q This medicinal product is subject to additional monitoring in Australia due to provisional approval of an extension of indication (AML). This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

# AUSTRALIAN PRODUCT INFORMATION

# VENCLEXTA® (VENETOCLAX) FILM-COATED TABLETS

## 1. NAME OF THE MEDICINE

Venetoclax

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VENCLEXTA 10 mg tablets: each film-coated tablet contains 10 mg venetoclax.

VENCLEXTA 50 mg tablets: each film-coated tablet contains 50 mg venetoclax.

VENCLEXTA 100 mg tablets: each film-coated tablet contains 100 mg venetoclax.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

VENCLEXTA 10 mg tablets: round, biconvex shaped, pale yellow debossed with “V” on one side and “10” on the other side.

VENCLEXTA 50 mg tablets: oblong, biconvex shaped, beige debossed with “V” on one side and “50” on the other side.

VENCLEXTA 100 mg tablets: oblong, biconvex shaped, pale yellow debossed with “V” on one side and “100” on the other side.

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

**Acute Myeloid Leukaemia**

VENCLEXTA, as part of combination therapy, is indicated for the treatment of newly diagnosed adult patients with Acute Myeloid Leukaemia (AML) who are ineligible for intensive chemotherapy.

This medicine has **provisional approval** in Australia for the treatment of newly diagnosed patients with AML who are ineligible for intensive chemotherapy. The decision to approve this indication has been made on the basis of interim data (overall response rate and duration of response). Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

**Chronic Lymphocytic Leukaemia**

VENCLEXTA in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

VENCLEXTA monotherapy is indicated for the treatment of:

- patients with relapsed or refractory CLL with 17p deletion, or
- patients with relapsed or refractory CLL for whom there are no other suitable treatment options.

## 4.2 Dose and method of administration

Patients should be instructed to take VENCLEXTA tablets with a meal and water at approximately the same time each day. VENCLEXTA tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

**Chronic Lymphocytic Leukaemia**

**5-week ramp-up schedule**

The starting dose of VENCLEXTA is 20 mg once daily for 7 days. The VENCLEXTA dose must be administered according to a weekly ramp-up schedule to the daily dose of 400 mg over a period of 5 weeks as shown in Table 1. The 5-week ramp-up schedule is designed to gradually reduce tumour burden (debulking) and decrease the risk of TLS.

**Table 1. Dosing schedule including ramp-up phase for patients with CLL**

| **Week** | **VENCLEXTA daily dose** |
|---|---|
| 1 | 20 mg |
| 2 | 50 mg |
| 3 | 100 mg |
| 4 | 200 mg |
| 5 and beyond | 400 mg |
| VENCLEXTA Starting Pack contains doses for Week 1 to Week 4. | |

**VENCLEXTA in combination with rituximab**

Start rituximab administration after the patient has completed the ramp-up schedule with VENCLEXTA (see Table 1) and has received a daily 400 mg dose of VENCLEXTA for 7 days.

Patients should continue VENCLEXTA 400 mg once daily for up to 24 months from Cycle 1 Day 1 of rituximab in the absence of disease progression or unacceptable toxicity.

**VENCLEXTA as monotherapy**

The recommended dose of VENCLEXTA is 400 mg once daily after the patient has completed the ramp-up schedule. Treatment should continue until disease progression or venetoclax is no longer tolerated by the patient.

**Acute Myeloid Leukaemia**

The dose of VENCLEXTA depends upon the combination agent. The VENCLEXTA dosing schedule (including ramp-up) is shown in Table 2. Initiate azacitidine or low-dose cytarabine on Day 1.

**Table 2. Dosing schedule including ramp-up phase for patients with AML**

| **Day** | **VENCLEXTA daily dose** | |
|---|---|---|
| 1 | 100 mg | |
| 2 | 200 mg | |
| 3 | 400 mg | |
| 4 and beyond | 400 mg<br>when dosing in combination with azacitidine | 600 mg<br>when dosing in combination with low-dose cytarabine |

VENCLEXTA, in combination with azacitidine or low-dose cytarabine, should be continued until disease progression or unacceptable toxicity is observed.

**Risk assessment for tumour lysis syndrome (TLS)**

Patients treated with VENCLEXTA may develop TLS. Refer to the appropriate section below for specific details on management.

**Chronic Lymphocytic Leukaemia**

VENCLEXTA can cause rapid tumour reduction and thus poses a risk for TLS in the initial 5-week ramp-up 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 VENCLEXTA and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumour burden and comorbidities. Reduced renal function (creatinine clearance [CrCl] <80 mL/min) further increases the risk. The risk may decrease as tumour burden decreases with VENCLEXTA treatment (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). Perform tumour burden assessments, including radiographic evaluation (e.g., CT scan), assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.

## Prophylaxis for tumour lysis syndrome

### Chronic Lymphocytic Leukaemia

Table 3 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumour burden determination from clinical trial data.

**Table 3. Recommended TLS prophylaxis based on tumour burden in patients with CLL from clinical trial data (consider all patient co-morbidities before final determination of prophylaxis and monitoring schedule)**

| **Tumour burden** | | **Prophylaxis** | | **Blood chemistry monitoring[c,d]** |
|---|---|---|---|---|
| | | **Hydration[a]** | **Anti-hyperuricaemics** | **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[b] | Outpatient<br>• Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg<br>• Pre-dose at subsequent ramp-up doses |
| 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>• Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg<br>• Pre-dose at subsequent ramp-up doses<br>• Consider hospitalisation for patients with CrCl <80ml/min at first dose of 20 mg and 50 mg; 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 (1.5-2L)<br>and intravenous<br>(150-200 mL/hr as tolerated) | Allopurinol; consider rasburicase if baseline uric acid is elevated | In hospital at first dose of 20 mg and 50 mg<br>• Pre-dose, 4, 8,12 and 24 hours<br>Outpatient at subsequent ramp-up doses<br>• Pre-dose, 6 to 8 hours, 24 hours |

ALC = absolute lymphocyte count; LN = lymph node.
[a]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 VENCLEXTA.
[c]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d]For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

### Acute Myeloid Leukaemia

Follow these TLS prophylaxis measures:

- All patients should have white blood cell count < 25 × $10^9$/L prior to initiation of VENCLEXTA and cytoreduction prior to treatment may be required.
- All patients should receive prophylactic measures including adequate hydration and anti-hyperuricaemic agents prior to initiation of first dose and during ramp-up phase.
- Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA.
    - Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during ramp-up and 24 hours after reaching the final dose.
- For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukaemia involvement in bone marrow, elevated pretreatment LDH levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reduced VENCLEXTA starting dose.

**Dose modifications based on toxicities**

**Chronic Lymphocytic Leukaemia**

Dosing interruption and/or dose reduction may be required. See Table 4 for dose modifications for haematological and other toxicities related to VENCLEXTA. For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks after completing the ramp-up phase, reassess the risk of TLS to determine if re-initiation with a reduced dose is necessary (e.g., at one of the prior levels of the ramp-up schedule) (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION; Chronic Lymphocytic Leukaemia 5-week ramp-up schedule, Risk assessment for tumour lysis syndrome** and **Prophylaxis for tumour lysis syndrome**).

**Table 4. Recommended dose modifications for toxicities during VENCLEXTA treatment of 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 24-48 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) (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION; *Risk assessment for tumour lysis syndrome*** and ***Prophylaxis for tumour lysis syndrome***). |
| | | For any events of clinical TLS, resume at a reduced dose following resolution (see Table 5) (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION; *Risk assessment for tumour lysis syndrome*** and ***Prophylaxis for tumour lysis syndrome***). |
| **Non-haematological toxicities** | | |
| Grade 3 or 4 non-haematological toxicities | 1st occurrence | Interrupt VENCLEXTA.<br>Once the toxicity has resolved to grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose. No dose modification is required. |
| | 2nd and subsequent occurrences | Interrupt VENCLEXTA.<br>Follow dose reduction guidelines in Table 5 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician. |
| **Haematological toxicities** | | |
| Grade 3 neutropenia with infection or fever; or any grade 4 haematological toxicity (except lymphopaenia) *(*see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE; *Neutropenia*)** | 1st occurrence | Interrupt VENCLEXTA.<br>To reduce the infection risks associated with neutropenia, G-CSF may be administered with VENCLEXTA if clinically indicated.<br>Once the toxicity has resolved to grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose. |
| | 2nd and subsequent occurrences | Interrupt VENCLEXTA.<br>Consider using G-CSF as clinically indicated.<br>Follow dose reduction guidelines in Table 5 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician. |
| Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for more than 2 weeks. | | |

**Table 5. Dose reduction for toxicity during VENCLEXTA treatment of CLL**

| Dose at interruption, mg | Restart dose, mg[a] |
|---|---|
| 400 | 300 |
| 300 | 200 |
| 200 | 100 |
| 100 | 50 |
| 50 | 20 |
| 20 | 10 |
| [a]Continue the reduced dose for 1 week before increasing the dose. | |

**Acute Myeloid Leukaemia**

Monitor blood counts frequently through resolution of cytopaenias. Management of some adverse reactions **(see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **Section 4.8 ADVERSE EFFECTS)** may require dose interruptions or permanent discontinuation of VENCLEXTA. Table 6 shows the dose modification guidelines for haematological toxicities.

**Table 6. Recommended dose modifications for toxicities[a] during VENCLEXTA treatment of AML**

| Event | Occurrence | Action |
|---|---|---|
| **Haematological toxicities** | | |
| Grade 4 neutropenia with or without fever or infection; or grade 4 thrombocytopenia (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**) | Occurrence prior to achieving remission | Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated. In most instances, VENCLEXTA and azacitidine or low-dose cytarabine cycles should not be interrupted due to cytopenias prior to achieving remission. |
| | First occurrence after achieving remission and lasting at least 7 days | Delay subsequent treatment cycle of VENCLEXTA and azacitidine or low-dose cytarabine and monitor blood counts.<br>Granulocyte-colony stimulating factor (G-CSF) may be administered if clinically indicated for neutropenia. Once the toxicity has resolved to grade 1 or 2, VENCLEXTA therapy may be resumed at the same dose in combination with azacitidine or low-dose cytarabine. |
| | Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer | Delay subsequent treatment cycle of VENCLEXTA and azacitidine or low-dose cytarabine and monitor blood counts.<br>G-CSF may be administered if clinically indicated for neutropenia. Once the toxicity has resolved to grade 1 or 2, VENCLEXTA therapy may be resumed at the same dose and the duration reduced by 7 days for each subsequent cycle. |
| [a]Adverse reactions were graded using NCI CTCAE version 4.0. | | |

**Dose modifications for use with CYP3A inhibitors**

Concomitant use of VENCLEXTA 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 dose ramp-up.

