

## 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

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.

##### *Note to monotherapy indications*

The monotherapy indications are approved based on overall response rates. Duration of response and improvements in overall survival, progression-free survival or health-related quality of life have not been established.

## 4.2 Dose and Method of Administration

VENCLEXTA should be taken orally once daily until disease progression or unacceptable toxicity is observed. 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.

### Recommended 5-week Dose Titration Schedule

The starting dose of VENCLEXTA is 20 mg once daily for 7 days. The VENCLEXTA dose must be administered according to a weekly dose titration schedule to the recommended daily dose of 400 mg over a period of 5 weeks as shown in Table 1.

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

**Table 1. Dosing Schedule for Dose Titration Phase**

Week	VENCLEXTA Daily Dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5	400 mg

### **VENCLEXTA in combination with rituximab**

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

Patients should continue VENCLEXTA 400 mg daily 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 dose titration schedule.

Treatment should continue until disease progression or venetoclax is no longer tolerated by the patient.

### **Risk Assessment and Prophylaxis for Tumour Lysis Syndrome**

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

Table 2 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumour burden determination from clinical trial data.

**Table 2. Recommended TLS Prophylaxis Based on Tumour Burden From Clinical Trial Data (consider all patient co-morbidities before final determination of prophylaxis and monitoring schedule)**

Tumour Burden		Prophylaxis		Blood Chemistry Monitoring <sup>c,d</sup>
		Hydration <sup>a</sup>	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 x10 <sup>9</sup> /L	Oral (1.5-2 L)	Allopurinol <sup>b</sup>	Outpatient <ul style="list-style-type: none"> <li>• Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg</li> <li>• Pre-dose at subsequent ramp-up doses</li> </ul>
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10 <sup>9</sup> /L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient <ul style="list-style-type: none"> <li>• Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg</li> <li>• Pre-dose at subsequent ramp-up doses</li> <li>• Consider hospitalisation for patients with CrCl &lt;80ml/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital</li> </ul>
High	Any LN ≥10 cm OR ALC ≥25 x10 <sup>9</sup> /L AND any LN ≥5 cm	Oral (1.5-2L) and intravenous (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 <ul style="list-style-type: none"> <li>• Pre-dose, 4, 8,12 and 24 hours</li> </ul> Outpatient at subsequent ramp-up doses <ul style="list-style-type: none"> <li>• Pre-dose, 6 to 8 hours, 24 hours</li> </ul>

ALC = absolute lymphocyte count; LN = lymph node.  
<sup>a</sup>Administer intravenous hydration for any patient who cannot tolerate oral hydration.  
<sup>b</sup>Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLEXTA.  
<sup>c</sup>Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.  
<sup>d</sup>For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

### Dose Modifications Based on Toxicities

Dosing interruption and/or dose reduction may be required. See Table 3 for dose modifications for haematologic and other toxicities related to VENCLEXTA. For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of dose titration phase or greater than 2 weeks after completing the dose titration phase, the risk of TLS is to be reassessed to determine if re-initiation with a reduced dose is necessary (e.g., all or some levels of the dose titration schedule) (see **Section 4.2 DOSE AND METHOD OF**

**ADMINISTRATION Recommended 5-week Dose Titration Schedule and Risk Assessment and Prophylaxis for Tumour Lysis Syndrome).**

**Table 3. Recommended Dose Modifications for Toxicities**

<b>Event</b>	<b>Occurrence</b>	<b>Action</b>
<b>Tumour Lysis Syndrome</b>		
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 4) (see <b>Section 4.2 DOSE AND METHOD OF ADMINISTRATION; Risk Assessment and Prophylaxis for Tumour Lysis Syndrome</b> ).
		For any events of clinical TLS, resume at a reduced dose following resolution (see Table 4) (see <b>Section 4.2 DOSE AND METHOD OF ADMINISTRATION; Risk Assessment and Prophylaxis for Tumour Lysis Syndrome</b> ).
<b>Non-Haematologic Toxicities</b>		
Grade 3 or 4 non-haematologic toxicities	1 <sup>st</sup> occurrence	Interrupt VENCLEXTA. 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.
	2 <sup>nd</sup> and subsequent occurrences	Interrupt VENCLEXTA. Follow dose reduction guidelines in Table 4 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
<b>Haematologic Toxicities</b>		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 haematologic toxicities (except lymphopaenia) (see <b>Section 4.4 Special Warnings and</b>	1 <sup>st</sup> occurrence	Interrupt VENCLEXTA. To reduce the infection risks associated with neutropenia, G-CSF may be administered with VENCLEXTA if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose.
	2 <sup>nd</sup> and subsequent occurrences	Interrupt VENCLEXTA. Consider using G-CSF as clinically

