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/Small Lymphocytic Lymphoma

VENCLEXTA in combination with obinutuzumab is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) who are considered unfit or unsuitable for chemo-immunotherapy.

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/Small Lymphocytic Lymphoma

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/SLL

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.	

First line CLL/SLL:

VENCLEXTA in combination with obinutuzumab

VENCLEXTA in combination with obinutuzumab should be given for a total of 12 cycles (28 days in each cycle) as shown in Table 2. Refer to the obinutuzumab Product Information for prophylaxis of tumour lysis syndrome and infusion related reactions.

Table 2. Dosing Schedule for VENCLEXTA in combination with obinutuzumab

Cycle, Day	**Obinutuzumab**	**VENCLEXTA**
Cycle 1, Day 1	Day 1: 100 mg Followed by 900 mg which may be administered on Day 1 or Day 2.	
Cycle 1, Day 8	1000 mg	
Cycle 1, Day 15	1000 mg	
Cycle 1, Day 22 – 28		20 mg daily[a]
Cycle 2, Day 1 – 7	Day 1 only: 1000 mg	50 mg daily[a]
Cycle 2, Day 8 – 14		100 mg daily[a]
Cycle 2, Day 15 – 21		200 mg daily[a]
Cycle 2, Day 22 – 28		400 mg daily[a]
Cycles 3 - 6, Day 1 - 28	Day 1 only: 1000 mg	400 mg daily
Cycles 7 - 12, Day 1 – 28		400 mg daily

[a]5 week ramp-up (see Table 1)

Previously treated CLL/SLL:

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 3. Initiate azacitidine or low-dose cytarabine on Day 1.

Table 3. 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 when dosing in combination with azacitidine	600 mg 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/Small Lymphocytic Lymphoma

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/Small Lymphocytic Lymphoma

Table 4 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumour burden determination from clinical trial data.

Table 4. Recommended TLS prophylaxis based on tumour burden in patients with CLL/SLL 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 AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol[b]	Outpatient Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg Pre-dose at subsequent ramp-up doses

Tumour burden		**Prophylaxis**		**Blood chemistry monitoring[c,d]**
		Hydration[a]	**Anti-hyperuricaemics**	**Setting and frequency of assessments**
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg Pre-dose at subsequent ramp-up doses 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 OR ALC ≥25 x10^9/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 Pre-dose, 4, 8,12 and 24 hours Outpatient at subsequent ramp-up doses 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/Small Lymphocytic Lymphoma

Dosing interruption and/or dose reduction may be required. See Table 5 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/Small Lymphocytic Lymphoma 5-week ramp-up schedule, Risk assessment for tumour lysis syndrome** and **Prophylaxis for tumour lysis syndrome**).

Table 5. Recommended dose modifications for toxicities during VENCLEXTA treatment of CLL/SLL

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 6) (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 6) (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. 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. Follow dose reduction guidelines in Table 6 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. 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.
	2nd and subsequent occurrences	Interrupt VENCLEXTA. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 6 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 6. Dose reduction for toxicity during VENCLEXTA treatment of CLL/SLL

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 7 shows the dose modification guidelines for haematological toxicities.

Table 7. 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. 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. 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/SLL, 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 8. 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 8. 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 Day 2 – 20 mg Day 3 – 50 mg 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 or SLL, 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 4) 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 developed in 63% to 64% of patients and grade 4 neutropenia developed in 31% to 33% of patients treated with VENCLEXTA in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients treated with VENCLEXTA in combination and monotherapy studies (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 or SLL 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 combination and 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_{∞} by 540%.

Co-administration of 50 mg once daily ritonavir, a strong CYP3A, P-gp and OATP1B1/B3 inhibitor, for 14 days in 6 healthy subjects increased venetoclax C_{max} by 140% and AUC by 690%.

Findings from a drug interaction sub-study (M14-358) involving 12 newly diagnosed patients with AML determined that, when compared to steady state conditions amongst the same patients receiving venetoclax 400 mg a day, the co-administration of 300 mg posaconazole (a strong CYP3A and P-gp inhibitor) with venetoclax 50 mg and 100 mg resulted in 61% and 86% higher venetoclax C_{max} levels and 90% and 144% higher AUC_{24} respectively.

For patients requiring concomitant use of VENCLEXTA with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, conivaptan, indinavir, lopinavir, telaprevir, and ritonavir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, dronedarone, fluconazole, verapamil) administer VENCLEXTA dose according to Table 8. Monitor patients more closely for signs of VENCLEXTA toxicities (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**).

