 (78.6, 98.5) | 92 (85.6, 95.6) |
| TTR, months, median (range) | 2.5 (1.6-14.9) | 2.5 (1.6-8.1) | 2.5 (1.6-14.9) |
| 17p deletion and/or *TP53* mutation status ORR, % (95% CI) | | | |
| Yes | (n=28) 61 (45.4, 74.9) | (n=7) 58 (27.7, 84.8) | (n=35) 60 (46.6, 73.0) |
| No | (n=31) 69 (53.4, 81.8) | (n=17) 71 (48.9, 87.4) | (n=48) 70 (57.3, 80.1) |

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery, nPR = nodular PR; NR = not reached, ORR = overall response rate;. OS = overall survival; PFS = progression-free survival, PR = partial remission, TTR = time to first response.

The efficacy data were further evaluated by an IRC demonstrating a combined ORR of 70% (Arm A: 70%; Arm B: 69%). One patient (ibrutinib failure) achieved complete remission with incomplete marrow recovery. The ORR for patients with 17p deletion and/or *TP53* mutation was 72% (33/46) (95% CI: 56.5, 84.0) in Arm A and 67% (8/12) (95% CI: 34.9, 90.1) in Arm B. For patients without 17p deletion and/or *TP53* mutation, the ORR was 69% (31/45) (95% CI: 53.4, 81.8) in Arm A and 71% (17/24) (95% CI: 48.9, 87.4) in Arm B.

Median OS and DOR were not reached with median follow-up of approximately 14.3 months for Arm A and 14.7 months for Arm B.

Twenty-five percent (32/127) of patients were MRD negative in the peripheral blood, including 8 patients who were also MRD negative in bone marrow.

Elderly patients

Of the 194 patients with previously treated CLL who received venetoclax in combination with rituximab, 50% were 65 years or older.

Of the 107 patients who were evaluated for efficacy from M13-982 study, 57% were 65 years or older. Of the 127 patients who were evaluated for efficacy from M14-032 study, 58% were 65 years or older.

Of the 352 patients evaluated for safety from 3 open-label monotherapy trials, 57% were 65 years or older.

There were no clinically meaningful differences in safety or efficacy observed between older and younger patients in the combination and monotherapy studies.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Venclyxto in all subsets of the paediatric population in CLL (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

Following multiple oral administrations, maximum plasma concentration of venetoclax was reached 5-8 hours after dose. Venetoclax steady state AUC increased proportionally over the dose range of 150-800 mg. Under low-fat meal conditions, venetoclax mean (± standard deviation) steady state $C_{max}$ was 2.1 ± 1.1 µg/ml and $AUC_{24}$ was 32.8 ± 16.9 µg•h/ml at the 400 mg once daily dose.

*Effect of food*

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared to fasting conditions. It is recommended that venetoclax should be administered with a meal (see section 4.2).

Distribution

Venetoclax is highly bound to human plasma protein with unbound fraction in plasma <0.01 across a concentration range of 1-30 µM (0.87-26 µg/ml). The mean blood-to-plasma ratio was 0.57. The population estimate for apparent volume of distribution ($Vd_{ss}/F$) of venetoclax ranged from 256-321 L in patients.

Biotransformation

*In vitro* studies demonstrated that venetoclax is predominantly metabolised by cytochrome P450 CYP3A4. M27 was identified as a major metabolite in plasma with an inhibitory activity against BCL-2 that is at least 58-fold lower than venetoclax *in vitro*.

*In vitro interaction studies*

*Co administration with CYP and UGT substrates*
*In vitro* studies indicated that venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C19, CYP2D6 or CYP3A4 at clinically relevant concentrations. Venetoclax is a weak inhibitor of CYP2C8, CYP2C9 and UGT1A1 *in vitro*, but it is not predicted to cause clinically relevant inhibition. Venetoclax is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7.

*Co administration with transporter substrates/inhibitors*
Venetoclax is a P-gp and BCRP substrate as well as a P-gp and BCRP inhibitor and a weak OATP1B1 inhibitor *in vitro* (see section 4.5). Venetoclax is not expected to inhibit OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K at clinically relevant concentrations.

