## SCHEDULING STATUS

S4

## 1 NAME OF MEDICINE

Venclexta 10 mg film-coated tablets

Venclexta 50 mg film-coated tablets

Venclexta 100 mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Venclexta 10 mg film-coated tablets

Each film-coated tablet contains 10 mg of venetoclax.

Venclexta 50 mg film-coated tablets

Each film-coated tablet contains 50 mg of venetoclax.

Venclexta 100 mg film-coated tablets

Each film-coated tablet contains 100 mg of venetoclax.

Sugar Free.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Venclexta 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.

Venclexta 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.

Venclexta 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

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

Venclexta in combination with rituximab is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (R/R CLL) to prior therapy.

Venclexta monotherapy is indicated for the treatment of adult patients with R/R CLL to prior therapy.

Venclexta in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

## 4.2 Posology and method of administration

Treatment with venetoclax should be initiated and supervised by a medical practitioner experienced in the use of anticancer medicines. Patients treated with venetoclax may develop tumour lysis syndrome (TLS). Information described in this section, including risk assessment, prophylactic measures, dose-titration schedule, laboratory monitoring, and drug interactions should be followed to prevent and reduce the risk of TLS.

### Posology

*Chronic Lymphocytic Leukaemia*

*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).

Rituximab should be administered after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days.

Rituximab should be administered on Day 1 of each 28-day cycle for 6 cycles, with rituximab dosed at 375 mg/$m^2$ intravenously for Cycle 1 and 500 mg/$m^2$ intravenously for Cycles 2-6.

Venetoclax should be taken for 24 months from Cycle 1 Day 1 of rituximab.

*Post-titration dose for venetoclax monotherapy*

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

*Acute Myeloid Leukaemia*

The recommended venetoclax dosing schedule (including dose titration) is shown in Table 2.

Table 2. Dosing Schedule for Ramp-Up Phase in Patients with AML

| Day | Venclexta Daily Dose |
|---|---|
| 1 | 100 mg |
| 2 | 200 mg |
| 3 and beyond | 400 mg |

Azacitidine should be administered at 75 mg/m$^2$ either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1.

Decitabine should be administered at 20 mg/m$^2$ intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1.

Venetoclax dosing may be interrupted as needed for management of haematologic toxicities and blood count recovery (see Table 6).

Venetoclax, in combination with a hypomethylating agent, should be continued until disease progression or unacceptable toxicity is observed.

*Prevention of tumour lysis syndrome (TLS)*

Patients treated with venetoclax may develop TLS. The appropriate section below should be referred to for specific details on management by disease indication.

Chronic Lymphocytic Leukaemia

Venetoclax can cause rapid reduction in tumour, and thus poses a risk for TLS in the initial 5-week dose-titration phase in all patients with CLL, regardless of tumour burden and other patient characteristics. 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. Assess patient-specific factors for level of TLS risk and provide prophylactic hydration and anti-hyperuricaemics to patients prior to first dose of venetoclax to reduce risk of TLS.

The risk of TLS is a continuum based on multiple factors, including comorbidities, particularly reduced renal function (creatinine clearance [CrCl] <80ml/min), and tumour burden. Splenomegaly may contribute to the overall TLS 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.

Table 3 below describes the recommended TLS prophylaxis and monitoring during venetoclax treatment based on tumour burden determination from clinical trial data (see section 4.4). In addition, all patient comorbidities should be considered for risk-appropriate prophylaxis and monitoring, either outpatient or in hospital.

Table 3. Recommended TLS prophylaxis based on tumour burden in patients with CLL

| **Tumour burden** | | **Prophylaxis** | | **Blood chemistry monitoring[c,d]** |
|---|---|---|---|---|
| | | Hydration[a] | Anti-hyperuricaemics[b] | Setting and frequency of assessments |
| Low | All LN <5 cm<br>AND<br>ALC <25 x$10^9$/L | Oral<br>(1.5-2 L) | Allopurinol | Outpatient<br>• For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours<br>• For subsequent dose increases: Pre-dose |
| Medium | Any LN 5 cm to <10 cm<br>OR<br>ALC ≥25 x$10^9$/L | Oral<br>(1.5-2 L)<br>and consider additional intravenous | Allopurinol | Outpatient<br>• For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours<br>• For subsequent dose increases: Pre-dose<br>• For first dose of 20 mg and 50 mg: Consider |

| | | | | |
|---|---|---|---|---|
| | | | | hospitalisation for patients with CrCl <80ml/min; see below for monitoring in hospital |
| High | Any LN ≥10 cm<br>OR<br>ALC ≥25 x$10^9$/L<br>AND<br>any LN ≥5 cm | Oral (1.5-2 L) and intravenous (150-200 ml/hr as tolerated) | Allopurinol; consider rasburicase if baseline uric acid is elevated | In hospital<br>• For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours<br>Outpatient<br>• For subsequent dose increases: Pre-dose, 6 to 8 hours, 24 hours |

ALC = absolute lymphocyte count; CrCl = creatinine clearance; LN = lymph node.

[a]Instruct patients to drink water daily starting 2 days before and throughout the dose-titration phase, specifically prior to and on the days of dosing at initiation and each subsequent dose increase. Administer intravenous hydration for any patient who cannot tolerate oral hydration.

[b]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.

[c]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.

[d]At subsequent dose increases, monitor blood chemistries at 6 to 8 hours and at 24 hours for patients who continue to be at risk of TLS.