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 with venetoclax 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. Additionally, administration of M27, the major human metabolite of venetoclax, at oral doses up to 250 mg/kg/day did not produce embryo-fetal toxicity or teratogenicity in a study in mice. Maternal exposure to M27 at this dose was approximately 9 times the human M27 AUC exposure at a dose of 400 mg/day of venetoclax. Limited placental transfer of venetoclax was shown in mice, rats and rabbits. Significant placental transfer of the M27 metabolite was evident in mice.

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.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class and by frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Clinical trial experience in CLL/SLL

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 obinutuzumab

The safety of venetoclax in combination with obinutuzumab versus obinutuzumab and chlorambucil was evaluated in an open-label randomised (1:1) phase 3 study (Study BO25323) in patients with previously untreated CLL and coexisting medical conditions. Details of the study treatment are described in **Section 5.1 PHARMACODYNAMIC PROPERTIES: Clinical trials: VENCLEXTA in combination with obinutuzumab**.

At the time of data analysis, the median duration of exposure to venetoclax was 10.5 months (range: 1 to 13.5 months). The median number of cycles was 6 for obinutuzumab and 12 for chlorambucil.

In the venetoclax + obinutuzumab arm, adverse events led to discontinuation in 16% of patients, dose reductions in 21% of patients and dose interruptions in 74% of patients. The most common adverse reaction that led to dose interruption of venetoclax was neutropenia.

In the venetoclax + obinutuzumab arm, fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were

reported in 2% (4/212) of patients, most often from infection. Serious adverse reactions were reported in 49% of patients in the venetoclax + obinutuzumab arm, most often due to febrile neutropenia and pneumonia (5% each).

Table 9 provides the adverse reactions reported in Study BO25323.

Table 9. Common (≥10%) adverse reactions in patients treated with VENCLEXTA + obinutuzumab compared with obinutuzumab + chlorambucil

Adverse Reaction by System Organ Class	VENCLEXTA + obinutuzumab (N=212)		Obinutuzumab + chlorambucil (N=214)	
	All grades %	Grade ≥3 %	All grades %	Grade ≥3 %
Blood & lymphatic system disorders				
Neutropenia[a]	60	56	62	52
Anaemia[a]	17	8	20	7
Gastrointestinal disorders				
Diarrhoea	28	4	15	<1
Nausea	19	0	22	1
Constipation	13	0	9	0
Vomiting	10	1	8	1
General disorders and administration site conditions				
Fatigue[a]	21	2	23	1
Infections and Infestations				
Upper respiratory tract infection[a]	17	1	17	1
[a]Includes multiple adverse reaction terms.				

Other adverse reactions reported in the venetoclax + obinutuzumab arm are presented below:

Blood & lymphatic system disorders: febrile neutropenia (6%), lymphopaenia (1%)

Infection and infestation disorder (all include multiple adverse reaction terms): pneumonia (9%), urinary tract infection (6%), sepsis[a] (4%)

Metabolism and nutrition disorder: hyperuricaemia (4%), hyperkalaemia (2%), hyperphosphataemia (2%), hypocalcaemia (1%), tumour lysis syndrome (1%)

Investigations: blood creatinine increased (3%)

[a]Includes the following terms: sepsis, septic shock, urosepsis.

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 interruption of venetoclax was neutropenia.

Table 10. Adverse events reported in ≥5% of patients treated with VENCLEXTA + rituximab in Study GO28667 which occurred at ≥2% higher incidence compared with bendamustine + rituximab

Adverse Events System Organ Class Preferred Term	VENCLEXTA + rituximab followed by single agent VENCLEXTA (N=194)		Bendamustine + rituximab (N=188)	
	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

Adverse Events System Organ Class Preferred Term	VENCLEXTA + rituximab followed by single agent VENCLEXTA (N=194)		Bendamustine + rituximab (N=188)	
	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥ 3 n (%)
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 10 are presented below by MedDRA body system organ class and by frequency.

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 or SLL, 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.

The frequencies of adverse drug reactions (ADRs) reported with VENCLEXTA are summarised in Table 11.

Table 11: Adverse drug reactions reported in patients with CLL/SLL treated with VENCLEXTA monotherapy

System Organ Class	Frequency (All grades)	Preferred Term
Blood and lymphatic system disorders	Very common	Neutropenia[a] Anaemia[b] Lymphopaenia[c]
	Common	Febrile neutropenia
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Nausea Constipation
General disorders and administration site conditions	Very common	Fatigue
Infections and infestations	Very common	Upper respiratory tract infection Pneumonia
	Common	Urinary tract infection Sepsis[d]
Investigations	Common	Blood creatinine increased
Metabolism and nutrition disorders[e]	Very common	Hyperkalaemia[f] Hyperphosphataemia[g] Hypocalcaemia[h]
	Common	Tumour lysis syndrome[i] 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 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 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 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 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 14.