Elimination

The population estimate for the terminal phase elimination half-life of venetoclax was approximately 26 hours. Venetoclax shows minimal accumulation with accumulation ratio of 1.30-1.44. After a single oral administration of 200 mg radiolabeled [$^{14}$C]-venetoclax to healthy subjects, >99.9% of the dose was recovered in faeces and <0.1% of the dose was excreted in urine within 9 days. Unchanged venetoclax accounted for 20.8% of the administered radioactive dose excreted in faeces. The pharmacokinetics of venetoclax do not change over time.

Special populations

*Renal impairment*
Based on a population pharmacokinetic analysis that included 219 subjects with mild renal impairment (CrCl ≥60 and <90 ml/min), 86 subjects with moderate renal impairment (CrCl ≥30 and <60 ml/min) and 217 subjects with normal renal function (CrCl ≥90 ml/min), venetoclax exposures in subjects with mild or moderate renal impairment are similar to those with normal renal function. The pharmacokinetics of venetoclax has not been studied in subjects with severe renal impairment (CrCl <30 ml/min) or patients on dialysis (see section 4.2).

*Hepatic impairment*
Based on a population pharmacokinetic analysis that included 74 subjects with mild hepatic impairment, 7 subjects with moderate hepatic impairment and 442 subjects with normal hepatic function, venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function. Mild hepatic impairment was defined as normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin >1.0 to 1.5 times ULN, moderate hepatic impairment as total bilirubin >1.5 to 3.0 times ULN, and severe hepatic impairment as total bilirubin >3.0 ULN.

In a dedicated hepatic impairment study, venetoclax $C_{max}$ and AUC in subjects with mild (Child-Pugh A; n=6) or moderate (Child-Pugh B; n=6) hepatic impairment were similar to subjects with normal hepatic function, after receiving a 50 mg single dose of venetoclax. In subjects with severe (Child-Pugh C; n=5) hepatic impairment, the mean venetoclax $C_{max}$ was similar to subjects with normal hepatic function but venetoclax $AUC_{inf}$ was on average 2.7-fold higher (range: no change to 5-fold higher) than venetoclax $AUC_{inf}$ in the subjects with normal hepatic function (see section 4.2).

Effects of age, sex, and weight

Based on population pharmacokinetic analyses, age, sex, and weight do not have an effect on venetoclax clearance.

## 5.3 Preclinical safety data

Toxicities observed in animal studies with venetoclax included dose-dependent reductions in lymphocytes and red blood cell mass. Both effects were reversible after cessation of dosing with venetoclax, with recovery of lymphocytes occurring 18 weeks post treatment. Both B- and T-cells were affected, but the most significant decreases occurred with B-cells.

Venetoclax also caused single cell necrosis in various tissues, including the gallbladder and exocrine pancreas, with no evidence of disruption of tissue integrity or organ dysfunction; these findings were minimal to mild in magnitude.

After approximately 3 months of daily dosing in dogs, venetoclax caused progressive white discoloration of the hair coat, due to loss of melanin pigment in the hair.

Carcinogenicity/genotoxicity

Venetoclax and the M27 major human metabolite were not carcinogenic in a 6-month transgenic (Tg.rasH2) mouse carcinogenicity study at oral doses up to 400 mg/kg/day of venetoclax and at a single dose level of 250 mg/kg/day of M27. Exposure margins (AUC), relative to the clinical AUC at 400 mg/day, were approximately 2-fold for venetoclax and 5.8-fold for M27.

Venetoclax was not genotoxic in bacterial mutagenicity assay, *in vitro* chromosome aberration assay and *in vivo* mouse micronucleus assay. The M27 metabolite was negative for genotoxicity in the bacterial mutagenicity and chromosomal aberration assays.

Reproductive toxicity

No effects on fertility were observed in fertility and early embryonic development studies in male and female mice. Testicular toxicity (germ cell loss) was observed in general toxicity studies in dogs at exposures of 0.5 to 18 times the human AUC exposure at a dose of 400 mg. Reversibility of this finding has not been demonstrated.