In patients with CLL, concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated (see **Section 4.3 CONTRAINDICATIONS).**

In all patients, if a CYP3A inhibitor is to be used concomitantly, follow the recommendations for VENCLEXTA dose modifications summarised in Table 7. Monitor these patients more closely for signs of toxicities (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION: Dose modifications based on toxicities**).

The VENCLEXTA dose that was used prior to initiating a CYP3A inhibitor may be resumed 2 to 3 days after discontinuation of the inhibitor (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION: Dose modifications based on toxicities** and **Section 4.5 INTERACTIONS WITH OTHER MEDICINES**).

**Table 7. VENCLEXTA dose modifications for use with CYP3A inhibitors**

| **Indication** | **Moderate CYP3A inhibitor** | | **Strong CYP3A inhibitor** | |
|---|---|---|---|---|
| | *Initiation and ramp up phase* | *Steady daily dose (after ramp-up phase)* | *Initiation and ramp up phase* | *Steady daily dose (after ramp-up phase)* |
| CLL | Reduce the VENCLEXTA dose by at least 50% of the original dose.[a] | | **Contraindicated** | Reduce the VENCLEXTA dose to 100 mg or less.[a] |
| AML | Reduce the VENCLEXTA dose by at least 50% of the original dose. | | Day 1 – 10 mg<br>Day 2 – 20 mg<br>Day 3 – 50 mg<br>Day 4 – 100 mg or less | Reduce the VENCLEXTA dose to 100 mg or less. |

a. Avoid concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors in CLL: consider alternative medications. If concomitant use of a CYP3A inhibitor can't be avoided, VENCLEXTA dosing should be reduced as described here.

**Missed dose**

If the patient misses a dose of VENCLEXTA within 8 hours of the time it is usually taken, the patient should be instructed to take the missed dose as soon as possible and resume the normal daily dosing schedule. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose but resume the usual dosing schedule the next day.

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

## 4.3 Contraindications

Hypersensitivity to venetoclax, or to any of the excipients within the formulation.

In patients with CLL, concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during the ramp-up phase is contraindicated (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION** and **Section 4.5 INTERACTIONS WITH OTHER MEDICINES**).

## 4.4 Special warnings and precautions for use

**Tumour lysis syndrome**

**Tumour lysis syndrome (TLS), which may be life-threatening or fatal, has occurred in patients treated with VENCLEXTA** (see **Section 4.8 ADVERSE EFFECTS**).

**Interrupt or discontinue VENCLEXTA, as recommended, if this adverse event occurs (**see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION).**

VENCLEXTA can cause rapid tumour reduction and thus poses a risk for TLS at initiation and during the ramp-up phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6-8 hours following the first dose of VENCLEXTA and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumour burden (see Table 3) and comorbidities. Reduced renal function 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. More intensive measures (intravenous hydration, frequent monitoring, and hospitalisation) should be employed as overall risk increases (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk of TLS at initiation and during ramp-up phase (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION** and **Section 4.5**

**INTERACTIONS WITH OTHER MEDICINES**). Inhibitors of P-gp may also increase venetoclax exposure (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES**).

**Neutropenia**

In patients with CLL, grade 3 or 4 neutropenia (ANC <1.0 x $10^9$/L) has occurred in 58% (112/194) of patients treated with VENCLEXTA in the combination study with rituximab (Study GO28667) and in 40.8% (98/240) of patients treated with VENCLEXTA monotherapy (see **Section 4.8 ADVERSE EFFECTS**). In patients with AML, grade 3 or 4 neutropenia is common before starting treatment. The neutrophil counts can worsen with VENCLEXTA in combination with azacitidine or low-dose cytarabine. Neutropenia can recur with subsequent cycles of therapy. Complete blood counts should be monitored throughout the treatment period. Dose interruptions or dose reductions are recommended for severe neutropenia. Supportive measures should be considered, including antimicrobials for any signs of infection, and use of growth factors (e.g., granulocyte-colony stimulating factor [G-CSF]) (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.3 CONTRAINDICATIONS, Section 4.5 INTERACTIONS WITH OTHER MEDICINES** and **Section 5.2 PHARMACOKINETIC PROPERTIES** for further information on potential interactions with CYP3A inhibitors/inducers).

**Serious infection**

Serious infections, including events of sepsis and events with fatal outcome, have been reported in patients treated with VENCLEXTA (see **Section 4.8 ADVERSE EFFECTS**). Monitor patients for fever and any symptoms of infection and treat promptly. Interrupt dosing as appropriate.

**Immunisation**

The safety and efficacy of immunisation with live attenuated vaccines during or following VENCLEXTA therapy have not been studied. Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs.

**Hepatic impairment**

No dose adjustment is recommended in patients with mild or moderate hepatic impairment based on results of the population pharmacokinetic analysis.

A 50% dose reduction throughout treatment is recommended for patients with severe hepatic impairment; monitor these patients more closely for signs of toxicity (see **Section 5.2 PHARMACOKINETIC PROPERTIES**).

**Renal impairment**

No specific clinical trials have been conducted in subjects with renal impairment. After a single oral administration of 200 mg radiolabeled [$^{14}$C]-venetoclax to healthy subjects, less than 0.1% of radioactive VENCLEXTA dose was detected in urine. No dose adjustment is needed for patients with mild or moderate renal impairment (CrCl ≥30 mL/min) based on the results of the population pharmacokinetic analysis (see **Section 5.2 PHARMACOKINETIC PROPERTIES**).

Patients with reduced renal function (CrCl <80 mL/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with VENCLEXTA (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**). A recommended dose has not been determined for patients with severe renal impairment (CrCl <30 mL/min) or patients on dialysis.

**Paediatric use**

The safety and efficacy of VENCLEXTA in children and adolescents less than 18 years of age have not been established.

**Use in the elderly**

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

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

Of the 164 previously treated patients with CLL evaluated for efficacy by an Independent Review Committee in Studies M13-982 and M12-175, 91 (55.5%) patients were ≥65 years of age and 28 (17.1%) patients were ≥75 years of age.

Of the 240 patients with CLL evaluated for safety from 3 open-label clinical trials, 138 (57.5%) patients were ≥65 years of age and 40 (16.7%) patients were ≥75 years of age.

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

**Increased mortality in patients with multiple myeloma (not an approved indication) when VENCLEXTA is added to bortezomib and dexamethasone**

In a randomised trial (BELLINI; NCT02755597) in patients with relapsed or refractory multiple myeloma, the addition of VENCLEXTA to bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

## 4.5 Interactions with other medicines and other forms of interactions

**Potential effects of other medicines on VENCLEXTA**

Venetoclax is predominantly metabolised by CYP3A4.

**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 130% and AUC

The VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor may be resumed 2 to 3 days after discontinuation of the inhibitor (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

Avoid grapefruit products, Seville oranges, and starfruit during treatment with VENCLEXTA, as they contain inhibitors of CYP3A.

**OATP1B1/1B3 and P-gp inhibitors**

Co-administration of a 600 mg single dose of rifampicin, an OATP1B1/1B3 and P-gp inhibitor, in 11 healthy subjects increased venetoclax $C_{max}$ by 106% and AUC by 78%.

Concomitant use of venetoclax with P-gp inhibitors (e.g., amiodarone, captopril, carvedilol, ciclosporin, felodipine, quercetin, quinidine, ranolazine, ticagrelor) at initiation and during the ramp-up phase should be avoided; if a P-gp inhibitor must be used, patients should be monitored closely for signs of toxicities.

**Azithromycin**

Co-administration of 500 mg of azithromycin on the first day followed by 250 mg of azithromycin for 4 days in 12 healthy subjects decreased venetoclax $C_{max}$ by 25% and AUC by 35%. No dose adjustment is needed when venetoclax is co-administered with azithromycin.

**CYP3A inducers**

Co-administration of 600 mg once daily rifampicin, a strong CYP3A inducer, for 13 days in 10 healthy subjects decreased venetoclax $C_{max}$ by 42% and AUC by 71%. Concomitant use of VENCLEXTA with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampicin, St. John's wort (*Hypericum perforatum*)) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered (see **Section 5.2 PHARMACOKINETIC PROPERTIES**).

**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.

**Potential effects of VENCLEXTA on other medicines**

**Warfarin**

In a drug-drug interaction study in three healthy volunteers, administration of a single 400 mg dose of venetoclax with 5 mg warfarin resulted in an 18% to 28% increase in $C_{max}$ and AUC of R-warfarin and S-warfarin. Because venetoclax was not dosed to steady state, it is recommended that the international normalised ratio (INR) be monitored closely in patients receiving warfarin.

**P-gp substrates**

Administration of a single 100 mg dose of venetoclax with 0.5 mg digoxin, a P-gp substrate, in 10 healthy subjects resulted in a 35% increase in digoxin $C_{max}$ and a 9% increase in digoxin AUC . Therefore, co- administration of narrow therapeutic index P-gp substrates (e.g., digoxin, everolimus, and sirolimus) with VENCLEXTA should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before VENCLEXTA.

## 4.6 Fertility, pregnancy and lactation

**Effects on fertility**

No human data on the effect of venetoclax on fertility are available. Based on findings in animals, male fertility may be compromised by treatment with VENCLEXTA.

Fertility and early embryonic development studies were conducted in male and female mice. These studies evaluated mating, fertilisation, and embryonic development through implantation. There were no effects of venetoclax on oestrus cycles, mating, fertility, corpora lutea, uterine implants or live embryos per litter at dosages up to 600 mg/kg/day (in male and female mice, approximately 1.8 times the human AUC exposure at the maximum recommended clinical dose of 600 mg/day). However, a risk to human male fertility exists based on testicular toxicity (germ cell loss) observed in dogs at all dose levels examined (exposures of 0.3 to 11 times the human AUC exposure at the 600 mg/day clinical dose). Reversibility of this finding has not been demonstrated.

## Use in pregnancy

### Pregnancy Category C

There are no adequate and well-controlled studies of venetoclax in pregnant women. Based on embryo-fetal toxicity observed in mice, VENCLEXTA may have effects on the fetus when administered to pregnant women.

VENCLEXTA should not be used during pregnancy. Women of child-bearing potential must use highly effective contraceptive measures during treatment with VENCLEXTA and for at least 30 days after the last dose of treatment. If venetoclax is used during pregnancy or if the patient becomes pregnant while taking VENCLEXTA, the patient should be apprised of the potential hazard to a fetus. The time period following treatment with VENCLEXTA where it is safe to become pregnant is unknown.

Women of child-bearing potential should undergo pregnancy testing before initiation of VENCLEXTA.

In embryo-fetal development studies, venetoclax was administered to pregnant mice and rabbits. These studies evaluated potential effects after implantation and subsequent embryo-fetal development during the respective periods of major organogenesis in mice and rabbits. In mice, venetoclax was associated with increased post-implantation loss and decreased fetal body weight at 150 mg/kg/day (maternal exposures approximately 0.7 times the human AUC exposure at the maximum recommended clinical dose of 600 mg/day). In rabbits, venetoclax at 300 mg/kg/day produced maternal toxicity, but no fetal toxicity (maternal exposures approximately 0.09 times the human AUC exposure at the 600 mg/day clinical dose). No teratogenicity was observed in either the mouse or the rabbit. Limited placental transfer of venetoclax was shown in mice, rats and rabbits.