*Dose modifications for tumour lysis syndrome and other toxicities*

Chronic Lymphocytic Leukaemia

Dosing interruption and/or dose reduction for toxicities may be required. See Table 4 and Table 5 for recommended dose modifications for toxicities related to venetoclax.

Table 4. Recommended venetoclax dose modifications for toxicities[a] in CLL

| Event | Occurrence | Action |
|---|---|---|
| Tumour lysis syndrome | | |
| Blood chemistry changes or symptoms suggestive of TLS | Any | Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose. |
| | | For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 5). |
| | | For any events of clinical TLS,[b] resume at a reduced dose following resolution (see Table 5). |
| Non-haematologic toxicities | | |
| Grade 3 or 4 non-haematologic toxicities | 1st occurrence | Interrupt venetoclax.<br>Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be |

| | | |
|---|---|---|
| | | resumed at the same dose. No dose modification is required. |
| | 2nd and subsequent occurrences | Interrupt venetoclax.<br>Follow dose reduction guidelines in Table 5 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician. |
| Haematologic toxicities | | |
| Grade 3 neutropenia with infection or fever; or Grade 4 haematologic toxicities (except lymphopenia) | 1st occurrence | Interrupt venetoclax.<br>To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. |
| | 2nd and subsequent occurrences | Interrupt venetoclax.<br>Consider using G-CSF as clinically indicated.<br>Follow dose reduction guidelines in Table 5 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician. |
| Consider discontinuing venetoclax for patients who require dose reductions to less than 100 mg for more than 2 weeks. | | |

[a]Adverse reactions were graded using NCI CTCAE version 4.0.

[b]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or seizures and/or sudden death (see section 4.8).

Table 5: Dose modification for TLS and other toxicities for patients with CLL

| **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 5).

Acute Myeloid Leukaemia

The venetoclax daily dose titration is 3 days with azacitidine or decitabine (see Table 2). Prophylaxis measures listed below should be followed:
All patients should have white blood cell count <25 × $10^9$/l prior to initiation of venetoclax and cytoreduction prior to treatment may be required.

All patients should be adequately hydrated and receive anti-hyperuricaemic agents prior to initiation of first dose of venetoclax and during dose-titration phase.

Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with venetoclax.

Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during titration and 24 hours after reaching final dose.

For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukaemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase [LDH] levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing venetoclax starting dose.

Monitor blood counts frequently through resolution of cytopenias. Dose modification and interruptions for cytopenias are dependent on remission status. Dose modifications of venetoclax for adverse reactions are provided in Table 6.

Table 6: Recommended dose modifications for adverse reactions in AML

| **Adverse Reaction** | **Occurrence** | **Dosage Modification** |
|---|---|---|
| **Haematologic Adverse Reactions** | | |
| Grade 4 neutropenia (ANC < 500/microlitre) with or without fever or infection; or grade 4 thrombocytopenia (platelet count <25 × $10^3$/microlitre) | Occurrence prior to achieving remission[a] | In most instances, do not interrupt venetoclax in combination with azacitidine or decitabine due to cytopenias prior to achieving remission. |
| | First occurrence after achieving remission and lasting at least 7 days | Delay subsequent cycle of venetoclax in combination with azacitidine or decitabine and monitor blood counts. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia.<br><br>Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine or decitabine. |
| | Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer | Delay subsequent cycle of venetoclax in combination with azacitidine or decitabine and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia.<br><br>Upon resolution to grade 1 or 2, resume venetoclax at the same dose in combination with azacitidine or |

| Adverse Reaction | Occurrence | Dosage Modification |
|---|---|---|
| | | decitabine, and reduce venetoclax duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days.<br><br>Refer to the azacitidine prescribing information for additional information. |
| **Non-Hematologic Adverse Reactions** | | |
| Grade 3 or 4 non-hematologic toxicities | Any occurrence | Interrupt venetoclax if not resolved with supportive care.<br>Upon resolution to grade 1 or baseline level, resume venetoclax at the same dose. |
| [a]Consider bone marrow evaluation. | | |

*Dose modifications for use with CYP3A inhibitors*

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure (i.e., $C_{max}$ and AUC) and may increase the risk for TLS at initiation and during the dose-titration phase and for other toxicities (see section 4.5).

In patients with CLL, concomitant use of venetoclax with strong CYP3A inhibitors is contraindicated at initiation and during the dose-titration phase (see sections 4.3, 4.4, and 4.5).

In all patients, if a CYP3A inhibitor must be used, follow the recommendations for managing drug-drug interactions summarized in Table 7. 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 7: Management of potential Venclexta interactions with CYP3A inhibitors

<table>
<tr><th>Inhibitor</th><th>Phase</th><th>CLL</th><th>AML</th></tr>
<tr><td rowspan="2">Strong CYP3A inhibitor</td><td>Initiation and dose-titration phase</td><td>Contraindicated</td><td>Day 1 – 10 mg<br>Day 2 – 20 mg<br>Day 3 – 50 mg<br>Day 4 – 100 mg or less</td></tr>
<tr><td>Steady daily dose (After dose-titration phase)</td><td colspan="2">Reduce the Venclexta dose to 100 mg or less (or by at least 75% if already modified for other reasons)</td></tr>
<tr><td>Moderate CYP3A inhibitor[a]</td><td>All</td><td colspan="2">Reduce the Venclexta dose by at least 50%</td></tr>
<tr><td colspan="4">[a]In patients with CLL, avoid concomitant use of Venclexta with moderate CYP3A inhibitors at initiation and during the dose-titration phase. Consider alternative medications or reduce the Venclexta dose as described in this table.</td></tr>
</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*

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). Venetoclax should be administered to patients with severe renal impairment (CrCl ≥15 ml/min and <30 ml/min) 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).