Event	Occurrence	Action
Precautions for use; <i>Neutropenia</i> )		indicated. Follow dose reduction guidelines in Table 4 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 4. Dose Reduction for Toxicity During VENCLEXTA Treatment**

Dose at Interruption, mg	Restart Dose, mg <sup>a</sup>
400	300
300	200
200	100
100	50
50	20
20	10
<sup>a</sup> Continue the reduced dose for 1 week before increasing the dose.	

### Dose Modifications for Use with CYP3A Inhibitors

Concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during dose titration phase is contraindicated. 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 titration phase (see **Section 4.3 CONTRAINDICATIONS**). For patients who have completed the dose titration phase and are on a steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by at least 75% of the original dose when strong CYP3A inhibitors must be used concomitantly.

Avoid concomitant use of VENCLEXTA with moderate CYP3A inhibitors at initiation and during dose titration phase. Consider alternative treatments. If a moderate CYP3A inhibitor must be used, reduce the initiation and dose titration doses of VENCLEXTA by at least 50% of the original dose (Table 5).

Monitor these patients more closely for signs of toxicities (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION: Dose Modifications Based on Toxicities**).

For patients who have completed the dose titration phase and are on a steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by at least 50% of the original dose when moderate CYP3A inhibitors must be used concomitantly.

Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor 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).

The recommendations for managing drug-drug interactions with CYP3A Inhibitors are summarised in Table 5.

**Table 5. Management of Potential VENCLEXTA Interactions with CYP3A Inhibitors**

Inhibitors	Initiation and Dose Titration Phase	Steady Daily Dose (After Dose Titration Phase)
Strong CYP3A inhibitor	Contraindicated	Avoid inhibitor use or reduce the VENCLEXTA dose by at least 75% of the original dose
Moderate CYP3A inhibitor	Avoid inhibitor use or reduce the VENCLEXTA dose by at least 50% of the original dose	

### 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.

Concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during the dose titration 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 in the initial 5-week dose titration 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 2) and comorbidities. Reduced renal function (CrCl < 80 mL/min) further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricaemics. Blood chemistries should be monitored and abnormalities managed promptly. Dosing should be interrupted, if needed. 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 dose titration 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**

Grade 3 or 4 neutropenia (ANC <1.0 x 10<sup>9</sup>/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**). 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).

### **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 specific clinical trials have been conducted in subjects with hepatic impairment. No dose adjustment is recommended in patients with mild or moderate hepatic impairment based on results of the population pharmacokinetic analysis (see **Section 5.2 Pharmacokinetic properties**). A recommended dose has not been determined for patients with severe hepatic impairment.

### **Renal Impairment**

No specific clinical trials have been conducted in subjects with renal impairment. After a single oral administration of 200 mg radiolabeled [<sup>14</sup>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  $\geq$ 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  $\geq$ 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  $\geq$ 65 years of age and 28 (17.1%) patients were  $\geq$ 75 years of age.

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

## **4.5 Interactions with Other Medicines and Other Forms of Interactions**

### **Potential Effects of Other Medicines on VENCLEXTA**

Venetoclax is predominantly metabolised by CYP3A4.

#### Strong CYP3A Inhibitors

##### *Initiation and Dose Titration Phase*

Concomitant use of VENCLEXTA with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, conivaptan, indinavir, lopinavir, telaprevir, and ritonavir) at initiation and during the ramp-up phase is contraindicated (see **Section 4.3 Contraindications** and **Section 5.2 Pharmacokinetic properties**).