Table 14. 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 15 describes common laboratory abnormalities reported throughout treatment that were new or worsening from baseline.

Table 15. 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/Small Lymphocytic Lymphoma

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%.

VENCLEXTA in combination with obinutuzumab

In the open-label, randomised phase 3 study (BO25323), the incidence of TLS was 1% (3/212) in patients treated with venetoclax + obinutuzumab (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Tumour Lysis Syndrome**). All three events of TLS resolved and did not lead to withdrawal from the study. Obinutuzumab administration was delayed in two cases in response to the TLS events.

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.

VENCLEXTA in combination with rituximab

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% (see **Section 4.8 ADVERSE EFFECTS: Serious infection**).

VENCLEXTA in combination with obinutuzumab

In Study BO25323, neutropenia (all grades) was reported in 58% of patients in the venetoclax + obinutuzumab arm. Forty-one percent experienced dose interruption, 13% had dose reduction and 2% discontinued venetoclax due to neutropenia. Grade 3 neutropenia was reported in 25% of patients and grade 4 neutropenia in 28% of patients. The median duration of grade 3 or 4 neutropenia was 22 days (range: 2 to 363 days). The following complications of neutropenia were reported in the venetoclax + obinutuzumab arm versus the obinutuzumab + chlorambucil arm, respectively: febrile neutropenia 6% versus 4%, grade ≥3 infections 19% versus 16%, and serious infections 19% versus 14% (see **Section 4.8 ADVERSE EFFECTS: Serious infection**).

Serious infection

Serious infection is an identified risk associated with VENCLEXTA treatment.

VENCLEXTA in combination with rituximab

The most commonly reported serious infection in the venetoclax + rituximab treated patients was pneumonia (8%).

VENCLEXTA in combination with obinutuzumab

There were 56 events of serious infection, including 8 with fatal outcome, in 40/212 patients in patients treated with venetoclax + obinutuzumab compared to 44 serious infection events, including 3 with fatal outcome, in 30/214 patients treated with chlorambucil + obinutuzumab. Of the 52/56 serious events in the patients treated with venetoclax + obinutuzumab for which neutrophil counts at the time of onset of the serious infection were available, 8/52 events occurred in the setting of neutropenia. Some serious infections occurred some time after completion of venetoclax treatment.

VENCLEXTA as monotherapy

The most frequently reported serious adverse reactions related to infection were pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). There have been 2 reports of death from septic shock occurring in the absence of disease progression and within 30 days of venetoclax treatment.

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 13 11 26.

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 B-cell lymphoma (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/Small Lymphocytic Lymphoma

VENCLEXTA in combination with obinutuzumab

Study BO25323

Study BO25323 was a randomised (1:1), multicentre, open label phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with obinutuzumab versus obinutuzumab in combination with chlorambucil for previously untreated CLL in patients with coexisting medical conditions (total Cumulative Illness Rating Scale [CIRS] score > 6 or creatinine clearance < 70 mL/min). The trial required hepatic transaminases and total bilirubin ≤ 2 times upper limit of normal and excluded patients with Richter's transformation or any individual organ/system impairment score of 4 by CIRS except eye, ear, nose, and throat organ system.

Patients in the study were assessed for risk of TLS and received prophylaxis and monitoring accordingly prior to obinutuzumab administration and during VENCLEXTA ramp-up. All patients received obinutuzumab at 1000 mg on Cycle 1 Day 1 (the first dose was split as 100 mg and 900 mg on Days 1 and 2), and 1000 mg doses on Days 8 and 15 of Cycle 1, and on

Day 1 of each subsequent cycle, for a total of 6 cycles. On Day 22 of Cycle 1, patients in the venetoclax + obinutuzumab arm began the 5-week VENCLEXTA ramp-up schedule (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION**). After completing the ramp-up schedule on Cycle 2 Day 28, patients received VENCLEXTA 400 mg once daily from Cycle 3 Day 1 until the last day of Cycle 12. Patients randomised to the obinutuzumab + chlorambucil arm received 0.5 mg/kg oral chlorambucil on Day 1 and Day 15 of Cycles 1 to 12, in the absence of disease progression or unacceptable toxicity. Each cycle was 28 days. Following completion of 12 cycles of VENCLEXTA, patients continued to be followed for disease progression and overall survival.