No dose adjustment is needed for patients with mild, moderate or severe renal impairment (CrCl ≥15 ml/min and <90 ml/min) (see section 5.2).

*Hepatic impairment*

No dose adjustment is recommended in patients with mild or moderate (Child-Pugh A or B) 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 (Child-Pugh C) (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*

Venclexta 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 with moderate or strong CYP3A4 inducers.

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

Pregnancy and Lactation.

Immunisation with live attenuated viral and/or bacterial vaccines.

## 4.4 Special warnings and precautions for use

*Tumour lysis syndrome*

Tumour lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients 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.
During post marketing surveillance, TLS, including fatal events, has been reported after a single 20 mg dose of venetoclax. Information described in section 4.2, including risk assessment, prophylactic measures, dose-titration and modification schedule, laboratory monitoring, and drug interactions should be followed to prevent and reduce the risk of TLS.

The risk of TLS is a continuum based on multiple factors, including comorbidities (particularly reduced renal function), tumour burden, and splenomegaly in CLL.

All 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. More intensive measures (intravenous hydration, frequent monitoring, hospitalisation) should be employed as overall risk increases. Dosing should be interrupted if needed; when restarting venetoclax, dose modification guidance should be followed (see Table 4 and Table 5). The instructions for “Prevention of tumour lysis syndrome” should be followed (see section 4.2).

Concomitant use of Venclexta 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*

In patients with CLL, 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).

In patients with AML, grade 3 or 4 neutropenia are common before starting treatment. The neutrophil counts can worsen with venetoclax in combination with a hypomethylating agent. Neutropenia can recur with subsequent cycles of therapy.

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 events of 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, dose interruption or reduction, and use of growth factors (e.g., G-CSF) 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 strong or moderate CYP3A4 inducers may lead to decreased venetoclax exposure with consequently a risk for lack of efficacy and 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 medicines 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. Compared with venetoclax 400 mg administered alone, co-administration of 300 mg posaconazole, a strong CYP3A and P-gp inhibitor, with venetoclax 50 mg and 100 mg for 7 days in 12 patients increased venetoclax $C_{max}$ to 1.6-fold and 1.9-fold, and AUC to 1.9-fold and 2.4-fold, respectively. Co-administration of venetoclax with other strong CYP3A4 inhibitors is predicted to increase venetoclax AUC by on average 5.8- to 7.8-fold.

For patients requiring concomitant use of venetoclax with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil), venetoclax dosing should be administered according to Table 7. 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 Venclexta 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*

Pregnant women should not be treated with Venclexta.
Based on embryo-foetal toxicity studies in animals (see section 5.3), there is a potential risk of serious harm to 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 should not be used during pregnancy and in women of childbearing potential not using highly effective contraception.

*Breastfeeding*

Women on treatment with Venclexta should not breastfeed their infants.
It is unknown whether venetoclax or its metabolites are excreted in human milk and harm to breastfed infant cannot be excluded.

Breastfeeding should be discontinued during treatment with Venclexta.

*Fertility*

No human data on the effect of Venclexta on fertility are available. Based on testicular toxicity in dogs at clinically relevant exposures, male fertility may be compromised by treatment with Venclexta (see section 5.3). It is unknown whether fertility would be restored to pre-treatment status after stopping Venclexta. Before starting treatment, counselling on sperm storage should be considered in male patients.

**4.7 Effects on ability to drive and use machines**

Venclexta may influence the ability to drive and use machines. Patient should not drive and use machines until they know how Venclexta affects them. Fatigue is very common in patients taking venetoclax and should be considered when assessing a patient's ability to drive or operate machines.

**4.8 Undesirable effects**

Summary of the safety profile

Chronic Lymphocytic Leukaemia

The overall safety profile of Venclexta 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 rituximab or obinutuzumab were pneumonia, sepsis, febrile neutropenia, and TLS. In the monotherapy studies, the most frequently reported serious adverse reactions (≥2%) were pneumonia and febrile neutropenia.

Acute Myeloid Leukaemia

The overall safety profile of Venclexta is based on data from 314 patients with newly diagnosed acute myeloid leukaemia (AML) treated in clinical trials with venetoclax in combination with a hypomethylating agent (azacitidine or decitabine) (VIALE-A phase 3 randomised, and M14-358 phase 1 non-randomised).

In the VIALE-A study, the most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in combination with azacitidine were thrombocytopenia, neutropenia, febrile neutropenia, nausea, diarrhoea, vomiting, anaemia, fatigue, pneumonia, hypokalaemia, and decreased appetite.

The most frequently reported serious adverse reactions (≥5%) in patients receiving venetoclax in combination with azacitidine were febrile neutropenia, pneumonia, sepsis and haemorrhage.

In the M14-358 study, the most commonly occurring adverse reactions (≥20%) of any grade in patients receiving venetoclax in combination with decitabine were thrombocytopenia, febrile neutropenia, nausea, haemorrhage, pneumonia, diarrhoea, fatigue, dizziness/syncope, vomiting, neutropenia, hypotension, hypokalaemia, decreased appetite, headache, abdominal pain and anaemia. The most frequently reported serious adverse reactions (≥5%) were febrile neutropenia, pneumonia, bacteraemia and sepsis.