### *After Dose Titration Phase*

For patients who have completed the dose titration phase and are on a steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by at least 75% of the original dose when used concomitantly with strong CYP3A inhibitors. Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor [see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION** and **Section 5.2 Pharmacokinetic properties**].

Co-administration of ketoconazole increased venetoclax  $C_{max}$  by 2.3-fold and  $AUC_{\infty}$  by 6.4-fold.

Co-administration of ritonavir increased venetoclax  $C_{max}$  by 2.4-fold and AUC by 7.9-fold..

### Moderate CYP3A Inhibitors

*Initiation and Dose Titration Phase* Avoid concomitant use of moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, dronedarone, fluconazole, verapamil) with VENCLEXTA at initiation and during the dose titration phase. Consider alternative treatments. If a moderate CYP3A inhibitor must be used, reduce the the initiation and dose titration doses of VENCLEXTA by at least 50% of the original dose. Monitor patients more closely for signs of VENCLEXTA toxicities (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION** and **Section 5.2 Pharmacokinetic properties**).

### *After Dose Titration Phase*

For patients who have completed the dose titration phase and are on a steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by at least 50% of the original dose when used concomitantly with moderate CYP3A inhibitors. Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION** and **Section 5.2 Pharmacokinetic properties**).

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 single dose of rifampin, an OATP1B1/1B3 and P-gp inhibitor, increased venetoclax  $C_{max}$  by 106% and  $AUC_{\infty}$  by 78%.

Concomitant use of venetoclax with P-gp inhibitors (e.g., amiodarone, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor) at initiation and during the dose titration 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  $C_{max}$  and  $AUC_{\infty}$  by 25% to 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  $AUC_{\infty}$  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, H<sub>2</sub>-receptor antagonists, antacids) do not affect venetoclax bioavailability.

## **Potential Effects of VENCLEXTA on Other Medicines**

### Warfarin

In a drug-drug interaction study in 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  $AUC_{\infty}$  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 in 10 healthy subjects resulted in a 35% increase in digoxin  $C_{max}$  and a 9% increase in digoxin  $AUC_{\infty}$ . 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 3 times the human  $AUC$  exposure at the recommended dose). 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 0.5 to 18 times the human AUC exposure at the recommend 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 1.2 times the human AUC exposure at the recommended dose). In rabbits, venetoclax at 300 mg/kg/day produced maternal toxicity, but no fetal toxicity (maternal exposures approximately 0.14 times the human AUC exposure at the recommended dose). No teratogenicity was observed in either the mouse or the rabbit.

## **Use in Lactation**

It is not known whether venetoclax or its metabolites are excreted in human breast milk. 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

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.

### Safety experience with 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 6. Adverse Events Reported in ≥5% of Patients Treated with VENCLEXTA + Rituximab in Study GO28667 which Occurred at ≥2% Higher Incidence Compared with Bendamustine + Rituximab**

	Venetoclax + Rituximab Followed by Single Agent Venetoclax (N=194)		Bendamustine + Rituximab (N=188)	
Adverse Events System Organ Class	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)

Preferred Term				
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 6 are presented below by MedDRA body system organ class and by frequency. Frequencies are defined as very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  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);

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

**Metabolism and nutrition disorders:** tumor 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 ( $\geq 5\%$  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  $\geq 3$  adverse events ( $\geq 2\%$  patients) were neutropaenia (11%), anaemia (3%), pneumonia (2%), and thrombocytopaenia (2%).

### Safety experience with VENCLEXTA monotherapy

The safety of single agent VENCLEXTA at the 400 mg recommended daily dose following a dose titration schedule was evaluated in 240 patients with previously treated CLL, including 160 patients with 17p del, in 3 open-label, non-randomised trials (two phase 2 studies and one phase 1 study). Study M13-982 enrolled previously treated patients with CLL with 17p del, Study M12-175 enrolled previously treated patients with CLL including those with 17p del, and Study M14-032 enrolled patients with CLL who had failed an inhibitor of the B-cell receptor pathway. In the pooled dataset, the median age of these patients was 66 years (range: 29 to 85 years), 94.5% were white, and 69.2% were male. The median number of prior therapies was 3 (range: 1 to 12) and the median duration of treatment at the time of data analysis was approximately 10.3 months (range: 0 to 34.1 months); approximately 46% of patients received VENCLEXTA for more than 48 weeks.