## Use in lactation

It is not known whether venetoclax or its metabolites are excreted in human breast milk. Venetoclax was shown to be readily excreted in milk in rats, along with trace amounts of metabolites. A risk to newborns/infants cannot be excluded. Because many drugs are excreted in human breast milk and because the potential for serious adverse reactions in breastfed infants from VENCLEXTA is unknown, nursing women should be advised to discontinue breastfeeding during treatment with VENCLEXTA.

## 4.7 Effects on ability to drive and use machines

No studies on the effects of VENCLEXTA on the ability to drive and use machines have been performed. The pharmacological activity and adverse events reported to date do not indicate that such an effect is likely.

## 4.8 Adverse effects (undesirable effects)

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

**Clinical trial experience in CLL**

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

**VENCLEXTA in combination with rituximab**

The safety of venetoclax in combination with rituximab versus bendamustine in combination with rituximab, was evaluated in an open-label randomised phase 3 study (Study GO28667), in patients with CLL who have received at least one prior therapy. Details of the study treatment are described in **Section 5.1 Pharmacodynamic properties: Clinical trials VENCLEXTA in combination with rituximab**. At the time of data analysis, the median duration of exposure was 22 months in the venetoclax + rituximab arm compared to 6 months in the bendamustine plus rituximab arm.

Discontinuations due to adverse events occurred in 16% of patients treated with venetoclax + rituximab. Dose reductions due to adverse events occurred in 15% of patients treated with venetoclax + rituximab. Dose interruptions due to adverse events occurred in 71% of patients treated with venetoclax + rituximab. The most common adverse reaction that led to dose modification of venetoclax was neutropenia.

**Table 8. Adverse events reported in ≥5% of patients treated with VENCLEXTA + rituximab in Study GO28667 which occurred at ≥2% higher incidence compared with bendamustine + rituximab**

| | VENCLEXTA + rituximab followed by single agent VENCLEXTA (N=194) | | Bendamustine + rituximab (N=188) | |
|---|---|---|---|---|
| **Adverse Events System Organ Class Preferred Term** | **Any grade n (%)** | **Grade ≥3 n (%)** | **Any grade n (%)** | **Grade ≥3 n (%)** |
| **Blood and lymphatic system disorders** | | | | |
| Neutropenia | 118 (61) | 112 (58) | 83 (44) | 73 (39) |
| **Gastrointestinal disorders** | | | | |
| Diarrhoea | 77 (40) | 5 (3) | 31 (16) | 2 (1) |
| Abdominal pain | 13 (7) | 2 (1) | 6 (3) | 0 |
| **Infections and infestations** | | | | |
| Upper respiratory tract infection | 43 (22) | 3 (2) | 29 (15) | 2 (1) |
| Nasopharyngitis | 22 (11) | 0 | 10 (5) | 0 |
| Bronchitis | 20 (10) | 1 (1) | 13 (7) | 2 (1) |
| Sinusitis | 18 (9) | 3 (2) | 5 (3) | 1 (1) |
| Pharyngitis | 13 (7) | 0 | 3 (2) | 1 (1) |
| Urinary tract infection | 12 (6) | 1 (1) | 7 (4) | 0 |
| Lower respiratory tract infection | 11 (6) | 0 | 5 (3) | 1 (1) |
| Respiratory tract infection | 11 (6) | 1 (1) | 6 (3) | 0 |
| Conjunctivitis | 10 (5) | 0 | 5 (3) | 0 |
| Influenza | 10 (5) | 2 (1) | 4 (2) | 2 (1) |
| **Metabolism and nutrition disorders** | | | | |
| Hyperkalaemia | 12 (6) | 2 (1) | 0 | 0 |
| Hypokalaemia | 12 (6) | 1 (1) | 7 (4) | 1 (1) |
| Hyperphosphataemia | 10 (5) | 3 (2) | 0 | 0 |
| **Psychiatric disorders** | | | | |
| Insomnia | 21 (11) | 0 | 12 (6) | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Productive cough | 12 (6) | 0 | 4 (2) | 0 |
| **Vascular disorders** | | | | |
| Hypertension | 12 (6) | 5 (3) | 7 (4) | 2 (1) |

Based on the existing safety profile of VENCLEXTA, adverse reactions reported in the venetoclax + rituximab arm of Study GO28667 that fall below the cut-off in Table 8 are presented 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).

**Blood & lymphatic system disorders**: anaemia (very common), febrile neutropenia (common), lymphopaenia/lymphocyte count decreased (common);

**Gastrointestinal disorders**: nausea (very common), constipation (very common), vomiting (common);

**General disorders and administration site conditions**: fatigue (very common);

**Infections & infestations**: pneumonia (common), sepsis (common);

**Investigations:** blood creatinine increased (common);

**Metabolism and nutrition disorders**: tumour lysis syndrome (common), hyperuricaemia (common), hypocalcaemia (common).

During treatment with single agent VENCLEXTA after completion of venetoclax + rituximab combination treatment, the most common all grade adverse events (≥5% patients) reported were diarrhoea (19%), neutropenia (14%), upper respiratory tract infection (12%), bronchitis (6%), cough (6%), fatigue (6%), nausea (6%), nasopharyngitis (5%), pyrexia (5%), rash (5%), and sinusitis (5%); the most common grade ≥3 adverse events (≥2% patients) were neutropenia (11%), anaemia (3%), pneumonia (2%), and thrombocytopenia (2%).

**VENCLEXTA as monotherapy**

The safety of VENCLEXTA is based on pooled data of 352 patients with R/R CLL/SLL treated with VENCLEXTA (400 mg once daily cohort who received at least one dose) in two phase 2 trials (Study M13-982 enrolled patients with previously treated CLL with 17p deletion and Study M14-032 enrolled patients with CLL who had failed an inhibitor of the B-cell receptor pathway), and one phase 1 trial (Study M12-175 enrolled patients with previously treated CLL, including those with 17p deletion). In the overall safety population, there were 212 patients with 17p deletion and 148 patients who had failed an inhibitor of the B cell receptor pathway. Patients were treated with VENCLEXTA 400 mg monotherapy once daily following the ramp-up schedule.

Tabulated list of adverse reactions

The frequencies of adverse drug reactions (ADRs) reported with VENCLEXTA are summarised in Table 9. 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 9: Adverse drug reactions reported in patients with CLL treated with VENCLEXTA monotherapy**

| System Organ Class | Frequency (All grades) | Preferred Term |
|---|---|---|
| **Blood and lymphatic system disorders** | Very common | Neutropenia[a]<br>Anaemia[b]<br>Lymphopaenia[c] |
| | Common | Febrile neutropenia |
| **Gastrointestinal disorders** | Very common | Diarrhoea<br>Vomiting<br>Nausea<br>Constipation |
| **General disorders and administration site conditions** | Very common | Fatigue |
| **Infections and infestations** | Very common | Upper respiratory tract infection<br>Pneumonia |
| | Common | Urinary tract infection<br>Sepsis[d] |
| **Investigations** | Common | Blood creatinine increased |
| **Metabolism and nutrition disorders[e]** | Very common | Hyperkalaemia[f]<br>Hyperphosphataemia[g]<br>Hypocalcaemia[h] |
| | Common | Tumour lysis syndrome[i]<br>Hyperuricaemia[j] |

[a]Includes neutropenia and neutrophil count decreased.
[b]Includes anaemia and haemoglobin decreased.
[c]Includes lymphopaenia and lymphocyte count decreased.
[d]Includes escherichia sepsis, sepsis, septic shock, urosepsis, corynebacterium bacteraemia, corynebacterium sepsis, klebsiella bacteraemia, klebsiella sepsis, pulmonary sepsis, staphylococcal bacteraemia, and staphylococcal sepsis.
[e]Adverse reactions for this body system are reported for patients who followed the 5-week ramp-up dosing schedule and TLS prophylaxis and monitoring measures described in Section 4.2 DOSE AND METHOD OF ADMINISTRATION.
[f]Includes hyperkalaemia and blood potassium increased.
[g]Includes hyperphosphataemia and blood phosphorus increased.
[h]Includes hypocalcaemia and blood calcium decreased.
[i]Reported as TLS events.
[j]Includes hyperuricaemia and blood uric acid increased.

The most frequently reported serious adverse reactions (≥2%) unrelated to disease progression were pneumonia and febrile neutropenia.

Discontinuations due to adverse events occurred in 10.5% of patients.

Dosage reductions due to adverse events occurred in 14% of patients. Dose interruptions due to adverse events occurred in 40% of patients. Of the most frequent adverse events (≥4%) leading to dose reductions or interruptions, the one identified as adverse reaction was neutropenia (5% and 4%, respectively).

**Clinical trial experience in AML**

The safety of VENCLEXTA (400 mg daily dose) in combination with azacitidine (n=84) and VENCLEXTA (600 mg daily dose) in combination with low-dose cytarabine (n=82) is based on two non-randomised trials of patients with newly diagnosed AML (see **Section 5 PHARMACOLOGICAL PROPERTIES**)**.** The median duration of exposure for patients taking VENCLEXTA in combination with azacitidine was 6.4 months (range: 0.1 to 31.9 months). The median duration of exposure for patient taking VENCLEXTA in combination with low-dose cytarabine was 4.2 months (range: 0.2 to 29.2 months).

The 30-day and 60-day mortality rates observed with VENCLEXTA in combination with azacitidine were 2.4% (2/84) and 8.3% (7/84), respectively. The 30-day and 60-day mortality rates observed with VENCLEXTA in combination with low-dose cytarabine were 6.1% (5/82) and 14.6% (12/82), respectively.

**VENCLEXTA in combination with azacitidine (Study M14-358)**

The most common adverse reactions (≥30%) of any grade were nausea, diarrhoea, thrombocytopenia, constipation, neutropenia, peripheral oedema, febrile neutropenia, vomiting, fatigue and pneumonia.

Serious adverse events were reported in 73% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia and pneumonia.

Discontinuations due to adverse events occurred in 19% of patients. The most frequent adverse reactions leading to drug discontinuation (≥2%) were febrile neutropenia and pneumonia.

Dosage interruptions due to adverse events occurred in 61% of patients. The most frequent adverse reactions leading to dose interruption (≥2%) were febrile neutropenia, neutrophil count decreased, neutropenia, pneumonia and thrombocytopenia.

Dosage reductions due to adverse reactions occurred in 10% of patients. The most frequent adverse reaction leading to dose reduction (≥2%) was neutrophil count decreased.