In embryo-foetal development studies in mice, venetoclax was associated with increased post-implantation loss and decreased foetal body weight at exposures of 1.1 times the human AUC exposure at a dose of 400 mg. The major human metabolite M27 was associated with post-implantation loss and resorptions at exposures approximately 9-times the human M27-AUC exposure at a 400 mg dose of venetoclax. In rabbits, venetoclax produced maternal toxicity, but no foetal toxicity at exposures of 0.1 times the human AUC exposure at a 400 mg dose.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Venclyxto 10 mg film-coated tablets

*Tablet core*
Copovidone (K 28)
Colloidal anhydrous silica (E551)
Polysorbate 80 (E433)
Sodium stearyl fumarate
Anhydrous calcium hydrogen phosphate (E341 (ii))

*Film-coating*
Iron oxide yellow (E172)
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)

Venclyxto 50 mg film-coated tablets

*Tablet core*
Copovidone (K 28)
Colloidal anhydrous silica (E551)
Polysorbate 80 (E433)
Sodium stearyl fumarate
Anhydrous calcium hydrogen phosphate (E341 (ii))

*Film-coating*
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)

Venclyxto 100 mg film-coated tablets

*Tablet core*
Copovidone (K 28)
Colloidal anhydrous silica (E551)
Polysorbate 80 (E433)
Sodium stearyl fumarate
Anhydrous calcium hydrogen phosphate (E341 (ii))

*Film-coating*
Iron oxide yellow (E172)
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

Venclyxto 10 mg film-coated tablets
2 years.

Venclyxto 50 mg film-coated tablets
2 years.

Venclyxto 100 mg film-coated tablets
3 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Venclyxto film-coated tablets are supplied in PVC/PE/PCTFE aluminium foil blisters containing either 1, 2 or 4 film-coated tablets.

Venclyxto 10 mg tablets
The film-coated tablets are supplied in cartons containing either 10 or 14 tablets (in blisters of 2 tablets).

Venclyxto 50 mg tablets
The film-coated tablets are supplied in cartons containing either 5 or 7 tablets (in blisters of 1 tablet).

Venclyxto 100 mg tablets
The film-coated tablets are supplied in cartons containing either 7 (in blisters of 1 tablet) or 14 tablets (in blisters of 2 tablets); or a multipack containing 112 tablets (4 x 28 tablets (in blisters of 4 tablets)).

Not all pack sizes may be marketed.

### 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

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/001 (10 mg, 10 tablets)
EU/1/16/1138/002 (10 mg, 14 tablets)
EU/1/16/1138/003 (50 mg, 5 tablets)
EU/1/16/1138/004 (50 mg, 7 tablets)
EU/1/16/1138/005 (100 mg 7 tablets)
EU/1/16/1138/006 (100 mg, 14 tablets)
EU/1/16/1138/007 (100 mg, 112 (4 x 28) tablets)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5 December 2016
Date of latest renewal: 6 September 2018

## 10. DATE OF REVISION OF THE TEXT

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

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

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

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

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

- **Riskmanagement plan (RMP)**

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

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

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER CARTON**

**CARTON (5 day pack)**

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 10 mg film-coated tablets
venetoclax

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg venetoclax

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

10 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

venclyxto 10 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE OUTER CARTON**

**CARTON (7 day pack)**

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 10 mg film-coated tablets
venetoclax

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg venetoclax

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

venclyxto 10 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 10 mg tablets
venetoclax

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER CARTON**

**CARTON (5 day pack)**

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 50 mg film-coated tablets
venetoclax

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg venetoclax

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

5 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/003

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

venclyxto 50 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE OUTER CARTON**

**CARTON (7 day pack)**

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 50 mg film-coated tablets
venetoclax

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg venetoclax

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

7 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/004

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

venclyxto 50 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 50 mg tablets
venetoclax

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER CARTON**

**CARTON (7 day pack)**

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 100 mg film-coated tablets
venetoclax

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg venetoclax

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

7 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/005

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

venclyxto 100 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 100 mg tablets
venetoclax

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER CARTON**

**CARTON (7 day pack)**

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 100 mg film-coated tablets
venetoclax

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg venetoclax

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose in the **morning** with a meal and water. Drink 1.5–2 litres of water a day.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/006

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

venclyxto 100 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE OUTER CARTON**

**CARTON Multipack (with blue box)**

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 100 mg film-coated tablets
venetoclax

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg venetoclax

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 112 (4 x 28) film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/007

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

venclyxto 100 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**CARTON multipack (without blue box)**

## 1. NAME OF THE MEDICINAL PRODUCT

Venclyxto 100 mg film-coated tablets
venetoclax

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg venetoclax

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
Component of a multipack, can't be sold separately.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take your dose at the same time each day with a meal and water.
Read the package leaflet before use. It is important to follow all of the instructions in the 'how to take' section of the leaflet.