### Tabulated list of adverse reactions

The frequencies of adverse drug reactions (ADRs) reported with VENCLEXTA are summarised in Table 7. Adverse reactions are listed below by MedDRA body system organ class and by frequency. Frequencies are defined as very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  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 7: Adverse drug reactions reported in patients with CLL treated with VENCLEXTA**

<b>System Organ Class</b>	<b>Frequency (All Grades)</b>	<b>Preferred Term</b>
<b>Infections and infestations</b>	Very common	Upper respiratory tract infection
	Common	Pneumonia Urinary tract infection
<b>Blood and lymphatic system disorders</b>	Very common	Neutropenia <sup>a</sup>
		Anaemia <sup>b</sup>
	Common	Febrile neutropenia
		Lymphopaenia <sup>c</sup>
<b>Metabolism and nutrition disorders<sup>d</sup></b>	Very Common	Hyperphosphataemia <sup>f</sup>
	Common	Tumour lysis syndrome <sup>e</sup>
		Hyperkalaemia <sup>g</sup>
		Hyperuricaemia <sup>h</sup>
		Hypocalcaemia <sup>i</sup>
<b>Gastrointestinal disorders</b>	Very common	Diarrhoea
		Vomiting
		Nausea
		Constipation
<b>General disorders and administration site conditions</b>	Very common	Fatigue
<b>Investigations</b>	Common	Blood creatinine increased
<sup>a</sup> Neutropenia/neutrophil count decreased. <sup>b</sup> Anaemia/haemoglobin decreased. <sup>c</sup> Lymphopaenia/lymphocyte count decreased <sup>d</sup> 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. <sup>e</sup> Reported as TLS events.		



<p><sup>f</sup>Hyperphosphataemia/blood phosphorus increased.</p> <p><sup>g</sup>Hyperkalaemia/blood potassium increased.</p> <p><sup>h</sup>Hyperuricaemia/blood uric acid increased.</p> <p><sup>i</sup>Hypocalcaemia/blood calcium decreased.</p>
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### *Summary of the safety profile for venetoclax monotherapy*

The most common adverse reactions ( $\geq 20\%$ ) of any grade were neutropenia/neutrophil count decreased, diarrhoea, nausea, anaemia, upper respiratory tract infection, fatigue, hyperphosphataemia, vomiting, and constipation.

The most frequently reported serious adverse reactions ( $\geq 2\%$ ) were pneumonia, febrile neutropenia, and TLS.

Discontinuations due to adverse reactions occurred in 8.3% of patients. No patients discontinued VENCLEXTA treatment due to neutropenia.

Dosage adjustments due to adverse reactions occurred in 9.6% of patients.

### 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**].

### *Monotherapy studies*

In the initial Phase 1 dose-finding trials, which had a relatively short (2-3 week) dose titration 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  $\geq 10$  cm or those with both an ALC  $\geq 25 \times 10^9/L$  and any measurable lymph node  $\geq 5$  cm were hospitalised to enable more intensive hydration and monitoring for the first day of dosing at 20 mg and 50 mg during the dose titration phase.

In 66 patients with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg, the rate of TLS was 6%. All events were laboratory TLS (laboratory abnormalities that met  $\geq 2$  of the following criteria within 24 hours of each other: potassium  $>6$  mmol/L, uric acid  $>476 \mu\text{mol/L}$ , 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)  $\geq 5$  cm or ALC  $\geq 25 \times 10^9/L$ . No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden death and/or seizures was observed in these patients. All patients had CrCl  $\geq 50$  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 dose titration phase and resolved within two days. All six patients completed the dose titration and reached the recommended daily dose of 400 mg of VENCLEXTA. No clinical TLS was observed in patients who followed the current 5-week dose titration dosing schedule and TLS prophylaxis and monitoring measures described [see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**]. The rates of grade  $\geq 3$  laboratory abnormalities relevant to TLS were hyperkalaemia 1%, hyperphosphataemia 1%, and hyperuricaemia 1%.