Adverse reactions reported in patients with newly diagnosed patients with AML using VENCLEXTA in combination with azacitidine are presented in Table 10.

**Table 10. Adverse reactions reported in ≥30% (any grade) or ≥5% (grade 3 or 4) of patients with AML treated with VENCLEXTA in combination with azacitidine**

| Adverse Reaction by System Organ Class | Frequency (any grade) | Any grade (%) N=84 | Grade 3 or 4 (%) N=84 |
|---|---|---|---|
| **Blood and lymphatic system disorders** | | | |
| Thrombocytopenia[a] | Very common | 50 | 46 |
| Neutropenia[b] | Very common | 48 | 48 |
| Febrile neutropenia | Very common | 37 | 37 |
| Anaemia[c] | Very common | 30 | 30 |
| **Gastrointestinal disorders** | | | |
| Nausea | Very common | 61 | 1 |
| Diarrhoea | Very common | 56 | 2 |
| Constipation | Very common | 49 | 2 |
| Vomiting | Very common | 36 | 0 |
| **General disorders and administration site conditions** | | | |
| Peripheral oedema | Very common | 38 | 1 |
| Fatigue | Very common | 32 | 6 |
| **Infections and infestations** | | | |
| Pneumonia[d] | Very common | 30 | 29 |
| Bacteraemia | Common | 4 | 2 |
| Sepsis | Common | 4 | 4 |

Adverse Reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0.
[a]Thrombocytopenia/platelet count decreased.
[b]Neutropenia/neutrophil count decreased.
[c]Anaemia/haemoglobin decreased.
[d]Pneumonia/atypical pneumonia/lung consolidation/pneumocystis jirovecii pneumonia/pneumonia influenza/pneumonia legionella/pneumonia streptococcal/pneumonia fungal/pneumonia respiratory syncytial viral/pneumonia klebsiella/lung infection/atypical mycobacterial pneumonia.

*Laboratory abnormalities*

Table 11 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

**Table 11. New or worsening laboratory abnormalities with VENCLEXTA reported in ≥40% (any grade) or ≥10% (grade 3 or 4) of patients with AML treated with VENCLEXTA in combination with azacitidine**

| Laboratory abnormality | All grades[a] (%) N=84 | Grade 3 or 4[a] (%) N=84 |
|---|---|---|
| **Haematology** | | |
| Absolute neutrophil count decrease | 100 | 98 |
| Absolute white cell count decrease | 100 | 99 |
| Platelet count decrease | 91 | 81 |
| Absolute lymphocyte count decrease | 89 | 75 |
| Decreased haemoglobin | 56 | 56 |
| **Chemistry** | | |
| High glucose | 75 | 12 |
| Low calcium | 61 | 8 |
| Low albumin | 55 | 5 |
| Low potassium | 51 | 7 |
| Low sodium | 50 | 8 |
| Low inorganic phosphate | 49 | 19 |
| High total bilirubin | 48 | 8 |
| Low magnesium | 29 | 0 |
| [a]Includes laboratory abnormalities that were new or worsening, or worsening from baseline unknown. | | |

**VENCLEXTA in combination with low-dose cytarabine (Study M14-387)**

The most common adverse reactions (≥30%) of any grade were nausea, thrombocytopenia, diarrhoea, neutropenia, febrile neutropenia, fatigue, constipation, and vomiting.

Serious adverse events were reported in 91% of patients. The most frequent serious adverse reactions (≥5%) were febrile neutropenia, pneumonia and sepsis.

Discontinuations due to adverse events occurred in 29% of patients. The most frequent adverse reactions leading to drug discontinuation (≥2%) were thrombocytopenia, and sepsis.

Dosage interruptions due to adverse events occurred in 55% of patients. The most frequent adverse reactions leading to dose interruption (≥2%) were thrombocytopenia, neutropenia, febrile neutropenia, vomiting, pneumonia, and sepsis.

Dosage reductions due to adverse events occurred in 7% of patients. The most frequent adverse reaction leading to dose reductions (≥2%) was thrombocytopenia.

Adverse reactions reported in newly diagnosed patients with AML receiving VENCLEXTA in combination with low-dose cytarabine are presented in Table 12.

**Table 12. Adverse reactions reported in ≥30% (any grade) or ≥5% (grade 3 or 4) of patients with AML treated with VENCLEXTA in combination with low-dose cytarabine**

| **Adverse Reaction by System Organ Class** | **Frequency (Any Grade)** | **Any Grade (%) N=82** | **Grade 3 or 4 (%) N=82** |
|---|---|---|---|
| **Blood and lymphatic system disorders** | | | |
| Thrombocytopenia[a] | Very common | 60 | 60 |
| Neutropenia[b] | Very common | 44 | 44 |
| Febrile neutropenia | Very common | 43 | 41 |
| Anaemia[c] | Very common | 28 | 28 |
| **Gastrointestinal disorders** | | | |
| Nausea | Very common | 70 | 2 |
| Diarrhoea | Very common | 49 | 2 |
| Constipation | Very common | 35 | 0 |
| Vomiting | Very common | 30 | 4 |
| **General disorders and administration site conditions** | | | |
| Fatigue | Very common | 43 | 7 |
| **Infections and infestations** | | | |
| Pneumonia[d] | Very common | 20 | 18 |
| Sepsis | Very common | 12 | 11 |

Adverse reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0.
[a]Thrombocytopenia/platelet count decreased.
[b]Neutropenia/neutrophil count decreased.
[c]Anaemia/haemoglobin decreased.
[d]Pneumonia/atypical pneumonia/lung consolidation/pneumocystis jirovecii pneumonia/pneumonia influenza/pneumonia legionella/pneumonia streptococcal/pneumonia fungal/pneumonia respiratory syncytial viral/pneumonia klebsiella/lung infection/atypical mycobacterial pneumonia.

*Laboratory abnormalities*

Table 13 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

**Table 13. New or worsening laboratory abnormalities with VENCLEXTA reported in ≥40% (any grade) or ≥10% (grade 3 or 4) of patients with AML treated with VENCLEXTA in combination with low-dose cytarabine**

| Laboratory abnormality | All grades[a] (%) N=82 | Grade 3 or 4[a] (%) N=82 |
|---|---|---|
| **Haematology** | | |
| Platelet count decrease | 98 | 95 |
| Absolute neutrophil count decrease | 97 | 94 |
| Absolute white cell count decrease | 96 | 95 |
| Absolute lymphocyte count decrease | 95 | 65 |
| Decreased haemoglobin | 63 | 62 |
| **Chemistry** | | |
| High glucose | 84 | 12 |
| Low calcium | 82 | 15 |
| Low sodium | 63 | 11 |
| High total bilirubin | 63 | 9 |
| Low albumin | 63 | 9 |
| Low potassium | 60 | 20 |
| Low inorganic phosphate | 55 | 23 |
| Low magnesium | 45 | 1 |
| High alkaline phosphatase | 41 | 1 |
| [a]Includes laboratory abnormalities that were new or worsening, or worsening from baseline unknown. | | |

## Tumour lysis syndrome

Tumour lysis syndrome is an important identified risk when initiating VENCLEXTA. TLS prophylaxis and monitoring measures are described in the Dosage and Administration section (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

### Chronic Lymphocytic Leukaemia

VENCLEXTA as monotherapy

In the initial Phase 1 dose-finding trials, which had a relatively short (2-3 week) ramp-up phase and relatively high 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 (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**). In venetoclax clinical trials, 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 ramp-up phase.

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 2.4%. 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. All events resolved within 5 days. 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.

VENCLEXTA in combination with rituximab

In the open-label, randomised phase 3 study (Study GO28667), 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 include the TLS prophylaxis and monitoring measures described in Dosage and Administration section (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**). All events of TLS occurred during the VENCLEXTA ramp-up phase and resolved within two days. All six patients completed the ramp-up and reached the recommended daily dose of 400 mg of VENCLEXTA. No clinical TLS was observed in patients who followed the current 5-week ramp-up dosing schedule and TLS prophylaxis and monitoring measures described (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**). The rates of grade ≥3 laboratory abnormalities relevant to TLS were hyperkalaemia 1%, hyperphosphataemia 1%, and hyperuricaemia 1%.

**Acute Myeloid Leukaemia**

VENCLEXTA in combination with azacitidine (Study M14-358)

There were no reported events of laboratory or clinical TLS reported with VENCLEXTA in combination with azacitidine with implementation of dosing ramp-up schedule in addition to standard prophylaxis and monitoring measures.

VENCLEXTA in combination with low-dose cytarabine (Study M14-387)

The incidence of TLS was 2.4% (2/82) with VENCLEXTA in combination with low-dose cytarabine with implementation of the ramp-up schedule in addition to standard prophylaxis and monitoring measures. All events were laboratory TLS, there were no reports of clinical TLS, and all patients were able to reach the target dose.

**Neutropenia**

Neutropenia is an identified risk associated with VENCLEXTA treatment and occurs very commonly. In Study GO28667 (venetoclax + rituximab versus bendamustine + rituximab for the treatment of patients with CLL), neutropenia of any grade was reported in 61%, and led to venetoclax interruption for 43% and discontinuation for 3% of patients in the venetoclax + rituximab arm. Grade 3 and grade 4 neutropenia were reported in 32% and 26% of venetoclax-treated patients, respectively. The median duration of grade 3 or 4 neutropenia was 8 days (range: 1-712 days). Clinical complications of neutropenia, including febrile neutropenia, grade ≥3 and serious infections were reported less frequently in the venetoclax + rituximab arm compared to the bendamustine + rituximab arm: febrile neutropenia 4% versus 10%, grade ≥3 infections 18% versus 23%, and serious infections 21% versus 24%.

## 4.9 Overdose

Daily doses of up to 1200 mg of VENCLEXTA have been evaluated in clinical trials. There has been no experience with overdose in clinical trials. If an overdose is suspected, treatment should consist of general supportive measures.

For information on the management of overdose in Australia contact the Poison Information Centre on 131126.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents

ATC code: L01XX52

**Mechanism of action**

Venetoclax is an orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in chronic lymphocytic leukaemia

(CLL) and acute myeloid leukaemia (AML) cells, as well as various other haematological and solid tumour malignancies, and has been implicated in resistance to certain therapeutic agents. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilisation, the release of cytochrome *c* from mitochondria and the activation of caspases. In nonclinical studies, venetoclax demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.

## Cardiac electrophysiology

The effect of multiple doses of VENCLEXTA up to 1200 mg once daily on the QTc interval was evaluated in an open-label, single-arm study in 176 patients with previously treated CLL or Non-Hodgkin Lymphoma (NHL). VENCLEXTA had no effect on QTc interval and there was no relationship between venetoclax exposure and change in QTc interval.