Baseline demographic and disease characteristics were similar between the study arms (Table 16).

Table 16. Demographics and baseline characteristics in Study BO25323

Characteristic	**VENCLEXTA + obinutuzumab (N = 216)**	**Obinutuzumab + chlorambucil (N = 216)**
Age, years; median (range)	72 (43-89)	71 (41-89)
White; %	89	90
Male; %	68	66
ECOG performance status; %		
0	41	48
1	46	41
2	13	12
CIRS score, median (range)	9 (0-23)	8 (1-28)
Creatinine clearance < 70 mL/min; %	60	56
Binet Stage at screening; %		
A	21	20
B	36	37
C	43	43
CLL subsets %		
17p deletion	9	7
11q deletion	18	20
TP53 mutation	11	9
IgVH unmutated	56	57

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

The median follow-up at the time of analysis was 28 months (range: 0 to 36 months).

The primary endpoint was progression-free survival (PFS) as assessed by investigators using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

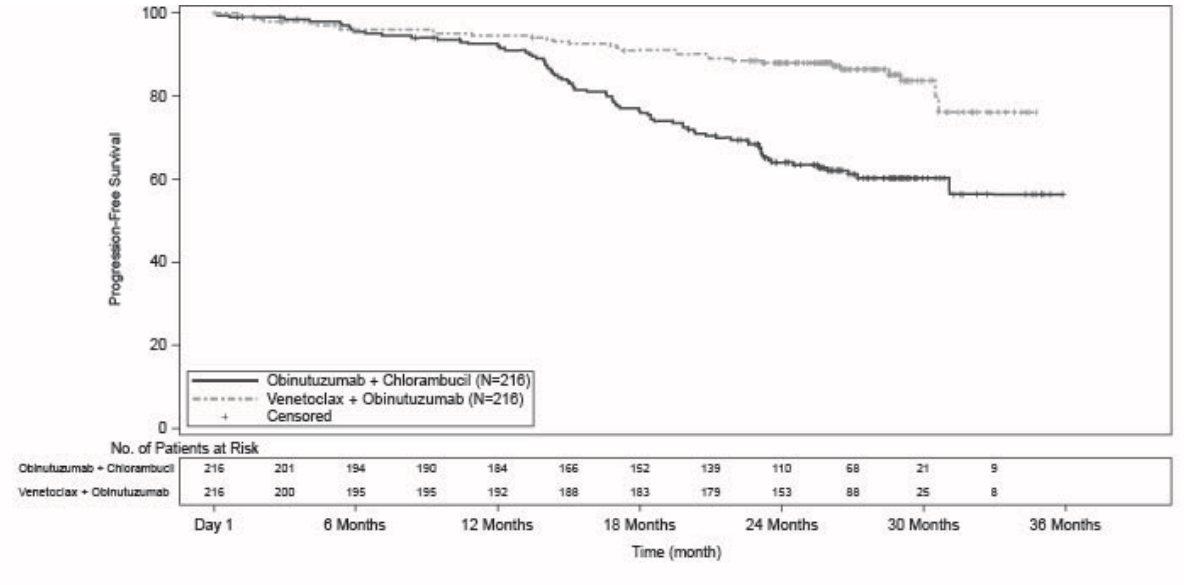
Efficacy results for Study BO25323 are shown in Table 17. The Kaplan-Meier curve for PFS is shown in Figure 1.

Table 17. Efficacy results for Study BO25323

	INV-assessed		IRC-assessed	
	VENCLEXTA + obinutuzumab (N = 216)	**Obinutuzumab + chlorambucil (N = 216)**	**VENCLEXTA + obinutuzumab (N = 216)**	**Obinutuzumab + chlorambucil (N = 216)**
Progression-free survival[a]				
Number of events (%)	30 (13.9)	77 (36)	29 (13)	79 (37)
Disease progression	14 (6)	69 (32)	14 (6)	71 (33)
Deaths	16 (7)	8 (4)	15 (7)	8 (4)
Median, months	Not reached	Not reached	Not reached	Not reached
HR (95% CI)[b]	0.35 (0.23, 0.53)		0.33 (0.22, 0.51)	
p-value	<0.0001		<0.0001	
12-month estimate, % (95% CI)	94.6 (91.5, 97.7)	92.1 (88.4, 95.8)	94.6 (91.5, 97.7)	91.1 (87.3, 95.1)
24-month estimate, % (95% CI)	88.2 (83.7, 95.1)	64.1 (57.4, 70.8)	88.6 (84.2, 93)	63.7 (57, 70.4)
Response rate[c], n (%)				
ORR (95% CI)	183 (85) (79.2, 89.2)	154 (71) (64.8, 77.2)	NA	NA
CR	100 (46)	47 (22)	NA	NA
CR+CRi	107 (50)	50 (23)	NA	NA
PR	76 (35)	104 (48)	NA	NA
Time to next anti-leukaemic therapy				
Number of events (%)	27 (13)	45 (21)	NA	NA
Median, months	Not reached	Not reached	NA	NA
Hazard ratio (95% CI)	0.6 (0.37, 0.97)		NA	NA