### Neutropenia

#### *VENCLEXTA in combination with rituximab*

Neutropenia is an identified risk associated with VENCLEXTA treatment.

In Study GO28667, neutropenia was reported in 61% (all grades) of patients on the venetoclax + rituximab arm. Forty-three percent of patients treated with venetoclax + rituximab experienced dose interruption and 3% of patients discontinued venetoclax due to neutropenia. Grade 3 neutropenia was reported in 32% of patients and grade 4 neutropenia in 26% of patients. The median duration of grade 3 or 4 neutropenia was 8 days (range: 1-712 days). Clinical complications of neutropenia, including febrile neutropenia, grade  $\geq 3$  and serious infections occurred at a lower rate in patients treated with venetoclax + rituximab arm compared with the rates reported in patients treated with bendamustine + rituximab: febrile neutropenia 4% versus 10%, grade  $\geq 3$  infections 18% versus 23%, 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) cells 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

#### 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 dose titration 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 dose titration at 375 mg/m<sup>2</sup> for cycle 1 and 500 mg/m<sup>2</sup> for cycles 2-6. Each cycle was 28 days. Patients randomised to bendamustine + rituximab received bendamustine at 70 mg/m<sup>2</sup> 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 8 shows the baseline demographic and disease characteristics were similar between the venetoclax + rituximab and bendamustine + rituximab arms.

**Table 8: Demographics and Baseline Characteristics in Study GO28667**

<b>Characteristic</b>	<b>VENCLEXTA + Rituximab (N = 194)</b>	<b>Bendamustine + Rituximab (N = 195)</b>
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

Tumor burden; %		
Absolute lymphocyte count $\geq 25 \times 10^9/L$	66.5	68.7
One or more nodes $\geq 5$ 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
$\geq 3$	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 bendamustine	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).

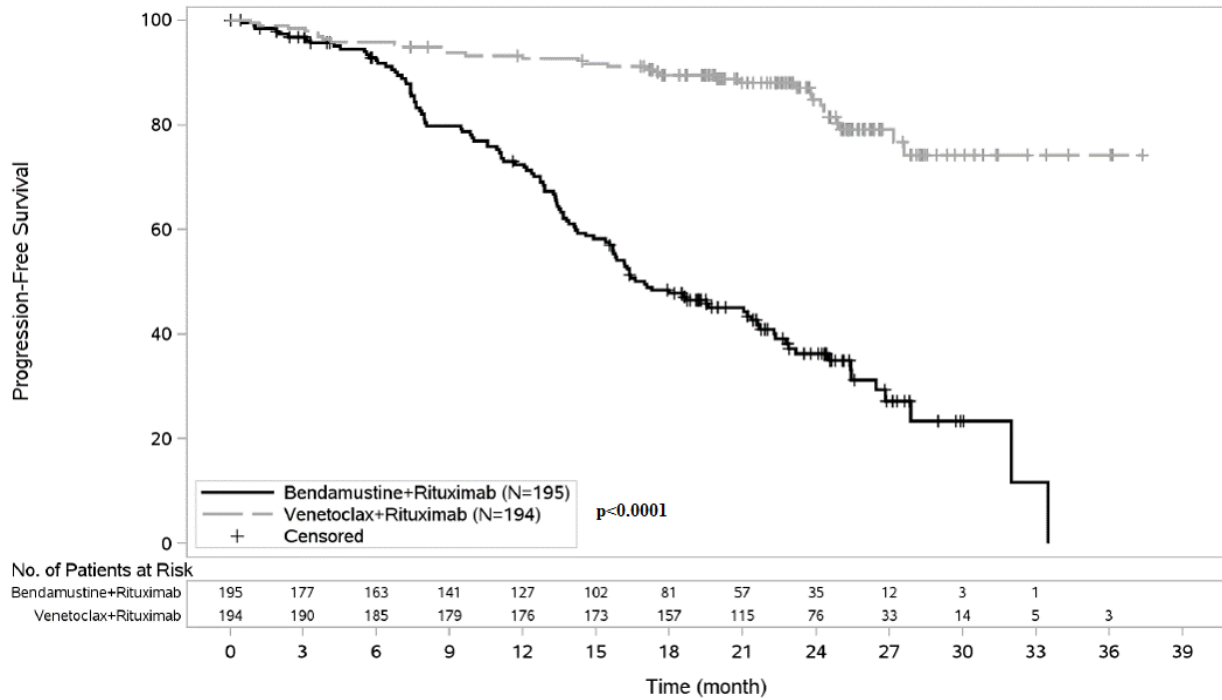
Efficacy results for Study GO28667 are shown in Table 9. The Kaplan-Meier curves for PFS and overall survival (OS) are shown in Figure 1 and 2, respectively.