## Clinical trials

### Chronic Lymphocytic Leukaemia

VENCLEXTA in combination with rituximab

Study GO28667 was a randomised (1:1), multicentre, open label phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with rituximab versus bendamustine in combination with rituximab in patients with CLL who had received at least one line of prior therapy. Patients in the venetoclax + rituximab arm completed the 5-week ramp-up schedule (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**) and were planned to receive 400 mg VENCLEXTA daily for a maximum of 2 years in the absence of disease progression or unacceptable toxicity. Rituximab was initiated after the 5-week ramp-up 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 bendamustine + rituximab received bendamustine at 70 mg/m$^2$ on Days 1 and 2 for 6 cycles and rituximab at the above described dose and schedule. Following completion of 24 months of venetoclax + rituximab regimen, patients continued to be followed for disease progression and overall survival.

A total of 389 patients were randomised; 194 to the venetoclax + rituximab arm and 195 to the bendamustine + rituximab arm. Table 14 shows the baseline demographic and disease characteristics were similar between the venetoclax + rituximab and bendamustine + rituximab arms.

**Attachment 1: Product AusPAR - VENCLEXTA - venetoclax - AbbVie Pty Ltd - PM-2018-05208-1-6 and PM-2019-04393-1-6 FINAL 24 September 2020. This Product information was approved at the time this AusPAR was published.**

**Table 14: Demographics and Baseline Characteristics in Study GO28667**

| Characteristic | VENCLEXTA + rituximab (N = 194) | Bendamustine + rituximab (N = 195) |
|---|---|---|
| Age, years; median (range) | 64.5 (28-83) | 66 (22-85) |
| White; % | 96.8 | 96.7 |
| Male; % | 70.1 | 77.4 |
| **ECOG performance status; %** | | |
| 0 | 57.2 | 55.7 |
| 1 | 42.3 | 43.3 |
| 2 | 0.5 | 1.0 |
| **Tumour burden; %** | | |
| Absolute lymphocyte count 25 x $10^9$/L | 66.5 | 68.7 |
| One or more nodes 5 cm | 45.7 | 47.6 |
| **Number of prior lines of therapy; %** | | |
| Median number (range) | 1 (1 – 5) | 1 (1 – 4) |
| 1 | 57.2 | 60.0 |
| 2 | 29.4 | 22.1 |
| ≥3 | 13.4 | 17.9 |
| **Previous CLL regimens** | | |
| Median number (range) | 1 (1-5) | 1 (1-4) |
| Prior alkylating agents, % | 93.3 | 95.4 |
| Prior purine analogs, % | 80.5 | 81.4 |
| Prior anti-CD20 antibodies, % | 76.3 | 78.6 |
| Prior B-cell receptor pathway inhibitors, % | 1.5 | 2.6 |
| FCR, % | 54.1 | 55.4 |
| Prior bendumustine, % | 2.1 | 2.6 |
| Fludarabine refractory, % | 14.1 | 15.5 |
| **CLL subsets %** | | |
| 17p deletion | 26.6 | 27.2 |
| 11q deletion | 35.3 | 37.9 |
| *TP53* mutation | 25.0 | 27.7 |
| *IgVH* unmutated | 68.3 | 68.3 |
| Time since diagnosis, years; median (range) | 6.44 (0.5–28.4) | 7.11 (0.3-29.5) |
| FCR = fludarabine, cyclophosphamide, rituximab | | |

The median survival follow-up at the time of analysis was 23.8 months (range: 0.0 to 37.4 months).

The primary endpoint was progression-free survival (PFS) as 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 Study GO28667 are shown in Table 15. The Kaplan-Meier curves for PFS and overall survival (OS) are shown in Figure 1 and 2, respectively.

### Table 15: Efficacy Results for Study GO28667

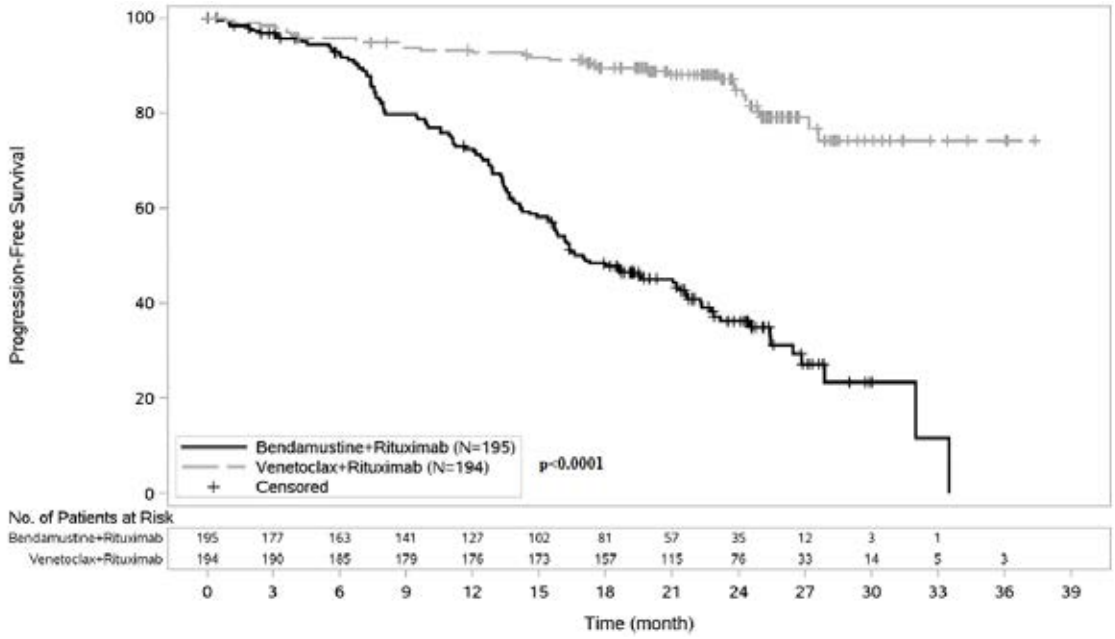
| | INV-assessed | | IRC-assessed | |
|---|---|---|---|---|
| | **VENCLEXTA + rituximab (N = 194)** | **Bendamustine + rituximab (N = 195)** | **VENCLEXTA + rituximab (N = 194)** | **Bendamustine + rituximab (N = 195)** |
| **Progression-free survival** | | | | |
| Number of events (%) | 32 (16.5) | 114 (58.5) | 35 (18.0) | 106 (54.4) |
| Disease progression | 21 | 98 | 26 | 91 |
| Death events | 11 | 16 | 9 | 15 |
| Median, months, (95% CI) | Not reached | 17.0 (15.5, 21.6) | Not reached | 18.1 (15.8, 22.3) |
| HR (95% CI) | 0.17 (0.11, 0.25) | | 0.19 (0.13, 0.28) | |
| p-value[a] | $p < 0.0001$ | | $p < 0.0001$ | |
| 12-month estimate, % (95% CI) | 92.7 (89.1, 96.4) | 72.5 (65.9, 79.1) | 91.2 (87.2, 95.2) | 74.1 (67.6, 80.7) |
| 24-month estimate, % (95% CI) | 84.9 (79.1, 90.6) | 36.3 (28.5, 44.0) | 82.8 (76.6, 88.9) | 37.4 (29.4, 45.4) |
| **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[b] | 3.6[b] |
| nPR, (%) | 3.1 | 6.2 | 1.5 | 0.5 |
| PR, (%) | 63.4 | 53.3 | 82.5 | 68.2 |
| **Overall survival** | | | | |
| Number of deaths (%) | 15 (7.7) | 27 (13.8) | NA | NA |
| Hazard Ratio (95% CI) | 0.48 (0.25, 0.90) | | NA | |
| **Time to next anti-leukaemic therapy** | | | | |
| Number of events (%) | 23 (11.9) | 83 (42.6) | NA | NA |
| Median, months | Not reached | 26.4 | NA | NA |
| Hazard ratio (95% CI) | 0.19 (0.12, 0.31) | | NA | |
| **Event-free survival** | | | | |
| Number of events (%) | 33 (17.0) | 118 (60.5) | NA | NA |
| Median, months | Not reached | 16.4 | NA | NA |
| Hazard ratio (95% CI) | 0.17 (0.11, 0.25) | | NA | |

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; INV = investigator; IRC = independent review committee; MRD = minimal residual disease; NA = not available; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission; HR = hazard ratio.

[a]Stratified log-rank test.

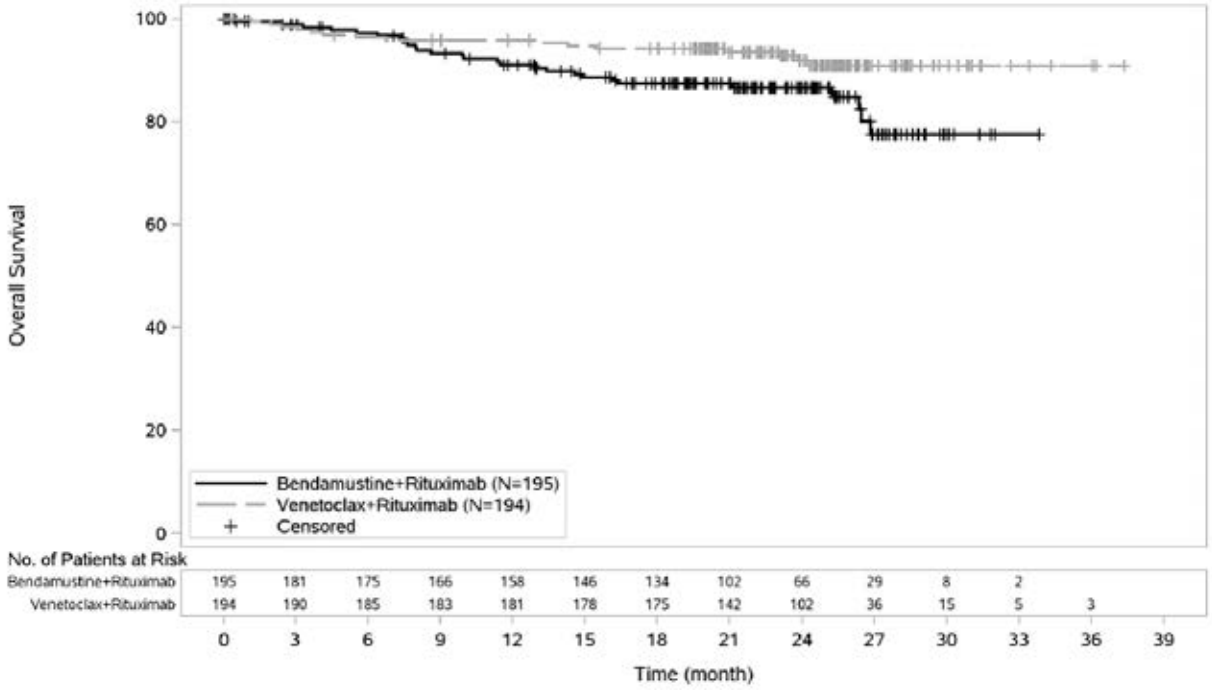
[b]The discrepancy between IRC- and investigator-assessed CR rate was primarily due to interpretation of residual adenopathy on CT scans. Eighteen patients in the venetoclax + rituximab arm and 3 patients in the bendamustine + rituximab arm had negative bone marrow and lymph nodes <2 cm.