The 30-day mortality rate in the VIALE-A study was 7.4% (21/283) with venetoclax in combination with azacitidine and 6.3% (9/144) in the placebo with azacitidine arm.

The 30-day mortality rate in the M14-358 study with venetoclax in combination with decitabine was 6.5% (2/31).

*Tabulated list of adverse reactions*

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.

*Chronic lymphocytic leukaemia*

The frequencies of adverse reactions reported with Venclexta, in combination with obinutuzumab, rituximab, or as monotherapy in patients with CLL are summarised in Table 8.

Table 8: 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<br>Cough | |
| | 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<br>Thrombocytopenia | Neutropenia<br>Anaemia<br>Thrombocytopenia<br>Lymphopenia |
| | Common | Febrile neutropenia | Febrile neutropenia |

| | | | |
|---|---|---|---|
| **Metabolism and nutrition disorders** | Very common | Hyperkalaemia<br>Hypokalaemia<br>Hyperphosphataemia<br>Hypophosphataemia<br>Hypocalcaemia<br>Hypoglycaemia<br>Hypernatraemia<br>Hyponatraemia<br>Hyperuricaemia<br>AST/ALT increase<br>Hyperbilirubinaemia<br>Hypoalbuminaemia | Hyperuricaemia<br>Hypophosphataemia<br>Hypocalcaemia |
| | Common | Tumour lysis syndrome | Tumour lysis syndrome<br>Hyperkalaemia<br>Hypokalaemia<br>Hyperphosphataemia<br>Hypoglycaemia<br>Hypernatraemia<br>Hyponatraemia<br>AST/ALT increase<br>Hyperbilirubinaemia<br>Hypoalbuminaemia<br>Hyperuricaemia |

| | | | |
|---|---|---|---|
| **Gastrointestinal disorders** | Very common | Diarrhoea<br>Vomiting<br>Nausea<br>Constipation<br>Abdominal pain | |
| | Common | Mucositis | Diarrhoea<br>Vomiting<br>Nausea<br>Constipation<br>Abdominal pain |
| | Uncommon | | Mucositis |
| **General disorders and administration site conditions** | Very common | Fatigue | |
| | Common | Pyrexia<br>Oedema | Fatigue<br>Pyrexia<br>Oedema |
| **Investigations** | Very common | Blood creatinine increased | |
| | Common | | Blood creatinine increased |
| **Musculoskeletal and connective tissue disorders** | Very Common | Musculoskeletal pain<br>Arthralgia | |
| | Common | | Musculoskeletal pain |
| | Uncommon | | Arthralgia |
| **Nervous system disorders** | Very Common | Dizziness<br>Headache<br>Insomnia | |
| | Common | | |

| | | | |
|---|---|---|---|
| | Uncommon | | Headache |
| **Skin and subcutaneous disorders** | Very Common | Rash | |
| | Uncommon | | Rash |
| [a]Only the highest frequency observed in the trials is reported (based on studies CLL14, MURANO, M13-982, M14-032, and M12-175). | | | |

*Acute myeloid leukaemia*

The frequencies of adverse reactions reported with Venclexta in combination with a hypomethylating agent in patients with AML are summarised in Table 9.

Table 9: Adverse drug reactions reported in patients with AML treated with venetoclax

| System organ class | Frequency | All grades[a] | Grade ≥3[a] |
|---|---|---|---|
| **Infections and infestations** | Very common | Pneumonia[b]<br>Sepsis[b]<br>Urinary tract infection | Pneumonia[b]<br>Sepsis[b] |
| | Common | | Urinary tract infection |
| **Blood and lymphatic system disorders** | Very common | Neutropenia[b]<br>Febrile neutropenia<br>Anaemia[b]<br>Thrombocytopenia[b] | Neutropenia[b]<br>Febrile neutropenia<br>Anaemia[b]<br>Thrombocytopenia[b] |
| **Metabolism and nutrition disorders** | Very common | Hypokalaemia<br>Decreased appetite | Hypokalaemia |
| | Common | Tumour lysis syndrome | Decreased appetite |
| | Uncommon | | Tumour lysis syndrome |
| **Nervous System Disorders** | Very common | Dizziness/syncope[b]<br>Headache | |
| | Common | | Dizziness/syncope[b] |
| | Uncommon | | Headache |
| **Vascular Disorders** | Very common | Hypotension<br>Haemorrhage[b] | Haemorrhage[b] |
| | Common | | Hypotension |
| **Respiratory, thoracic, and mediastinal disorder** | Very common | Dyspnoea | |
| | Common | | Dyspnoea |

| | | | |
|---|---|---|---|
| **Gastrointestinal disorders** | Very common | Nausea<br>Diarrhoea<br>Vomiting<br>Stomatitis<br>Abdominal pain | |
| | Common | | Nausea<br>Diarrhoea<br>Vomiting |
| | Uncommon | | Stomatitis |
| **Hepatobiliary Disorders** | Common | Cholecystitis/cholelithiasis[b] | Cholecystitis/cholelithiasis[b] |
| **Musculoskeletal disorders and connective tissue disorders** | Very common | Arthralgia | |
| | Uncommon | | Arthralgia |
| **General disorders and administration site conditions** | Very common | Fatigue<br>Asthenia | |
| | Common | | Fatigue<br>Asthenia |
| **Investigations** | Very common | Weight decreased<br>Blood bilirubin increased | |
| | Common | | Weight decreased<br>Blood bilirubin increased |

[a]Only the highest frequency observed in the trials is reported (based on studies VIALE-A and M14-358).