**Table 9: Efficacy Results for Study GO28667**

	INV Assessed		IRC Assessed	
	[Venetoclax] + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)	[Venetoclax] + Rituximab (N = 194)	Bendamustine + Rituximab (N = 195)
<b>Progression-free survival</b>				
Number of events (%)	32 (16.5)	114 (58.5)	35 (18.0)	106 (54.4)
Disease progression	21	98	26	91

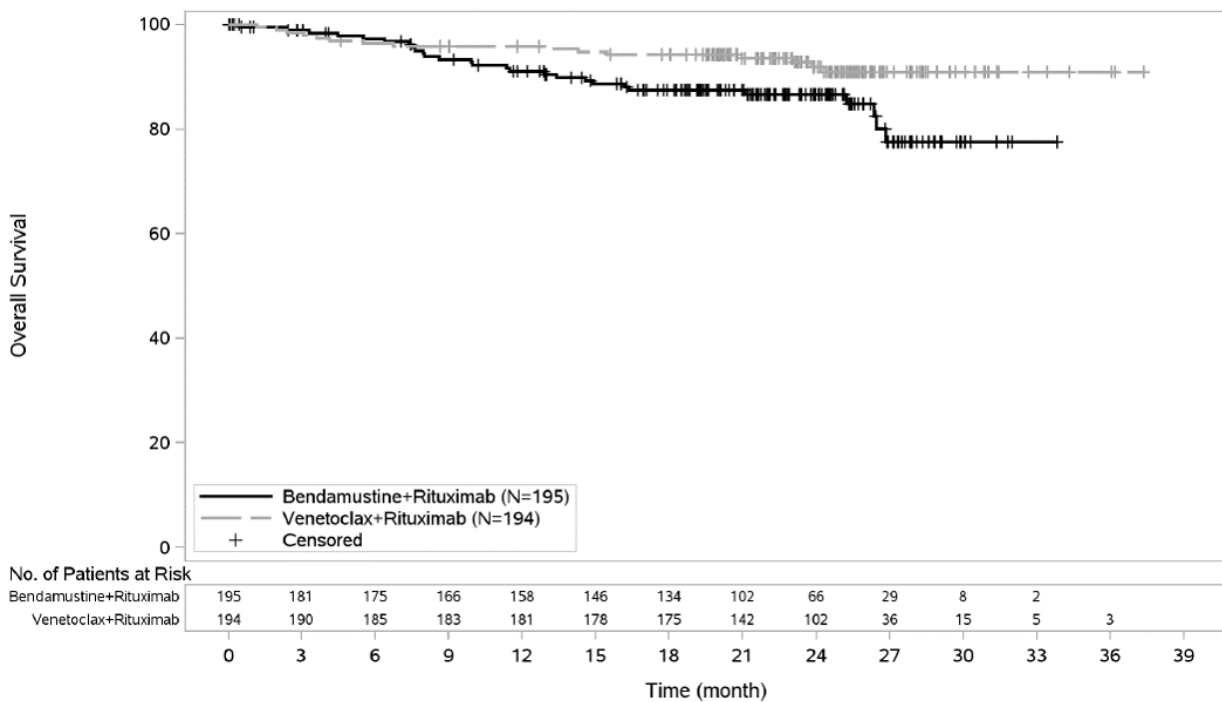
Death events	11	16	9	15
Median, months, (95% CI)	Not reached	17.0 (15.5, 21.6)	Not reached	18.1 (15.8, 22.3)
HR (95% CI)	0.17 (0.11, 0.25)		0.19 (0.13, 0.28)	
p-value <sup>a</sup>	p < 0.0001		p < 0.0001	
12-month estimate, % (95% CI)	92.7 (89.1, 96.4)	72.5 (65.9, 79.1)	91.2 (87.2, 95.2)	74.1 (67.6, 80.7)
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)
<b>Response rate</b>				
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 <sup>b</sup>	3.6 <sup>b</sup>
nPR, (%)	3.1	6.2	1.5	0.5
PR, (%)	63.4	53.3	82.5	68.2
<b>Overall Survival</b>				
Number of deaths (%)	15 (7.7)	27 (13.8)	NA	NA
Hazard Ratio (95% CI)	0.48 (0.25, 0.90)			
<b>Time to next anti-leukemic therapy</b>				
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	
<b>Event-free survival</b>				
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	
<p>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.</p> <p><sup>a</sup>Stratified log-rank test.</p> <p><sup>b</sup>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 &lt;2 cm.</p>				