CI = confidence interval; CR = complete response; CRi = complete response with incomplete marrow recovery; INV = investigator; IRC = independent review committee; MRD = minimal residual disease; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial response; HR = hazard ratio.
[a] From randomisation until earliest event of disease progression or death due to any cause. Kaplan-Meier estimate.
[b] HR estimate is based on Cox-proportional hazards model stratified by Binet Stage and geographic region; p-value based on log rank test stratified by the same factors.
[C] Per 2008 International Workshop for Chronic Lymphocytic Leukemia (IWCLL) guidelines.

Figure 1. Kaplan-Meier curve of Investigator-assessed progression-free survival (ITT Population) in Study BO25323



At the time of analysis, median overall survival (OS) had not been reached, with fewer than 10% of patients experiencing an event. The median duration of follow-up for OS was 28 months.

Minimal residual disease (MRD) was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The cutoff for a negative status was <1 CLL cell per 10^4 leukocytes. Rates of MRD negativity 3 months after the completion of treatment regardless of response and in patients with CR/CRi are shown in Table 18. At this assessment, 134 patients in the venetoclax + obinutuzumab arm who were MRD negative in peripheral blood had matched bone marrow specimens; of these, 122 patients (91%) were MRD negative in both peripheral blood and bone marrow.

Table 18: Minimal residual disease negativity rates three months after the completion of treatment in Study BO25323

Twelve months after the completion of treatment, MRD negativity rates in peripheral blood

	VENCLEXTA + obinutuzumab (N = 216)	**Obinutuzumab + chlorambucil (N = 216)**
Peripheral blood		
MRD negativity rate, n (%)	163 (76)	76 (35)
[95% CI]	[69.17, 81.05]	[28.83, 41.95]
p-value[a]	<0.0001	
MRD negativity rate in patients with CR/CRi, n (%)	91 (42)	31 (14)
[95% CI]	[35.46, 49.02]	[9.96, 19.75]
p-value[a]	<0.0001	
Bone marrow		
MRD negativity rate, n (%)	123 (57)	37 (17)
[95% CI]	[50.05, 63.64]	[12.36, 22.83]
p-value[a]	<0.0001	
MRD negativity rate in patients with CR/CRi, n (%)	73 (34)	23 (11)
[95% CI]	[27.52, 40.53]	[6.87, 15.55]
p-value[a]	<0.0001	

CI = confidence interval; CR = complete response
[a] p-value based on Chi-square test

were 58% (126/216) in patients treated with venetoclax + obinutuzumab and 9% (20/216) in patients treated with obinutuzumab + chlorambucil.

In paired samples, the concordance of MRD negativity between peripheral blood and bone marrow samples at end of treatment was 91% in the venetoclax + obinutuzumab arm and 58% in the obinutuzumab + chlorambucil arm.

Sub-group analyses were limited by small participant numbers and/or small numbers of events but appear to indicate that, at median follow-up of 28 months, a PFS benefit with venetoclax + obinutuzumab versus obinutuzumab + chlorambucil occurred in patients with and without high risk mutations (17p deletion or *TP53* mutation) and patients with unmutated *IGHV*.

Patient-Reported Outcomes

Health-Related Quality of Life (HRQoL) was evaluated using the M. D. Anderson Symptom Inventory (MDASI)-CLL and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). The HRQoL was maintained in both arms with no increase in symptom burden or worsening observed in any quality of life domains.

Study GP28331

Study GP28331 was a multicentre, open-label, non-randomised study of venetoclax administered in combination with obinutuzumab that included 32 patients with previously untreated CLL. Twenty-two patients had a baseline creatinine clearance ≥70 mL/min and a baseline ECOG of 0 or 1, and were therefore eligible to receive chemo-immunotherapy (e.g. FCR or BR) as treatment. All 22 patients responded and 16 patients (73%) achieved a CR/CRi (investigator-assessed) with a median duration of follow-up of 26.7 months (range: 16 to 39 months). The 24-month PFS rate was 86% (95%CI: 72.02 to 100.00).