**Figure 1: Kaplan-Meier curve of Investigator-assessed progression-free survival (ITT Population) in Study GO28667**




At the time of primary analysis (data cutoff date 8 May 2017), 65 patients completed the 24 month venetoclax + rituximab treatment regimen without progression and 78 patients were still receiving venetoclax (+18 months of treatment). Of the 65 patients who remained progression free at 24 months, only 2 patients progressed after treatment completion. Twelve patients had a 3-month follow-up visit and remained progression free. Of the 12 patients, 5 were also assessed at 6-month follow-up and remained progression free.

**Figure 2: Kaplan-Meier curve of Overall Survival (ITT Population) in Study GO28667**




Minimal residual disease (MRD) was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and/or flow cytometry. The cutoff for a negative status was less than one CLL cell per $10^4$ leukocytes in the sample. MRD data were available in peripheral blood in nearly all patients (187/194 in the venetoclax + rituximab arm versus 179/195 in the bendamustine + rituximab arm) and in a subset of patients for bone marrow (74/194 in the venetoclax + rituximab arm versus 41/195 in the bendamustine + rituximab arm). Peripheral blood MRD negativity rates, assessed at any time during the study, were observed in 84% (162/194) of patients in the venetoclax + rituximab arm versus 23% (45/195) of patients in the bendamustine + rituximab arm. Bone marrow MRD negativity rates were 27.3% (53/194 patients) in the venetoclax + rituximab arm versus 1.5% (3/195 patients) in the bendamustine + rituximab arm. At the 9-month response assessment, MRD negativity in the peripheral blood was 62.4% in the venetoclax + rituximab arm versus 13.3% in the bendamustine + rituximab arm and this rate was maintained in the venetoclax + rituximab arm for at least an additional 9 months (59.8% in venetoclax + rituximab versus 5.1% in bendamustine + rituximab), the last visit for which complete data were available prior to the clinical cutoff date.

The PFS benefit with venetoclax + rituximab versus bendamustine + rituximab treatment was observed across all subgroups examined including age (< 65, ≥ 65 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.

VENCLEXTA as monotherapy

The safety and efficacy of VENCLEXTA were established in three open-label, multicentre clinical trials of patients with CLL who had received at least one prior therapy, including those with deletion of the p13 locus on chromosome 17 (17p deletion).

*Study M13-982*

Study M13-982 was a multicentre, single-arm open-label trial of 107 patients with previously treated CLL with 17p deletion. Table 16 summarises the baseline demographic and disease characteristics of the study population.

**Table 16. Baseline patient characteristics in Study M13-982**

| **Characteristic** | **N = 107[a]** |
|---|---|
| Age, years; median (range) | 67 (37-85) |
| White; % | 97.2 |
| Male; % | 65.4 |
| ECOG performance status; %<br>0<br>1<br>2 | <br>39.3<br>52.3<br>8.4 |
| Tumour burden; %<br>Absolute lymphocyte count ≥25 x $10^9$/L<br>One or more nodes ≥5 cm | <br>50.5<br>53.3 |
| Number of prior therapies; median (range) | 2 (1-10) |
| Time since diagnosis, years; median (range)[b] | 6.8 (0.1-32) |
| [a]One patient did not harbour the 17p deletion.<br>[b]N=106. | |

Among the patients, 37.4% (34/91) were fludarabine refractory, 81.1% (30/37) had unmutated *IGHV*, and 23.8% (19/80) had 11q deletion.

In the study, patients with 17p deletion were identified using Vysis CLL FISH Probe Kit. Patients received VENCLEXTA via a weekly ramp-up schedule starting at 20 mg and titrating to 50 mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive 400 mg of VENCLEXTA orally once daily until disease progression or unacceptable toxicity. The median time on treatment at the time of evaluation was 12.1 months (range: 0 to 21.5 months).

The primary efficacy endpoint was overall response rate (ORR) as assessed by an IRC using the IWCLL updated NCI-WG guidelines (2008). Efficacy results for Study M13-982 are shown in Table 17.

**Table 17. Efficacy results in study M13-982**

| | **IRC assessment (N=107)[a]** | **Investigator assessment (N=107)[a]** |
|---|---|---|
| ORR, % (95% CI) | 79.4 (70.5, 86.6) | 73.8 (64.4, 81.9) |
| CR + CRi (%) | 7.5 | 15.9 |
| nPR (%) | 2.8 | 3.7 |
| PR (%) | 69.2 | 54.2 |
| DOR, % (95% CI) 12-month estimate | 84.7 (74.5, 91.0) | 89.1 (79.2, 94.4) |

[a]One patient did not harbour the 17p deletion.

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.

Based on a later data cutoff (15 June 2017), which included an additional 51 patients enrolled in a safety expansion cohort, and investigator-assessed efficacy (N=158), the median duration of response (DOR) was 36.2 months (95% CI: 27.2, NA). The median duration of progression-free survival (mPFS) was 28.2 months (95% CI: 23.4, 37.0).

Minimal residual disease was evaluated using flow cytometry in 45 of 107 patients who achieved complete remission (CR), complete remission with incomplete marrow recovery (CRi), or partial remission (PR) with limited remaining disease with VENCLEXTA treatment. The cut-off for a negative status was one CLL cell per $10^4$ leukocytes in the sample (i.e., an MRD value of $<10^{-4}$ was considered MRD negative). Seventeen percent (18/107) of patients were MRD negative in the peripheral blood, including six patients who were also MRD negative in the bone marrow.

There were 73 patients who completed the Global Health Status assessment (GHS) and 76 patients who completed both the Emotional (EF) and Social Functioning (SF) assessments in the EORTC QLQ-C30 questionnaire at both baseline and week 24. There were 74 and 77 patients, respectively, who completed the Role functioning (RF) and the Fatigue symptom scale assessments at both baseline and week 24. Following treatment with VENCLEXTA, patients showed improvement in GHS (16%), EF (10.6%), SF (17.1%), RF (16.2%), and the Fatigue symptom score (17.5%) at week 24. Improvements in these measures were seen as early as week 4.

*Study M12-175*

Study M12-175 was a multicentre, open-label trial that enrolled patients with previously treated CLL, including those with 17p deletion. Efficacy was evaluated in 57 patients who had received a daily dose of 400 mg of VENCLEXTA following a ramp-up schedule. Patients continued to receive 400 mg of VENCLEXTA monotherapy orally once daily until disease progression or unacceptable toxicity. The median time on treatment at the time of evaluation was 11.5 months (range: 0.5 - 34.1 months). Table 18 summarises the baseline demographic and disease characteristics of the study population.

**Table 18. Baseline patient characteristics of evaluable patients in Study M12-175**

| **Characteristic** | **N=57** |
|---|---|
| Age, years; median (range) | 66 (42-84) |
| White; % | 91.2 |
| Male; % | 75.4 |
| ECOG performance status[a]; %<br>0<br>1<br>2 | <br>45.5<br>52.7<br>1.8 |
| Tumour burden; %<br>Absolute lymphocyte count ≥25 x $10^9$/L<br>One or more nodes ≥5 cm | <br>35.1<br>66.7 |
| Number of prior therapies; median (range) | 3 (1-11) |
| Time since diagnosis, years; median (range) | 9 (1.1-27.3) |
| [a]Missing for two patients. | |

Among the patients, 75.4% were fludarabine refractory, 65.6% (21/32) had unmutated *IGHV*, 30.4% (17/56) had 11q deletion, and 21.4% (12/56) had 17p deletion.

Overall response rate and duration of response were evaluated by both investigators and an IRC according to the IWCLL NCI-WG criteria. Efficacy results are shown in Table 19:

**Table 19. Efficacy results in Study M12-175**

| | **IRC assessment N=57** | **Investigator assessment N=57** |
|---|---|---|
| ORR, %<br>(95% CI) | 73.7<br>(60.3, 84.5) | 80.7<br>(68.1, 90.0) |
| CR + CRi (%) | 7.0 | 12.3 |
| nPR (%) | 0 | 3.5 |
| PR (%) | 66.7 | 64.9 |
| DOR, % (95% CI)<br>12-month estimate | 88.8 (67.5, 96.5) | 96.6 (77.9, 99.5) |

| | **IRC assessment N=57** | **Investigator assessment N=57** |
|---|---|---|
| CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission. | | |

Study M14-032

Study M14-032 was an open label, multicentre, study that evaluated the efficacy of venetoclax in patients with CLL who had been previously treated with and progressed on or after ibrutinib (Arm A) or idelalisib (Arm B). Patients received a daily dose of 400 mg of venetoclax following the ramp-up schedule. Patients continued to receive venetoclax 400 mg once daily until disease progression or unacceptable toxicity was observed.

Efficacy was evaluated by investigators and an IRC according to IWCLL updated NCI WG guidelines (2008). Response assessments were performed at 8 weeks, 24 weeks, and every 12 weeks thereafter for the 64 patients in the main cohort, while the patients enrolled in the expansion had disease assessment at weeks 12 and 36.

A total of 127 patients were enrolled in the study, which included 64 patients in the main cohort (43 with prior ibrutinib, 21 with prior idelalisib) and 63 patients in an expansion cohort (48 with prior ibrutinib, 15 with prior idelalisib). Table 20 summarises the baseline demographic and disease characteristics of the study population.

**Table 20: Baseline patient characteristics of evaluable patients in Study M14-032**

| **Characteristic** | **N=127** |
|---|---|
| Age, years; median (range) | 66 (28-85) |
| White; % | 92 |
| Male; % | 70 |
| Tumour burden; %<br>Absolute lymphocyte count ≥25 x $10^9$/L<br>One or more nodes ≥5 cm | <br>31<br>41 |
| Number of prior therapies; median (range) | 4 (1-15) |
| Time since diagnosis, years; median (range) | 8.3 (0.3-18.5)[a] |
| [a] N = 96 | |

Efficacy data are presented with data cutoff date of 26 July 2017. Investigator-assessment of disease responses to venetoclax treatment are available for all 127 subjects (64 in the main cohort and 63 in the expansion cohort). The IRC assessments of disease responses are available for 123 of the 127 subjects.

Efficacy results for 127 patients assessed by investigator and 127 patients assessed by IRC at the same time points are shown in Table 21.