**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 2 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 del).

#### Study M13-982

Study M13-982 was a multicentre, single-arm open-label trial of 107 previously treated patients with CLL with 17p del. Table 10 summarises the baseline demographic and disease characteristics of the study population.

**Table 10. Baseline Patient Characteristics in Study M13-982**

<b>Characteristics</b>	<b>N = 107<sup>a</sup></b>
Age, years; median (range)	67 (37 to 85)
White; %	97.2
Male; %	65.4
ECOG performance status; %	
0	39.3
1	52.3
2	8.4
Tumour burden; %	
Absolute lymphocyte count ≥25 x 10 <sup>9</sup> /L	50.5
One or more nodes ≥5 cm	53.3
Number of prior therapies; median (range)	2 (1-10)
Time since diagnosis, months; median (range) <sup>b</sup>	81.7 (1.2-385.6)

Characteristics	N = 107 <sup>a</sup>
<sup>a</sup> One patient did not harbour the 17p deletion. <sup>b</sup> 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 del were identified using Vysis CLL FISH Probe Kit. Patients received VENCLEXTA via a weekly dose titration 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 - 21.5 months).

The primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). Efficacy results for Study M13-982 are shown in Table 11.

**Table 11. Efficacy Results in Study M13-982**

	IRC Assessment (N=107) <sup>a</sup>	Investigator Assessment (N=107)
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)
<sup>a</sup> 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.		

Median duration of response (DOR) or median progression-free survival (PFS) has not been reached with approximately 12 months median follow-up.

Minimal residual disease (MRD) 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<sup>4</sup> leukocytes in the sample (i.e., an MRD value of <10<sup>-4</sup> 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.

### Study M12-175

Study M12-175 was a multicentre, open-label trial that enrolled previously treated patients with CLL, including those with 17p del. Efficacy was evaluated in 57 patients who had received a daily dose of 400 mg of VENCLEXTA following a dose titration 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 12 summarises the baseline demographic and disease characteristics of the study population.

**Table 12. Baseline Patient Characteristics of Evaluable Patients in Study M12-175**

Characteristics	N=57
Age, years; median (range)	66 (42 to 84)
White; %	91.2
Male; %	75.4
ECOG performance status <sup>a</sup> ; %	
0	45.5
1	52.7
2	1.8
Tumour burden; %	
Absolute lymphocyte count $\geq 25 \times 10^9/L$	35.1
One or more nodes $\geq 5$ cm	66.7
Number of prior therapies; median (range)	3 (1-11)
Time since diagnosis, months; median (range)	108 (13.7-327.6)
<sup>a</sup> 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 del.