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 19 shows the baseline demographic and disease characteristics were similar between the venetoclax + rituximab and bendamustine + rituximab arms.

Table 19: 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 20. The Kaplan-Meier curves for PFS and overall survival (OS) are shown in Figure 2 and 3, respectively.

Table 20: Efficacy results for Study GO28667

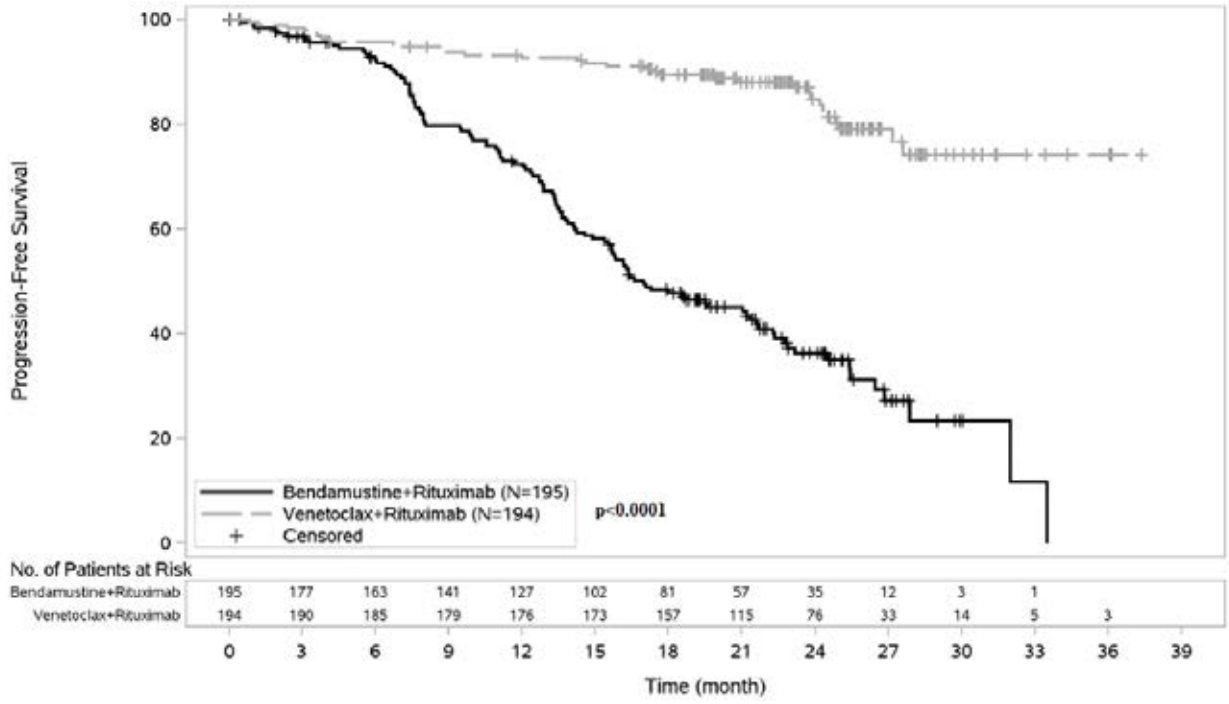
	INV-assessed		IRC-assessed	
	VENCLEXTA + rituximab (N = 194)	**Bendamustine + rituximab (N = 195)**	**VENCLEXTA + rituximab (N = 194)**	**Bendamustine + rituximab (N = 195)**
Progression-free survival				
Number of events (%)	32 (16.5)	114 (58.5)	35 (18.0)	106 (54.4)
Disease progression	21	98	26	91
Death 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.