Oral use.

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1138/007

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

venclyxto 100 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**Venclyxto 10 mg film-coated tablets**
**Venclyxto 50 mg film-coated tablets**
**Venclyxto 100 mg film-coated tablets**
venetoclax

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

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

**What is in this leaflet**


## 1. What Venclyxto is and what it is used for

**What Venclyxto is**
Venclyxto is a cancer medicine that contains the active substance venetoclax. It belongs to a group of medicines called “BCL-2 inhibitors”.

**What Venclyxto is used for**
Venclyxto is used to treat patients with chronic lymphocytic leukaemia (CLL).

Venclyxto may be given to you in combination with other medicines or alone.

CLL is a type of cancer affecting white blood cells called lymphocytes and the lymph nodes. In CLL, the lymphocytes multiply too quickly and live for too long, so that there are too many of them in the blood.

**How Venclyxto works**
Venclyxto works by blocking a protein in the body called “BCL-2”. This protein helps cancer cells survive. Blocking this protein helps to kill and lower the number of cancer cells. It also slows down the worsening of the disease.

## 2. What you need to know before you take Venclyxto

**Do not take Venclyxto if:**
- you are allergic to the active substance venetoclax or any of the other ingredients of this medicine (listed in section 6).

- you are taking any of the medicines listed below when you start your treatment and while your dose is gradually being increased (usually over 5 weeks). This is because serious and life-threatening effects can occur when Venclyxto is taken with these medicines:

    - itraconazole ketoconazole, posaconazole, or voriconazole for fungal infections
    - clarithromycin for bacterial infections
    - ritonavir for HIV infection.

  When your Venclyxto dose has been increased to the full standard dose, check with your doctor if you can start taking these medicines again.

- you are taking a herbal medicine called St. John's wort, used for depression. If you are not sure about this, talk to your doctor, pharmacist or nurse before taking Venclyxto.

It is important that you tell your doctor, pharmacist, or nurse about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Your doctor may need to stop certain medicines when you first start taking Venclyxto and during the first five weeks when your dose is gradually increased to the full standard dose.

**Warnings and precautions**
Talk to your doctor, pharmacist, or nurse before taking Venclyxto if:

- you have any kidney problems as your risk for a side effect called tumour lysis syndrome may increase
- you have liver problems as this may increase your risk for side effects. Your doctor may need to reduce your dose of Venclyxto
- you think you may have an infection or have had a long-lasting or repeated infection
- you are due to have a vaccine.

If any of the above apply to you, or you are not sure, talk to your doctor, pharmacist, or nurse before taking this medicine.

**Tumour Lysis Syndrome**
Some people may develop unusual levels of some body salts (such as potassium and uric acid) in the blood caused by the fast breakdown of cancer cells during treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. This is called tumour lysis syndrome (TLS). The risk for TLS is in the first 5 weeks of treatment with Venclyxto.

Your doctor, pharmacist or nurse will do blood tests to check for TLS.

Your doctor may also give you medicines to help prevent the build up of uric acid in your body before you start treatment with Venclyxto.

Drinking plenty of water, at least 1.5 to 2 litres per day, helps to remove cancer cell breakdown products from your body through urine, and may decrease your risk of getting TLS (see section 3).

Tell your doctor, pharmacist or nurse immediately if you get any of the symptoms of TLS listed in section 4.

If you are at risk of TLS you may be treated in hospital so that you can be given fluids into the vein if needed, have blood tests done more often and to check for side effects. This is to see if you can continue to take this medicine safely.

**Children and adolescents**
Venclyxto should not be used in children and adolescents. This is because it has not been studied in these age groups.

**Other medicines and Venclyxto**

Tell your doctor or pharmacist if you take any of the following medicines as they can increase or decrease the amount of venetoclax in your blood:

- medicines for fungal infections – fluconazole, itraconazole, ketoconazole, posaconazole, or voriconazole
- antibiotics to treat bacterial infections – ciprofloxacin, clarithromycin, erythromycin, nafcillin, or rifampicin
- medicines to prevent seizures or to treat epilepsy – carbamazepine, phenytoin
- medicines for HIV infection – efavirenz, etravirine, ritonavir
- medicines to treat raised blood pressure or angina – diltiazem, verapamil
- medicines to lower cholesterol levels in the blood – cholestyramine, colestipol, colesevelam
- a medicine used to treat a lung condition called pulmonary arterial hypertension – bosentan
- a medicine to treat sleep disorder (narcolepsy) known as modafinil
- a herbal medicine known as St. John's wort

Your doctor may change your dose of Venclyxto.