[b]Includes multiple adverse reaction terms.

*Discontinuation and dose reductions due to adverse reactions*

Chronic Lymphocytic Leukaemia

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%).

Acute Myeloid Leukaemia

In the VIALE-A study, discontinuations of venetoclax due to adverse reactions occurred in 24% of patients treated with the combination of venetoclax and azacitidine. Venetoclax dosage reductions due to adverse reactions occurred in 2% of patients. Venetoclax dose interruptions due to adverse reactions occurred in 72% of patients. Among patients who

achieved bone marrow clearance of leukaemia, 53% underwent dose interruptions for ANC <500/microlitre. The most common adverse reaction that led to dose interruption (>10%) of venetoclax were febrile neutropenia, neutropenia, pneumonia, and thrombocytopenia.

In the M14-358 study, discontinuations due to adverse reactions occurred in 26% of patients treated with the combination of venetoclax and decitabine. Dose reductions due to adverse reactions occurred in 6% of patients. Dose interruptions due to adverse reactions occurred in 65% of patients; the most common adverse reactions that led to dose interruption (≥5%) of venetoclax were febrile neutropenia, neutropenia/neutrophil count decreased, pneumonia, platelet count decreased, and white blood cell count decreased.

*Description of selected adverse reactions*

*Tumour lysis syndrome*

Tumour lysis syndrome is an important identified risk when initiating venetoclax.

Chronic Lymphocytic Leukaemia

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 dysrhythmias 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.

During post-marketing surveillance, TLS, including fatal events, has been reported after a single 20 mg dose of venetoclax (see sections 4.2 and 4.4).

Acute Myeloid Leukaemia

In the randomised, phase 3 study (VIALE-A) with venetoclax in combination with azacitidine the incidence of TLS was 1.1% (3/283, 1 clinical TLS). The study required reduction of white blood cell count to $<25 \times 10^9$/l prior to venetoclax initiation and a dose-titration schedule in addition to standard prophylaxis and monitoring measures (see section 4.2). All cases of TLS occurred during dose titration.

In M14-358 study, no events of laboratory or clinical TLS were reported with venetoclax in combination with decitabine.

*Neutropenia and infections*

Neutropenia is an identified risk with Venclexta treatment.

Chronic Lymphocytic Leukaemia

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% (all grades) of patients on 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: 1-712 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.

Acute Myeloid Leukaemia

In the VIALE-A study, grade ≥3 neutropenia was reported in 45% of patients. The following were also reported in the venetoclax + azacitidine arm versus the placebo + azacitidine arm, respectively: febrile neutropenia 42% versus 19%, grade ≥3 infections 64% versus 51%, and serious infections 57% versus 44%.

In the M14-358 study, neutropenia was reported in 35% (all grades) and 35% (grade 3 or 4) of patients in the venetoclax + decitabine arm.

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of Venclexta is important. It allows continued monitoring of the benefit/risk balance of Venclexta.

## 4.9 Overdose

There is no specific antidote for Venclexta. Patients who experience overdose should be closely monitored and appropriate symptomatic and 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 PHARMACOLOGIC PROPERTIES

## 5.1 Pharmacodynamic properties

A.26 Cytostatic agents

Mechanism of action

Venetoclax is a 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

*Chronic Lymphocytic Leukaemia*

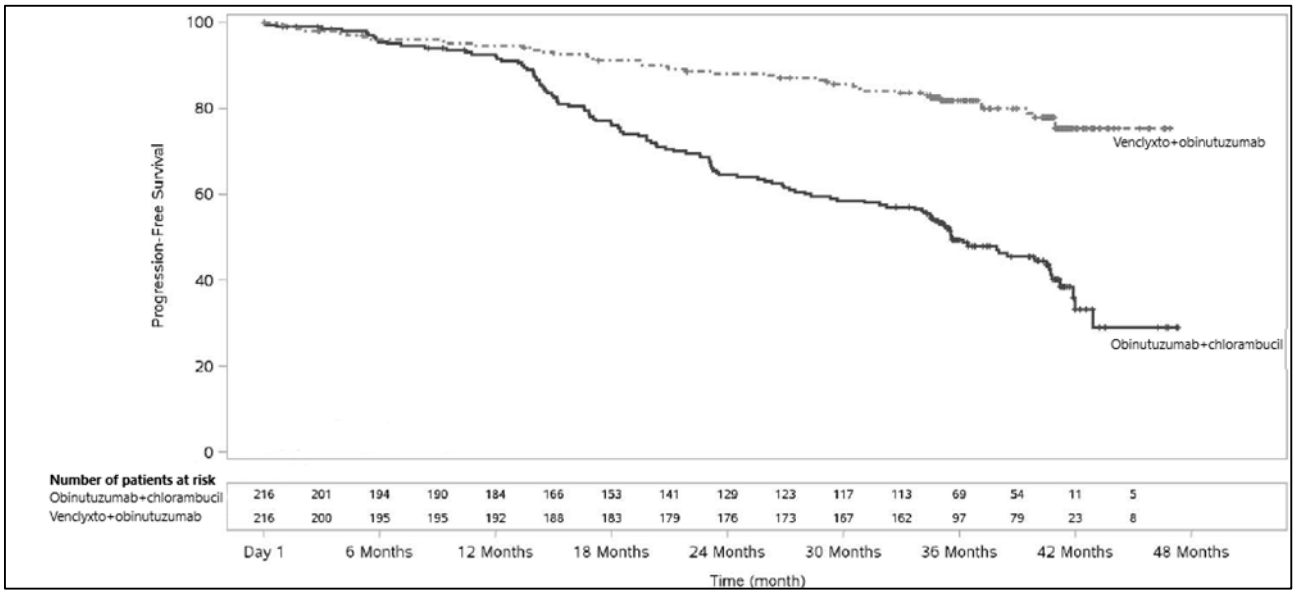
*Venetoclax in combination with obinutuzumab: Study BO25323 (CLL14)*