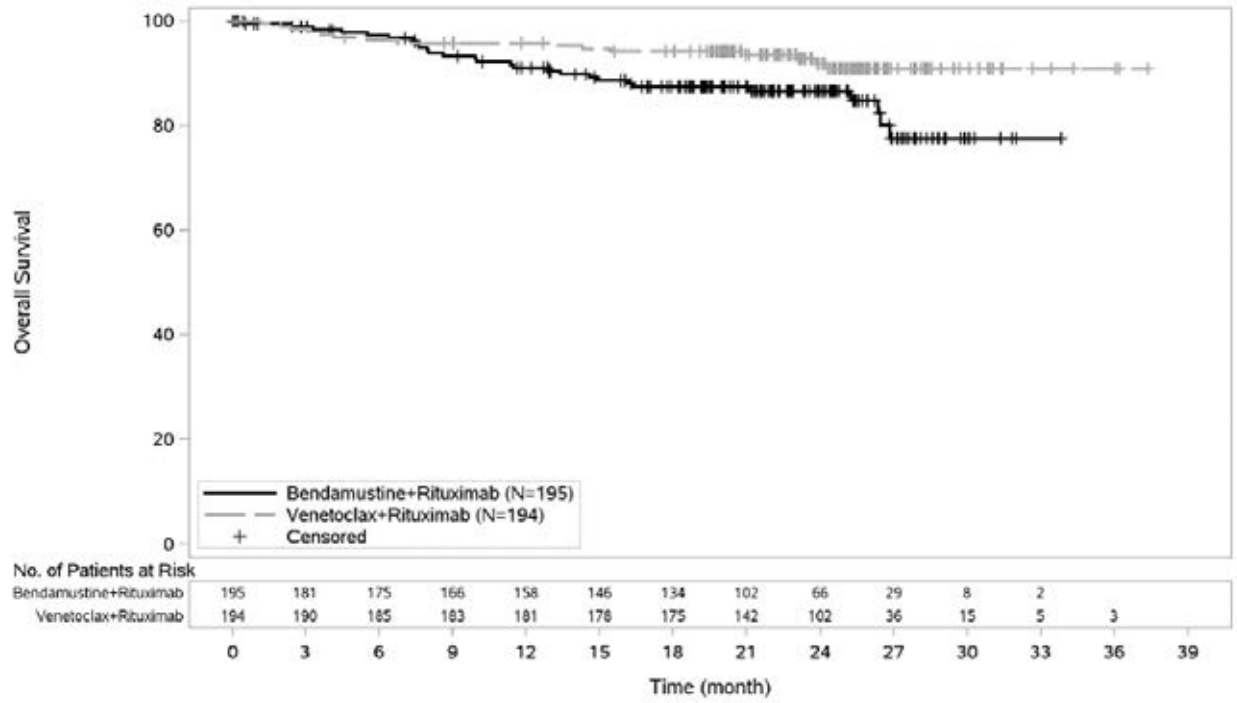
[b]The discrepancy between IRC- and investigator-assessed CR rate was primarily due to interpretation of residual adenopathy on CT scans. Eighteen patients in the venetoclax + rituximab arm and 3 patients in the bendamustine + rituximab arm had negative bone marrow and lymph nodes <2 cm.

Figure 2: 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 3: Kaplan-Meier curve of Overall Survival (ITT Population) in Study GO28667



Minimal residual disease was evaluated using 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 or SLL 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 21 summarises the baseline demographic and disease characteristics of the study population.

Table 21. 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; % 0 1 2	 39.3 52.3 8.4
Tumour burden; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 50.5 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. [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 22.

Table 22. 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 or SLL, including those with 17p deletion. Efficacy was evaluated in 67 patients

(59 with CLL, 8 with SLL) 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 22.1 months (range: 0.5 – 50.1 months). Table 23 summarises the baseline demographic and disease characteristics of the study population.

Table 23. Baseline patient characteristics of evaluable patients in Study M12-175

Characteristic	**N=67**
Age, years; median (range)	66 (42-84)
White; %	86.6
Male; %	77.6
ECOG performance status[a]; % 0 1 2	 47.7 52.3 0
Tumour burden; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 29.9 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, 70.1% were fludarabine refractory, 66.7% (22/33) had unmutated *IGHV*, 31.0% (18/58) had 11q deletion, and 24.1% (14/58) 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 24:

Table 24. Efficacy results in Study M12-175

	IRC assessment N=57	**Investigator assessment N=67**
ORR, % (95% CI)	73.7 (60.3, 84.5)	82.1 (70.8, 90.4)
CR + CRi (%)	7.0	13.4
nPR (%)	0	3.0
PR (%)	66.7	65.7
DOR, % (95% CI) 12-month estimate	88.8 (67.5, 96.5)	92.1 (80.2, 96.9)
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.		

For the 8 patients with SLL, the investigator-assessed ORR was 100%.

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

Table 25: 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; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 31 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 26:

Table 26: Efficacy results in Study M14-032

	IRC assessment N=127[a]	Investigator assessment N=127
ORR,% (95% CI)	70.1 (61.3, 77.9)	63.0 (54.0, 71.4)
CR + CRi (%)	0.8	8.7
nPR (%)	0	2.4
PR (%)	69.3	52.0
DOR, % (95% CI) 6-month estimate 12-month estimate	N=89 97.4 (90.0, 99.4) NA	N=83 96.2 (88.7, 98.8) 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 27 summarises the baseline demographic and disease characteristics of the study population.