Tell your doctor if you take any of the following medicines as Venclyxto may affect how they work:

- medicines that prevent blood clots, warfarin, dabigatran
- a medicine used to treat heart problems known as digoxin
- a medicine for cancer known as everolimus
- a medicine used to prevent organ rejection known as sirolimus
- medicines to lower cholesterol levels in the blood known as statins

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, herbal medicines and supplements. This is because Venclyxto may affect the way some other medicines work. Also, some other medicines can affect the way Venclyxto works.

**Venclyxto with food and drink**
Do not eat grapefruit products, Seville oranges (bitter oranges), or starfruit (carambola) while you are taking Venclyxto – this includes eating them, drinking the juice or taking a supplement that might contain them. This is because they can increase the amount of venetoclax in your blood.

**Pregnancy**
- Do not get pregnant while you are taking this medicine. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist, or nurse for advice before taking this medicine.
- Venclyxto should not be used during pregnancy. There is no information about the safety of venetoclax in pregnant women.

**Contraception**
- Women of childbearing age must use a highly effective method of contraception during treatment and for at least 30 days after receiving Venclyxto to avoid becoming pregnant. If you are using hormonal contraceptive pills or devices, you must also use a barrier method of contraception (such as condoms) as the effect of hormonal contraceptive pills or devices may be affected by Venclyxto.
- Tell your doctor immediately if you become pregnant while you are taking this medicine.

**Breast-feeding**
Do not breast-feed while you are taking this medicine. It is not known whether the active substance in Venclyxto passes into breast milk.

**Fertility**
Based on findings in animals, Venclyxto may cause male infertility (low or no sperm count). This may affect your ability to father a child. Ask your doctor for advice on sperm storage before starting treatment with Venclyxto.

**Driving and using machines**
You may feel tired after taking Venclyxto, which may affect your ability to drive or use tools or machines.

## 3. How to take Venclyxto

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

**How much to take**
You will begin treatment with Venclyxto at a low dose for 1 week. Your doctor will gradually increase the dose over the next 4 weeks to the full standard dose. For the first 4 weeks you will get a new pack each week.

- the starting dose is 20 mg (two 10 mg tablets) once a day for 7 days.
- the dose will be increased to 50 mg (one 50 mg tablet) once a day for 7 days.
- the dose will be increased to 100 mg (one 100 mg tablet) once a day for 7 days.
- the dose will be increased to 200 mg (two 100 mg tablets) once a day for 7 days.
- the dose will be increased to 400 mg (four 100 mg tablets) once a day for 7 days.
    - When you are receiving Venclyxto therapy alone, you will stay on the 400 mg daily dose, which is the standard dose, for as long as necessary.
    - When you are receiving Venclyxto therapy in combination with rituximab, you will receive the 400 mg daily dose for 24 months.
    - When you are receiving Venclyxto therapy in combination with obinutuzumab, you will receive the 400 mg daily dose for approximately 10 months.

Your dose may need to be adjusted for side effects. Your doctor will advise what your dose should be.

**How to take Venclyxto**
- Take the tablets with a meal at around the same time each day
- Swallow the tablets whole with a glass of water
- Do not chew, crush, or break the tablets
- During the first 5 weeks of treatment, you should take the tablets in the morning to help you follow-up with blood tests, if needed.

If you vomit after taking Venclyxto, do not take an extra dose that day. Take the next dose at the usual time the next day. If you have problems taking this medicine, talk to your doctor.

**Drink plenty of water**
It is very important that you drink plenty of water when taking Venclyxto during the first 5 weeks of treatment. This will help to remove cancer cell breakdown products from your blood through your urine.

You should start drinking at least 1.5 to 2 litres of water daily two days before starting Venclyxto. You may also include non-alcoholic and non-caffeinated drinks in this amount, but exclude grapefruit, Seville orange, or starfruit (carambola) juices. You should continue to drink at least 1.5 to 2 litres of water on the day you start Venclyxto. Drink the same amount of water (at least 1.5 to 2 litres daily) two days before and on the day that your dose is increased.