The safety and efficacy of venetoclax in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab in patients with previously untreated CLL was evaluated in a randomized (1:1), multicentre, open-label phase 3 study. A total of 432 patients were randomized (VEN+ obinutuzumab: 216; obinutuzumab + chlorambucil: 216). The median age was 72 years, 67 % were male, and 89 % were white.

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). Median follow-up time was 28 months at the time of the primary analysis (data cut-off date 17 Aug 2018). Treatment with VEN+ obinutuzumab resulted in a statistically significant 65 % reduction in the risk of disease progression or death for patients treated with VEN + G compared to patients treated with obinutuzumab + chlorambucil (hazard ratio: 0.35 [95 % CI: 0.23, 0.53]; P<0.0001). The median PFS was not reached in both arms.

The investigator assessed PFS curves at an updated efficacy analysis (data cut-off date 23 Aug 2019 and median follow-up of 40 months) are shown in Figure 1.

**Figure 1: Kaplan-Meier Curve of Investigator-Assessed Progression-Free Survival (ITT Population) in CLL14 with 40 months follow-up**



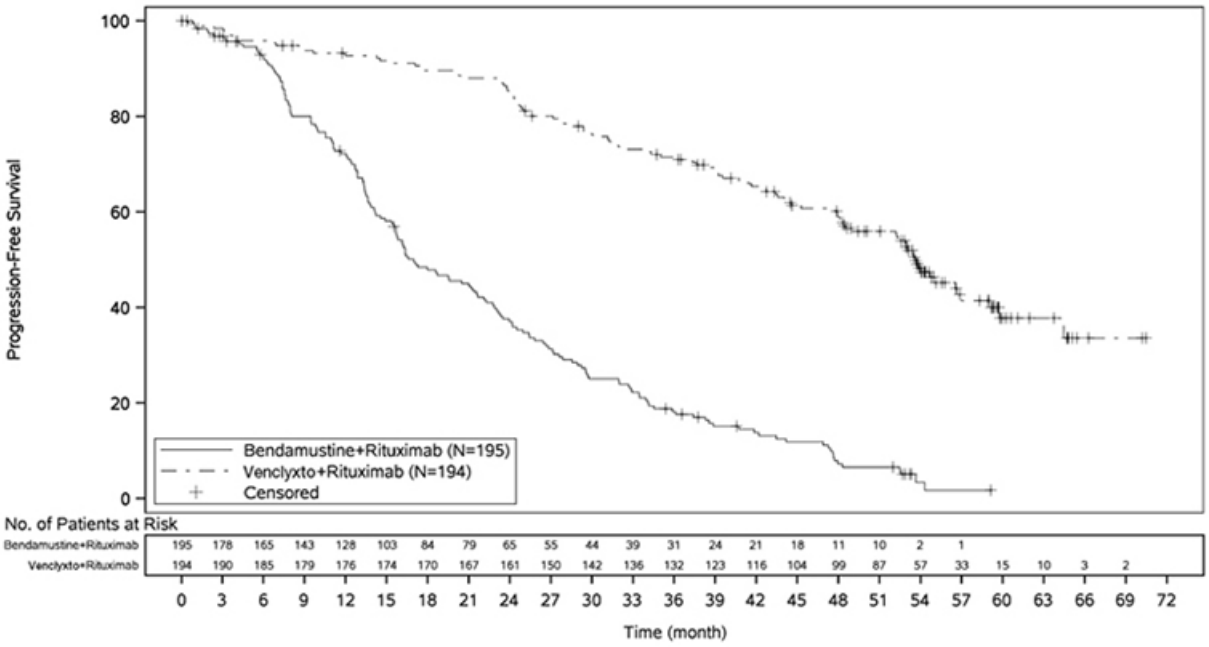

*Venetoclax in combination with rituximab: Study GO28667 (MURANO)*

The safety and efficacy of Venclexta in combination with rituximab (VENCLEXTA + R) versus bendamustine in combination with rituximab (BR) in patients with CLL who had received at least one prior therapy was evaluated in a randomized (1:1), multicentre, open-label phase 3 study (MURANO). A total of 389 patients were randomized (VENCLEXTA + R: 194; BR: 195). The median age was 65 years, 74% were male, and 97% were white. Median follow-up time was 23.8 months for the primary interim analysis (data cut-off date 8 May 2017).