Table 27. 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; % 0-1 2 3	 69.0 28.6 2.4
Bone marrow blast; % <30% ≥30% - <50% ≥50%	 28.6 33.3 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 28 and 29.

Table 28. 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 (%) 95% CI Median DOR[a] (months) 95% CI	34 (40.5) [29.9, 51.7] >14.6[b] [14.6, 30.3]
CRi, n (%) 95% CI Median DOR[c] (months) 95% CI	25 (29.8) [20.3, 40.7] 7.8 [5.6, NR]
CR+CRi, n (%) 95% CI Median DOR[c] (months) 95% CI	59 (70.2) [59.3, 79.7] >8.2[b] [8.2, 30.2]
CRh, n (%) 95% CI Median DOR[a] (months) 95% CI	20 (23.8) [15.2, 34.3] 7.9 [5.8, NR]
CR+CRh, n (%) 95% CI Median DOR[a] (months) 95% CI	54 (64.3) [53.1, 74.4] >8.2[b] [8.2, 30.3]
Transfusion independence, n/N (%) Red blood cell[d] Platelet[e]	 25/50 (50.0) 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 29. 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) Range (months)	1.9 (0.7–10.9)
Median time to FIRST response of CR+CRh (months) Range (months)	1.0 (0.7–8.9)
Median time to FIRST response of CR+CRi (months) Range (months)	1.2 (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 10^3leukocytes 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.

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

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 30 summarises the baseline demographic and disease characteristics of the study population.

Table 30. 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; % 0-1 2 3	 70.7 28.0 1.2
Bone marrow blast; % <30% ≥30% - <50% ≥50%	 32.9 22.0 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 31 and 32.

Table 31. 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 (%) 95% CI Median DOR[a] (months) 95% CI	21 (25.6) [16.6 - 36.4] NR [10.2, NR]
CRi, n (%) 95% CI Median DOR[b] (months) 95% CI	23 (28.0) [18.7, 39.1] 4.7 [2.6, 5.6]
CR+CRi, n (%) 95% CI Median DOR[b] (months) 95% CI	44 (53.7) [42.3, 64.7] 8.1 [5.3, 14.9]
CRh, n (%) 95% CI Median DOR[a] (months) 95% CI	17 (20.7) [12.6, 31.1] 6.6 [2.8, 11.0]
CR+CRh, n (%) 95% CI Median DOR[a] (months) 95% CI	38 (46.3) [35.3, 57.7] 11.0 [6.1, NR]
Transfusion independence, n/N (%) Red blood cell[c] Platelet[d]	 23/53 (43.4) 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 32. 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) Range (months)	3.0 (0.9–22.4)
Median time to FIRST response of CR+CRh (months) Range (months)	1.0 (0.8–9.4)
Median time to FIRST response of CR+CRi (months) Range (months)	1.4 (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.

The M27 metabolite orally administered to mice had effects similar to venetoclax (decreased lymphocytes and red blood cell mass) but of lesser magnitude, consistent with its low pharmacologic activity *in vitro*.

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

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

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/SLL	Each Starting Pack contains four weekly wallets: • Week 1 (14 x 10 mg tablets) • Week 2 (7 x 50 mg tablets) • Week 3 (7 x 100 mg tablets) • Week 4 (14 x 100 mg tablets) 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.

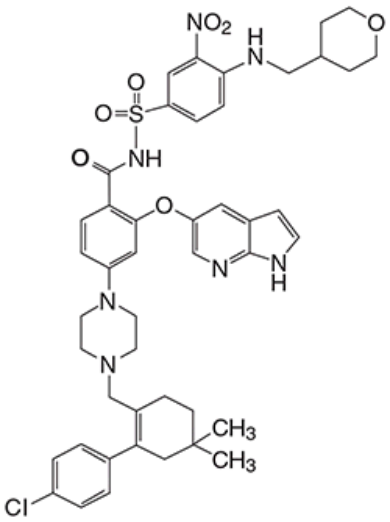
6.6 Special precautions for disposal

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

29 April 2020

Summary table of changes

Section changed	Summary of new information
All	CLL and SLL information clarified.
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 Studies BO25323 and GP28331.
4.6	Recommended dose now clarified. Addition of M27 metabolite information.
4.8	Safety update to include information from Studies BO25323 and GP28331 and update to the TLS and neutropenia subsections.
5.1	Clinical trial information added from Studies BO25323 and GP28331. Inclusion of SLL patients from Study M12-175.
5.3	Additional M27 metabolite safety information. Preliminary carcinogenicity data now available.