**Attachment 1: Product AusPAR - VENCLEXTA - venetoclax - AbbVie Pty Ltd - PM-2018-05208-1-6 and PM-2019-04393-1-6 FINAL 24 September 2020. This Product information was approved at the time this AusPAR was published.**

**Table 21: Efficacy results in study M14-032**

| | **IRC assessment N=127[a]** | **Investigator assessment N=127** |
|---|---|---|
| ORR,%<br>(95% CI) | 70.1<br>(61.3, 77.9) | 63.0<br>(54.0, 71.4) |
| CR + CRi (%) | 0.8 | 8.7 |
| nPR (%) | 0 | 2.4 |
| PR (%) | 69.3 | 52.0 |
| DOR, % (95% CI)<br>6-month estimate<br>12-month estimate | N=89<br>97.4 (90.0, 99.4)<br>NA | N=83<br>96.2 (88.7, 98.8)<br>87.6 (77.4, 93.3) |
| Time to first response, median, months (range) | 2.5 (1.0-8.9) | 2.5 (1.6, 14.9) |

[a] Not assessed = 4
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response;
IRC = independent review committee; nPR = nodular partial remission;
ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.

The median duration of treatment with venetoclax for 127 patients was 14.3 months (range: 0.1 to 31.4 months).

The MRD negativity rate in peripheral blood for all 127 patients was 25.2% (32/127), including 8 patients who achieved MRD negativity in bone marrow.

**Acute Myeloid Leukaemia**

The efficacy of VENCLEXTA was studied in two non-randomised trials in patients with newly diagnosed AML who were ineligible for intensive chemotherapy.

Efficacy was established based on the rate of complete remission (CR)/complete remission with partial haematological recovery (CRh), CR/complete remission with incomplete blood recovery (CRi), the duration of CR/CRh and CR/CRi, and the rate of conversion from transfusion dependence to transfusion independence.

Transfusion independence was based on the absence of any red blood cell or platelet transfusion during any consecutive 56 days during the study treatment period and was assessed in all patients.

VENCLEXTA in combination with azacitidine (Study M14-358)

The efficacy of VENCLEXTA was established in a non-randomised clinical trial of VENCLEXTA in combination with azacitidine (n=84) in newly diagnosed patients with AML who were ineligible for intensive chemotherapy.

Patients received VENCLEXTA via a daily ramp-up to a final 400 mg once daily dose. During the ramp-up, patients received TLS prophylaxis and were hospitalised for monitoring.

Azacitidine at 75 mg/m$^2$ was administered either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Azacitidine dose reduction was implemented in the clinical trial for management of haematological toxicity (see azacitidine full product information).

Table 22 summarises the baseline demographic and disease characteristics of the study population.

**Table 22. Baseline patient characteristics for patients with AML treated with VENCLEXTA in combination with azacitidine**

| **Characteristic** | **VENCLEXTA in combination with azacitidine N =84** |
|---|---|
| Age, years; median (range) | 74.5 (61-90) |
| White; % | 91.0 |
| Male; % | 60.7 |
| ECOG performance status; %<br>0-1<br>2<br>3 | <br>69.0<br>28.6<br>2.4 |
| Bone marrow blast; %<br><30%<br>≥30% - <50%<br>≥50% | <br>28.6<br>33.3<br>36.9 |
| History of antecedent haematological disorder; % | 25 |
| **Mutation analyses; % (identified/tested)** | |
| *TP53* | 27.0 (20/74) |
| *IDH1* or *IDH2* | 27.0 (20/74) |
| *FLT- 3* | 14.9 (11/74) |
| *NPM1* | 18.9 (14/74) |
| **Cytogenetic risk[a,b]; %** | |
| Intermediate | 59.5 |
| Poor | 39.3 |

[a]As defined by the National Comprehensive Cancer Network (NCCN) risk categorisation v2014.
[b]No mitosis in 1 patient (excluded favorable risk by Fluorescence in situ Hybridisation [FISH] analysis).

The median follow-up was 8.2 months (range: 0.4 to 35.5 months) for VENCLEXTA in combination with azacitidine.

The efficacy results are shown in Table 23 and 24.

**Table 23. Efficacy results for newly diagnosed patients with AML treated with VENCLEXTA in combination with azacitidine**

| **Endpoint** | **VENCLEXTA in combination with azacitidine N=84** |
|---|---|
| CR, n (%)<br>95% CI<br>Median DOR[a] (months)<br>95% CI | 34 (40.5)<br>[29.9, 51.7]<br>>14.6[b]<br>[14.6, 30.3] |
| CRi, n (%)<br>95% CI<br>Median DOR[c] (months)<br>95% CI | 25 (29.8)<br>[20.3, 40.7]<br>7.8<br>[5.6, NR] |
| CR+CRi, n (%)<br>95% CI<br>Median DOR[c] (months)<br>95% CI | 59 (70.2)<br>[59.3, 79.7]<br>>8.2[b]<br>[8.2, 30.2] |
| CRh, n (%)<br>95% CI<br>Median DOR[a] (months)<br>95% CI | 20 (23.8)<br>[15.2, 34.3]<br>7.9<br>[5.8, NR] |
| CR+CRh, n (%)<br>95% CI<br>Median DOR[a] (months)<br>95% CI | 54 (64.3)<br>[53.1, 74.4]<br>>8.2[b]<br>[8.2, 30.3] |
| Transfusion independence, n/N (%)<br>Red blood cell[d]<br>Platelet[e] | <br>25/50 (50.0)<br>15/26 (57.7) |

CI = confidence interval; NR = not reached.

CR (complete remission) was defined as absolute neutrophil count ≥1,000/microlitre, platelets ≥100,000/microlitre, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.

CRh (complete remission with partial haematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microlitre and ANC >500/microlitre).

CRi (complete remission with incomplete blood recovery) was defined as same as all of the criteria for CR except for residual neutropenia <1,000/microlitre or thrombocytopenia <100,000/microlitre.

[a]DOR (duration of response) was defined as time since first response of CR or CRh to the first date of relapse, clinical disease progression, or death due to disease progression, whichever occurred earlier.

[b]Data are not yet mature.

[c]DOR (duration of response) was defined as time since first response of CR or CRi to the first date of relapse, clinical disease progression, or death due to disease progression, whichever occurred earlier.

[d]Evaluated for patients who were dependent at baseline for red blood cell transfusion and refers to patients who had red blood cell transfusion within 8 weeks prior to first dose of VENCLEXTA.

[e]Evaluated for patients who were dependent at baseline for platelet transfusion and refers to patients who had platelet transfusion within 8 weeks prior to first dose of VENCLEXTA.

**Table 24. Time to response in patients with AML treated with VENCLEXTA in combination with a hypomethylating agent**

| **Endpoint** | **VENCLEXTA in combination with azacitidine N=84** |
|---|---|
| Median time to BEST response of CR (months)<br>Range (months) | 1.9<br>(0.7–10.9) |
| Median time to FIRST response of CR+CRh (months)<br>Range (months) | 1.0<br>(0.7–8.9) |
| Median time to FIRST response of CR+CRi (months)<br>Range (months) | 1.2<br>(0.7–5.5) |

Median overall survival for patients on VENCLEXTA in combination with azacitidine was 14.9 months (95% CI: 10.2, NR).

Remissions (CR or CRh) were observed across subgroups with different baseline characteristics. For patients with poor or intermediate risk cytogenetics similar remissions rates were observed, the rate was 57.6% or 70.0%, respectively. For patients with the following identified mutations, the remissions were as follows: *TP53*: 65.0%, *IDH1/2*: 75.0%, *FLT-3*: 72.7% and *NPM1*: 71.4%.

Minimal residual disease was evaluated from bone marrow aspirate specimens for patients who achieved CR or CRh following treatment with VENCLEXTA in combination with azacitidine. Of those patients, 50% (27/54) achieved MRD less than one AML cell per $10^3$leukocytes in the bone marrow.

Of patients treated with VENCLEXTA in combination with azacitidine, 9.5% (8/84) achieved a CR/CRi and subsequently received stem cell transplant.

<u>VENCLEXTA in combination with low-dose cytarabine (Study M14-387)</u>

The efficacy of VENCLEXTA was established in a non-randomised clinical trial of VENCLEXTA in combination with low-dose cytarabine (n=82) in newly diagnosed patients with AML who were ineligible for intensive chemotherapy, including patients with previous exposure to a hypomethylating agent for an antecedent haematological disorder. Specifically, the study included patients aged ≥ 75 years and patients aged 60 to 74 years who were ineligible for standard anthracycline-based induction therapy due to co-morbidities.

Patients initiated VENCLEXTA via daily ramp-up to a final 600 mg once daily dose. During the ramp-up, patients received TLS prophylaxis and were hospitalised for monitoring.

Cytarabine at a dose of 20 mg/m$^2$ was administered subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1 Day 1. Patients continued to receive treatment cycles until disease progression or unacceptable toxicity. Dose reduction for low-dose cytarabine was not implemented in the clinical trials.

Table 25 summarises the baseline demographic and disease characteristics of the study population.

**Table 25. Baseline patient characteristics for patients with AML treated with VENCLEXTA in combination with low-dose cytarabine**

| **Characteristic** | **VENCLEXTA in combination with low-dose cytarabine N =82** |
|---|---|
| Age, years; median (range) | 74.0 (63-90) |
| White; % | 94.9 |
| Male; % | 64.6 |
| ECOG performance status; %<br>0-1<br>2<br>3 | <br>70.7<br>28.0<br>1.2 |
| Bone marrow blast; %<br><30%<br>≥30% - <50%<br>≥50% | <br>32.9<br>22.0<br>43.9 |
| History of antecedent haematological disorder; % | 48.8 |
| **Mutation analyses; % (identified/tested)** | |
| *TP53* | 14.1 (10/71) |
| *IDH1* or *IDH2* | 25.4 (18/71) |
| *FLT- 3* | 22.5 (16/71) |
| *NPM1* | 12.7 (9/71) |
| **Cytogenetic risk [a]; %** | |
| Intermediate | 59.8 |
| Poor | 31.7 |
| No mitoses | 8.5 |
| [a]As defined by the National Comprehensive Cancer Network (NCCN) risk categorisation v2014 | |

The median follow-up was 7.1 months (range: 0.3 to 34.3 months). Efficacy results are shown in Tables 26 and 27.

**Table 26. Efficacy results for newly diagnosed patients with AML treated with VENCLEXTA in combination with low-dose cytarabine**

| **Endpoint** | **VENCLEXTA in combination with low-dose cytarabine N=82** |
|---|---|
| CR, n (%)<br>95% CI<br>Median DOR[a] (months)<br>95% CI | 21 (25.6)<br>[16.6 - 36.4]<br>NR<br>[10.2, NR] |
| CRi, n (%)<br>95% CI<br>Median DOR[b] (months)<br>95% CI | 23 (28.0)<br>[18.7, 39.1]<br>4.7<br>[2.6, 5.6] |
| CR+CRi, n (%)<br>95% CI<br>Median DOR[b] (months)<br>95% CI | 44 (53.7)<br>[42.3, 64.7]<br>8.1<br>[5.3, 14.9] |
| CRh, n (%)<br>95% CI<br>Median DOR[a] (months)<br>95% CI | 17 (20.7)<br>[12.6, 31.1]<br>6.6<br>[2.8, 11.0] |
| CR+CRh, n (%)<br>95% CI<br>Median DOR[a] (months)<br>95% CI | 38 (46.3)<br>[35.3, 57.7]<br>11.0<br>[6.1, NR] |
| Transfusion independence, n/N (%)<br>Red blood cell[c]<br>Platelet[d] | <br>23/53 (43.4)<br>15/23 (65.2) |

CI = confidence interval; NR = not reached.