The primary endpoint was (PFS) as assessed by investigators using the 2008 IWCLL updated NCI-WG guidelines. Efficacy results for PFS at a pre-specified primary interim analysis (data cut-off date 8 May 2017) indicated a statistically significant 83% reduction in the risk of disease progression or death for patients treated with VENCLEXTA + R compared to patients treated with BR (hazard ratio: 0.17 [95% CI: 0.11, 0.25]; P<0.0001).

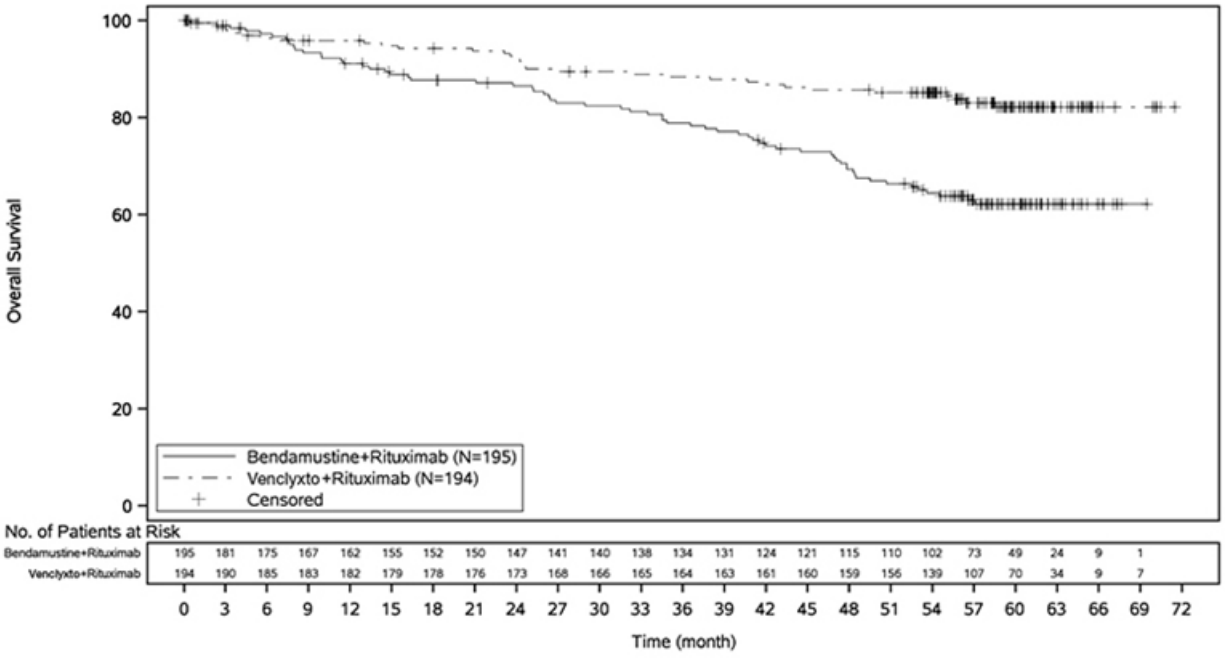
Efficacy was assessed after a median follow-up of 59 months (data cut-off date 8 May 2020). The investigator assessed median PFS was 53.6 months (95% CI: 48.4, 57.0) in the VENCLEXTA + R arm and 17.0 months (95% CI: 15.5, 21.7) in the BR arm (hazard ratio: 0.19; [95% CI: 0.15, 0.26]). The investigator assessed PFS curves with all patients off treatment and 59-month follow-up are shown in Figure 2.

**Figure 2: Kaplan-Meier curves of investigator-assessed progression-free survival (intent-to-treat population) in MURANO (data cut-off date 8 May 2020) with 59-month follow-up**




Death occurred in 17% (32/194) of patients in the VENCLEXTA + R arm and 33% (64/195) of patients in the BR arm (stratified HR 0.40; 95% CI [0.26, 0.62]). The Kaplan-Meier curve for overall survival is shown in Figure 3.

**Figure 3. Kaplan-Meier Curve of Overall Survival in MURANO with (data cut-off date 8 May 2020) with 59-month follow-up**




*Venetoclax as monotherapy (Studies M13-982 and M14-032)*

The safety and efficacy of venetoclax monotherapy in 107 patients with previously treated CLL with 17p deletion were evaluated in a single arm, open-label, multi-center study (M13 982). The median age was 67 years, 65% were male, and 97% were white. The median time on treatment was 12 months. The primary efficacy endpoint was ORR (overall response rate) according to IWCLL updated NCI WG guidelines by an IRC (independent review committee). The ORR was 79% (95% CI: 70.5, 86.6); the CR (complete remission) + CRi (complete remission with incomplete marrow recovery) rate was 8%.

The efficacy and safety of venetoclax in 127 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). The median age was 66 years, 70% were male, and 92% were white. As of the cut-off date 26 July 2017, the median duration of treatment with venetoclax was 14.3 months. The primary efficacy endpoint was ORR according to IWCLL updated NCI WG guidelines by an IRC (independent review committee). The ORR was 70% (95% CI: 61.3, 77.9); the CR + CRi rate was 1%.