Overall response rate (ORR) and duration of response (DOR) were evaluated by both investigators and an IRC according to the IWCLL NCI-WG criteria. Efficacy results are shown in Table 13:

**Table 13. Efficacy Results in Study M12-175**

	IRC Assessment N=57	Investigator Assessment N=57
ORR, % (95% CI)	73.7 (60.3, 84.5)	80.7 (68.1, 90.0)
CR + CRi (%)	7.0	12.3
nPR (%)	0	3.5
PR (%)	66.7	64.9

	IRC Assessment N=57	Investigator Assessment N=57
DOR, % (95% CI) 12-month estimate	88.8 (67.5, 96.5)	96.6 (77.9, 99.5)
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.		

## 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 ( $\pm$  standard deviation) steady state  $C_{max}$  was  $2.1 \pm 1.1$  micrograms/mL and  $AUC_{24}$  was  $32.8 \pm 16.9$  micrograms•h/mL at the 400 mg once daily dose.

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 ( $V_{dss}/F$ ) 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*. To avoid a potential interaction in the gastrointestinal tract, digoxin, a narrow therapeutic range P-gp substrate, should be taken at least 6 hours before VENCLEXTA. 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 [<sup>14</sup>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. The pharmacokinetics of venetoclax have not been studied in subjects with severe hepatic impairment (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-dependant 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 (~3 times the clinical C<sub>max</sub> at the maximum recommended dose of 400 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 stearyl fumarate, 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 stearyl fumarate, 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 stearyl fumarate, 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	Each Starting Pack contains four weekly wallets: <ul style="list-style-type: none"><li>• Week 1 (14 x 10 mg tablets)</li><li>• Week 2 (7 x 50 mg tablets)</li><li>• Week 3 (7 x 100 mg tablets)</li><li>• Week 4 (14 x 100 mg tablets)</li></ul> Each wallet contains one blister pack.
10 mg Wallet	14 x 10 mg tablets
50 mg Wallet	7 x 50 mg tablets

Packaging Presentation	Number of Tablets
100 mg Blister pack	7, 14, 112 x 100 mg tablets
100 mg Bottle	120 x 100 mg tablets

Not all presentations may be marketed.

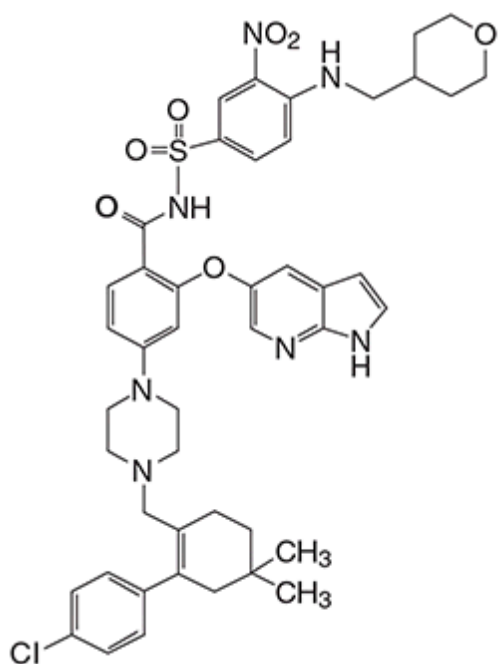
## 6.6 Special Precautions for Disposal

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-2H-pyran-4-ylmethyl)amino]phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

## Chemical Structure



Empirical formula: C<sub>45</sub>H<sub>50</sub>ClN<sub>7</sub>O<sub>7</sub>S

Molecular weight: 868.44

CAS Number: 1257044-40-8

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

## 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

08 October 2018

## Summary table of changes

<b>Section changed</b>	<b>Summary of new information</b>
All sections	Reformat to align with revised TGA PI requirements
4.1	Updated to include new indication
4.2	Added dosage instructions for combination therapy
4.4	Safety update to Neutropenia and Use in the Elderly subsections to include information from Study GO28667.
4.5	Safety related change to include medicine interaction of venetoclax with ritonavir, azithromycin and P-gp substrates.
4.8	Safety update to include information from Study GO28667 and update to the TLS and neutropenia subsections.
5.1	Clinical trial information added from Study GO28667.