If your doctor thinks that you are at risk of TLS, you may be treated in the hospital so that you can be given extra fluids into the vein if needed, have your blood tests more often and be checked for side effects. This is to see if you can continue to take this medicine safely.

**If you take more Venclyxto than you should**
If you take more Venclyxto than you should, talk to your doctor, pharmacist, or nurse or go to hospital immediately. Take the tablets and this leaflet with you.

**If you forget to take Venclyxto**
- If it is less than 8 hours since the time you usually take your dose, take it as soon as possible.
- If it is more than 8 hours since the time you usually take your dose, do not take the dose that day. Return to your normal dose schedule the next day.
- Do not take a double dose to make up for a forgotten dose.
- If you are not sure talk to your doctor, pharmacist or nurse.

**Do not stop taking Venclyxto**
Do not stop taking this medicine unless your doctor tells you to. If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following serious side effects may happen with this medicine:

**Tumour lysis syndrome** (common – may affect up to 1 in 10 people)
Stop taking Venclyxto and seek medical attention immediately if you notice any of the symptoms of TLS:
- fever or chills
- feeling or being sick (nausea or vomiting)
- feeling confused
- feeling short of breath
- irregular heart beat
- dark or cloudy urine
- feeling unusually tired
- muscle pain or uncomfortable joints
- fits or seizures
- abdominal pain and distension

**Low white blood cell count (neutropenia) and infections** (very common – may affect more than 1 in 10 people)
Your doctor will check your blood count during treatment with Venclyxto. Low white blood cell count can increase your risk for infection. Signs may include fever, chills, feeling weak or confused, cough, pain or burning feeling when passing urine. Some infections can be serious and may lead to death. Tell your doctor immediately if you have signs of an infection while taking this medicine.

**Tell your doctor if you notice any of the following side effects:**

**Very common** (may affect more than 1 in 10 people)
- pneumonia
- upper respiratory tract infection – signs include runny nose, sore throat or cough
- diarrhoea
- feeling or being sick (nausea or vomiting)
- constipation
- feeling tired

Blood tests may also show
- lower number of red blood cells
- lower number of white blood cells called lymphocytes
- higher level of potassium
- higher level of a body salt (electrolyte) called phosphate
- lower level of calcium

**Common** (may affect up to 1 in 10 people)
- severe infection in the blood (sepsis)

- urinary tract infection
- low number of white blood cells with fever (febrile neutropenia)

Blood tests may also show:
- higher level of creatinine
- higher level of urea

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

## 5. How to store Venclyxto

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

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP.

This medicine does not require any special storage conditions.

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

## 6. Contents of the pack and other information

**What Venclyxto contains**

The active substance is venetoclax.
- Venclyxto 10 mg film-coated tablets: Each film-coated tablet contains 10 mg venetoclax.
- Venclyxto 50 mg film-coated tablets: Each film-coated tablet contains 50 mg venetoclax.
- Venclyxto 100 mg film-coated tablets: Each film-coated tablet contains 100 mg venetoclax.

The other ingredients are:
- In the tablet core: copovidone (K 28), polysorbate 80 (E433), colloidal anhydrous silica (E551), anydrous calcium hydrogen phosphate (E341 (ii)), sodium stearyl fumarate.

In the film-coating:
- Venclyxto 10 mg film-coated tablets: iron oxide yellow (E172), polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b).
- Venclyxto 50 mg film-coated tablets: iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172), polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b)
- Venclyxto 100 mg film-coated tablets: iron oxide yellow (E172), polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b).

**What Venclyxto looks like and contents of the pack**
Venclyxto 10 mg film-coated tablet is pale yellow, round 6 mm diameter, with V on one side and 10 on the other.
Venclyxto 50 mg film-coated tablet is beige, oblong 14 mm long, with V on one side and 50 on the other.
Venclyxto 100 mg film-coated tablet is pale yellow, oblong 17.2 mm long with V on one side and 100 on the other.