CR (complete remission) was defined as absolute neutrophil count ≥1,000/microlitre, platelets ≥100,000/microlitre, red blood cell transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.

CRh (complete remission with partial haematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microlitre and ANC >500/microlitre).

CRi (complete remission with incomplete blood recovery) was defined as same as all of the criteria for CR except for residual neutropenia <1,000/microlitre or thrombocytopenia <100,000/microlitre.

[a]DOR (duration of response) was defined as time since first response of CR or CRh to the first date of relapse, clinical disease progression, or death due to disease progression, whichever occurred earlier.

[b]DOR (duration of response) was defined as time since first response of CR or CRi to the first date of relapse, clinical disease progression, or death due to disease progression, whichever occurred earlier.

[c]Evaluated for patients who were dependent at baseline for red blood cell transfusion and refers to patients who had red blood cell transfusion within 8 weeks prior to first dose of VENCLEXTA.

[d]Evaluated for patients who were dependent at baseline for platelet transfusion and refers to patients who had platelet transfusion within 8 weeks prior to first dose of VENCLEXTA.

**Table 27. Time to response in patients with AML treated with VENCLEXTA in combination with low-dose cytarabine**

| **Endpoint** | **VENCLEXTA in combination with low-dose cytarabine N=82** |
|---|---|
| Median time to BEST response of CR (months)<br>Range (months) | 3.0<br>(0.9–22.4) |
| Median time to FIRST response of CR+CRh (months)<br>Range (months) | 1.0<br>(0.8–9.4) |
| Median time to FIRST response of CR+CRi (months)<br>Range (months) | 1.4<br>(0.8–14.9) |

Median overall survival for patients on VENCLEXTA in combination with low-dose cytarabine was 10.1 months (95% CI: 5.7, 14.2).

Remissions (CR or CRh) were observed across subgroups defined by baseline characteristics. Remissions were seen in 34.6% of patients with poor risk cytogenetics and 57.1% of patients with intermediate risk cytogenetics.

For patients with the following identified mutations, remission rates were as follows: *TP53*: 20.0%, *IDH1/2*: 66.7%, *FLT-3*: 31.3% and *NPM1*: 88.9%.

Minimal residual disease was evaluated in bone marrow for patients who achieved CR or CRh following treatment with VENCLEXTA in combination with low-dose cytarabine. Of those patients, 34.2% (13/38) achieved MRD less than one AML cell per $10^3$ leukocytes in the bone marrow.

Of patients treated with VENCLEXTA in combination with low-dose cytarabine, 1.2% (1/82) achieved a CR/CRh and subsequently received stem cell transplant.

## 5.2 Pharmacokinetic properties

**Absorption**

Following multiple oral administrations, the maximum plasma concentration of venetoclax was reached 5 to 8 hours after dosing. 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 micrograms/mL and $AUC_{0\text{-}24h}$ was 32.8 ± 16.9 micrograms•h/mL at the 400 mg once daily dose, and 2.7 ± 1.6 micrograms/mL and 45.6 ± 30.6 micrograms•h/mL, respectively, at 600 mg/day.

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. Venetoclax should be administered with a meal (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

**Distribution**

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

**Metabolism**

*In vitro* studies demonstrated that venetoclax is predominantly metabolised by 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* studies**

*In vitro* studies indicated that venetoclax is not an inhibitor of CYP1A2, CYP2B6, CYP2C19, CYP2D6 or CYP3A4 and not an inducer of CYP1A2, 2B6 or 3A4 at clinically relevant concentrations. Venetoclax is a weak inhibitor of UGT1A1, CYP2C8 and CYP2C9 *in vitro*, but it is not predicted to cause clinically relevant inhibition of these enzymes due to high plasma protein binding. Venetoclax is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7.

Venetoclax is a P-gp and BCRP substrate as well as a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor *in vitro*. 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 elimination half-life of venetoclax is approximately 26 hours.

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 does not change over time.

**Special populations**

**Age, race, sex and weight**

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

**Paediatric population (<18 years)**

The pharmacokinetics of VENCLEXTA has not been evaluated in patients <18 years of age (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Paediatric use**).

**Renal impairment**

Based on a population pharmacokinetic analysis that included 211 subjects with mild renal impairment (CrCl ≥60 and <90 mL/min), 83 subjects with moderate renal impairment (CrCl ≥30 and <60 mL/min) and 210 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 subjects on dialysis (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Renal impairment**).

**Hepatic impairment**

Based on a population pharmacokinetic analysis that included 69 subjects with mild hepatic impairment, 7 subjects with moderate hepatic impairment and 429 subjects with normal hepatic function, venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function. The National Cancer Institute (NCI) Organ Dysfunction Working Group criteria for hepatic impairment were used in the analysis. 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) or moderate (Child-Pugh B) hepatic impairment were similar to subjects with normal hepatic function. In subjects with severe (Child-Pugh C) hepatic impairment, the mean venetoclax $C_{max}$ was similar to subjects with normal hepatic function but venetoclax

AUC was 2.3- to 2.7 fold higher than subjects with normal hepatic function. (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Hepatic impairment**).

## 5.3 Preclinical safety data

**Animal pharmacology and/or toxicology**

Toxicities observed in animal studies with venetoclax included dose-dependent reductions in lymphocytes and red blood cell mass. After cessation of dosing with venetoclax, red blood cell effects were reversible, whereas partial reversibility of lymphocytes was observed at the end of an 18-week recovery period. 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. Following a 4-week dosing period and subsequent 4-week recovery period, minimal single-cell necrosis was still present in some tissues and reversibility has not been assessed following longer periods of dosing or recovery.

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. No changes in the quality of the hair coat or skin were observed, nor in other pigmented tissues examined (e.g., the iris and the ocular fundus of the eye). Reversibility of the hair coat changes has not been assessed in dogs.

**Genotoxicity**

Venetoclax was not mutagenic in an *in vitro* bacterial mutagenicity (Ames) assay, did not induce numerical or structural aberrations in an *in vitro* chromosome aberration assay using human peripheral blood lymphocytes, and was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay at a single oral dose up to 835 mg/kg (~5 times the clinical $C_{max}$ at the maximum recommended dose of 600 mg/day). The M27 metabolite was negative for genotoxic activity in *in vitro* Ames and chromosome aberration assays.

**Carcinogenicity**

Carcinogenicity studies have not been conducted with venetoclax.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

VENCLEXTA 10 mg film-coated tablets contain the following inactive ingredients: copovidone, colloidal anhydrous silica, polysorbate 80, sodium stearylfumarate, calcium hydrogen phosphate, iron oxide yellow, polyvinyl alcohol, macrogol 3350, purified talc and titanium dioxide.

VENCLEXTA 50 mg film-coated tablets contain the following inactive ingredients: copovidone, colloidal anhydrous silica, polysorbate 80, sodium stearylfumarate, calcium hydrogen phosphate, iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, purified talc, macrogol 3350 and titanium dioxide.

VENCLEXTA 100 mg film-coated tablets contain the following inactive ingredients: copovidone, colloidal anhydrous silica, polysorbate 80, sodium stearylfumarate, calcium hydrogen phosphate, iron oxide yellow, polyvinyl alcohol, macrogol 3350, purified talc and titanium dioxide.

## 6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 Special precautions for storage

Store below 30°C.

## 6.5 Nature and contents of container

VENCLEXTA is dispensed as follows:

| **Packaging presentation** | **Number of tablets** |
|---|---|
| Starting Pack for CLL | Each Starting Pack contains four weekly wallets:<br>• Week 1 (14 x 10 mg tablets)<br>• Week 2 (7 x 50 mg tablets) |

| **Packaging presentation** | **Number of tablets** |
|---|---|
| | • Week 3 (7 x 100 mg tablets)<br>• Week 4 (14 x 100 mg tablets)<br>Each wallet contains one blister pack. |
| 10 mg Wallet | 14 x 10 mg tablets |
| 50 mg Wallet | 7 x 50 mg tablets |
| 100 mg Blister pack | 7, 14, 112 x 100 mg tablets |
| 100 mg Bottle | 120, 180 x 100 mg tablets |

Not all presentations may be marketed.

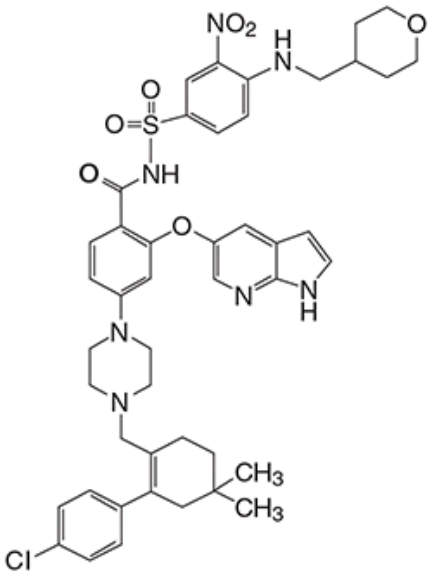
## 6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 Physicochemical properties

Venetoclax is described chemically as 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide.

**Chemical structure**




Empirical formula: $C_{45}H_{50}ClN_7O_7S$

Molecular weight: 868.44

CAS Number: 1257044-40-8

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8. SPONSOR

AbbVie Pty Ltd

241 O'Riordan Street

Mascot NSW 2020

Australia

## 9. DATE OF FIRST APPROVAL

05 January 2017

## 10. DATE OF REVISION

05 February 2020

**Summary table of changes**

| Section changed | Summary of new information |
|---|---|
| 4.1 | Updated to include new indication (AML). |
| 4.2 | Updated to include dosing instructions for AML patients. Prophylactic measures for TLS in AML patients added. Dose modifications for toxicities in AML patients added. Revisions to dose modifications for use with CYP3A inhibitors. |
| 4.4 | Neutropenia experience in AML patients added. Mortality information from BELLINI study included. |
| 4.5 | Revisions to advice regarding concomitant use with CYP3A inhibitors. Additional study information added. |
| 4.6 | Updated due to new higher maximum recommended human dose for AML. |
| 4.8 | Adverse events from AML clinical trials experience added. TLS experience from AML clinical studies added. |
| 5.1 | Mechanism of action amended due to AML indication. Clinical trial information for AML studies added. |
| 5.3 | Updated due to new higher maximum recommended human dose for AML. |