*Acute Myeloid Leukaemia*

*Venetoclax in combination with azacitidine for the treatment of patients with newly diagnosed AML - study M15-656 (VIALE-A).*

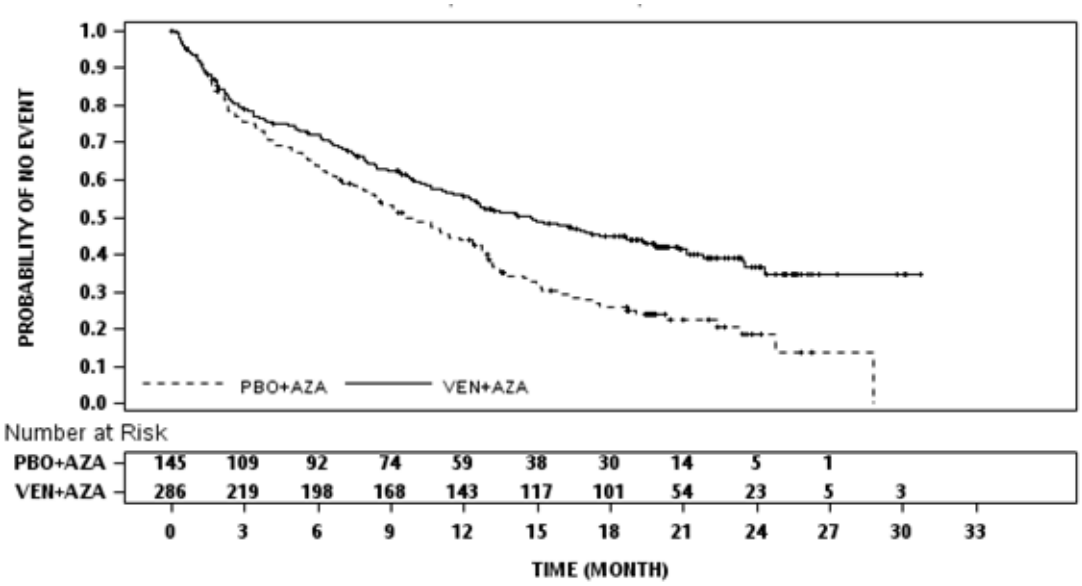
VIALE-A was a randomised (2:1), double-blind, placebo-controlled phase 3 study that evaluated the efficacy and safety of venetoclax in combination with azacitidine (aza) in patients with newly diagnosed AML who were ≥ 75 years of age, or who had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2–3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, creatinine clearance (CLcr) < 45 mL/min, or other comorbidity.

A total of 431 patients were randomized (VENCLEXTA + aza: 286; placebo +aza: 145). The median age was 75 years, 60% were male, and 96% were white. Median follow-up time was 20.5 months (range: <0.1 to 30.7 months).

The primary efficacy endpoints of the study were OS, and composite complete remission rate (complete remission + complete remission with incomplete blood count recovery [CR+CRi]).

Venclexta + aza demonstrated a 34% reduction in the risk of death compared with placebo + aza (HR: 0.66, [95% CI: 0.52, 0.85]; P <0.001). The median overall survival was 14.7 months with Venclexta + aza, and 9.6 month with placebo + aza. The CR+CRi rate based on a planned interim analysis of the first 226 patients randomized with 6 months of follow-up was 65% (95% CI: 57, 73) with Venclexta + aza (N=147) and 25% (95% CI: 16, 36) with placebo + aza (N=79) (p< 0.001). The Kaplan-Meier curve for overall survival is shown in Figure 5.

**Figure 5: Kaplan-Meier curve for overall survival in VIALE-A**




*Elderly patients (≥65 years of age)*

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

*Paediatric population*

Safety and efficacy have not been established in patients ≤18 years of age

## 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 321 subjects with mild renal impairment (CrCl ≥60 and <90 ml/min), 219 subjects with moderate renal impairment (CrCl ≥30 and <60 ml/min), 5 subjects with severe renal impairment (CrCl ≥15 and <30 ml/min) and 224 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 (CrCl <15 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 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

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

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.

No effects on fertility were observed in fertility and early embryonic development studies in male and female mice.

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

Venclexta 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)

Venclexta 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)

Venclexta 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**

Venclexta 10 mg film-coated tablets

2 years.

Venclexta 50 mg film-coated tablets

2 years.

Venclexta 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

Venclexta is available as follows:

| Packaging Presentation | Number of Tablets |
|---|---|
| CLL Starting Pack | Each pack contains four weekly wallet blister packs:<br>• Week 1 (14 x 10 mg tablets)<br>• Week 2 (7 x 50 mg tablets)<br>• Week 3 (7 x 100 mg tablets)<br>• Week 4 (14 x 100 mg tablets) |
| Wallet containing 10 mg tablets | 14 x 10 mg tablets |
| Wallet containing 50 mg tablets | 7 x 50 mg tablets |
| Unit dose blister containing 10 mg tablets | 2 x 10 mg tablets |
| Unit dose blister containing 50 mg tablet | 1 x 50 mg tablet |
| Unit dose blister containing 100 mg tablet | 1 x 100 mg tablet |
| Bottle containing 100 mg tablets | 120 x 100 mg tablets |

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Any unused Venclexta or waste material should be disposed of in accordance with local requirements.

## 7 NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AbbVie (Pty) Ltd

Abbott Place

219 Golf Club Terrace

Constantia Kloof

1709

## 8 REGISTRATION NUMBER

Venclexta 10 mg: 51/26/0580

Venclexta 50 mg: 51/26/0581

Venclexta 100 mg: 51/26/0582

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

8th September 2020

## 10 DATE OF REVISION OF THE TEXT

6th May 2022

CCDS04961220V15