Venclyxto tablets are provided in blisters which are packed in cartons as follows:

Venclyxto 10 mg film-coated tablets:

- 10 tablets (5 blisters each with 2 tablets)
- 14 tablets (7 blisters each with 2 tablets)

Venclyxto 50 mg film-coated tablets:
- 5 tablets (5 blisters each with 1 tablet)
- 7 tablets (7 blisters each with 1 tablet)

Venclyxto 100 mg film-coated tablets:
- 7 tablets (7 blisters each with 1 tablet)
- 14 tablets (7 blisters each with 2 tablets)
- 112 (4 x 28) tablets (4 cartons of 7 blisters each with 4 tablets).

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
AbbVie SA
Tél/Tel: +32 10 477811

**България**
АбВи ЕООД
Тел:+359 2 90 30 430

**Česká republika**
AbbVie s.r.o.
Tel: +420 233 098 111

**Danmark**
AbbVie A/S
Tlf: +45 72 30-20-28

**Deutschland**
AbbVie Deutschland GmbH & Co. KG
Tel: 00800 222843 33 (gebührenfrei)
Tel: +49 (0) 611 / 1720-0

**Eesti**
AbbVie Biopharmaceuticals GmbH Eesti filiaal
Tel: +372 623 1011

**Ελλάδα**
AbbVie ΦΑΡΜΑΚΕΥΤΙΚΗ Α.Ε.
Τηλ: +30 214 4165 555

**Lietuva**
AbbVie UAB
Tel: +370 5 205 3023

**Luxembourg/Luxemburg**
AbbVie SA
Belgique/Belgien
Tél/Tel: +32 10 477811

**Magyarország**
AbbVie Kft.
Tel:+36 1 455 8600

**Malta**
V.J.Salomone Pharma Limited
Tel: +356 22983201

**Nederland**
AbbVie B.V.
Tel: +31 (0)88 322 2843

**Norge**
AbbVie AS
Tlf: +47 67 81 80 00

**Österreich**
AbbVie GmbH
Tel: +43 1 20589-0

**España**

AbbVie Spain, S.L.U.
Tel: +34 91 384 09 10

**France**
AbbVie
Tél: +33 (0) 1 45 60 13 00

**Hrvatska**
AbbVie d.o.o.
Tel: + 385 (0)1 5625 501

**Ireland**
AbbVie Limited
Tel: +353 (0)1 4287900

**Ísland**
Vistor hf.
Tel: +354 535 7000

**Italia**
AbbVie S.r.l.
Tel: +39 06 928921

**Κύπρος**
Lifepharma (Z.A.M.) Ltd
Τηλ: +357 22 34 74 40

**Latvija**
AbbVie SIA
Tel: +371 67605000

**Polska**
AbbVie Polska Sp. z o.o.
Tel: +48 22 372 78 00

**Portugal**
AbbVie, Lda.
Tel: +351 (0)21 1908400

**România**
AbbVie S.R.L.
Tel: +40 21 529 30 35

**Slovenija**
AbbVie Biofarmacevtska družba d.o.o.
Tel: +386 (1)32 08 060

**Slovenská republika**
AbbVie s.r.o.
Tel: +421 2 5050 0777

**Suomi/Finland**
AbbVie Oy
Puh/Tel: +358 (0)10 2411 200

**Sverige**
AbbVie AB
Tel: +46 (0)8 684 44 600

**United Kingdom**
AbbVie Ltd
Tel: +44 (0)1628 561090

**This leaflet was last revised in**

**Other sources of information**

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

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

**To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.**

# ANNEX IV

# SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

**Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for venetoclax, the scientific conclusions of CHMP are as follows:

The serious infections (such as sepsis, pneumonia, septic shock etc.) are considered to be the most common cause of death (after those associated with the underlying malignancy or disease progression) in relation to venetoclax treatment. In this reporting interval, a total of 765 reports of serious infections were identified. Since the overall number of events of serious infections is high, the healthcare professionals should be explicitly reminded of these cases. Section 4.4 of the SmPC for Venclyxto should therefore include a standalone undersection entitled “infections”, including the warning statement regarding the risk of infections and their monitoring. The Package leaflet should be updated accordingly.

In addition, the actual format of text for recommendation for dose reduction in case of concomitant use with CYP3A inhibitors is considered difficult to read and respective data would be more easily readable when displayed in tabular format. The relevant information in section 4.2 of the SmPC for Venclyxto should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

**Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for venetoclax the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing venetoclax is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.