PRODUCT INFORMATION
VENCLEXTA® (VENETOCLAX) FILM-COATED TABLETS

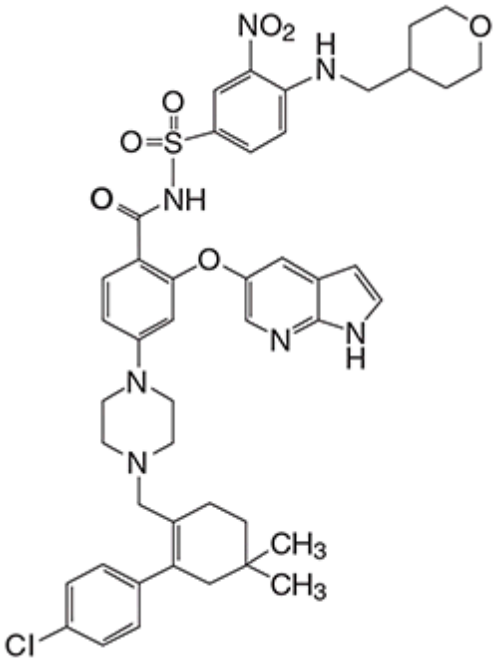
NAME OF THE MEDICINE

Venetoclax

CHEMICAL STRUCTURE

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 Daltons

CAS Number: 1257044-40-8

DESCRIPTION

Venetoclax is a light yellow to dark yellow solid, and has very low aqueous solubility.

VENCLEXTA tablets for oral administration are supplied as pale yellow or beige film-coated tablets that contain 10, 50, or 100 mg venetoclax as the active ingredient.

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.

PHARMACOLOGY

PHARMACODYNAMICS

Pharmacotherapeutic group: other antineoplastic agents

ATC code: not yet assigned

Venetoclax is an orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in chronic lymphocytic leukaemia (CLL) cells and has been implicated in resistance to certain therapeutic agents. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilisation, the release of cytochrome *c* from mitochondria and the activation of caspases. In nonclinical studies, venetoclax demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.

Cardiac Electrophysiology

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

PHARMACOKINETICS

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 µg/mL and AUC_{24} was 32.8 ± 16.9 µg•h/mL at the 400 mg once daily dose.

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared to fasting conditions. Venetoclax should be administered with a meal (see DOSAGE AND 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 (Vdss/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*.

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 PRECAUTIONS: 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 PRECAUTIONS: Renal Impairment).

Hepatic Impairment

Based on a population pharmacokinetic analysis that included 69 subjects with mild hepatic impairment, 7 subjects with moderate hepatic impairment and 429 subjects with normal hepatic function, venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function. The National Cancer Institute (NCI) Organ Dysfunction Working Group criteria for hepatic impairment were used in the analysis. Mild hepatic impairment was defined as normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin >1.0 to 1.5 times ULN, moderate hepatic impairment as total bilirubin >1.5 to 3.0 times ULN, and severe hepatic impairment as total bilirubin >3.0 ULN. The pharmacokinetics of venetoclax have not been studied in subjects with severe hepatic impairment (see PRECAUTIONS: Hepatic Impairment).

In vitro Studies

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

Venetoclax is a P-gp and BCRP substrate as well as a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor *in vitro*. To avoid a potential interaction in the gastrointestinal tract, digoxin, a narrow therapeutic range P-gp substrate, should be taken at least 6 hours before VENCLEXTA. Venetoclax is not expected to inhibit OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K at clinically relevant concentrations.

Animal Pharmacology and/or Toxicology

Toxicities observed in animal studies with venetoclax included dose-dependant reductions in lymphocytes and red blood cell mass. After cessation of dosing with venetoclax, red blood cell effects were reversible, whereas partial reversibility of lymphocytes was observed at the end

of an 18-week recovery period. Both B- and T- cells were affected, but the most significant decreases occurred with B-cells.

Venetoclax also caused single-cell necrosis in various tissues, including the gallbladder and exocrine pancreas, with no evidence of disruption of tissue integrity or organ dysfunction; these findings were minimal to mild in magnitude. Following a 4-week dosing period and subsequent 4-week recovery period, minimal single-cell necrosis was still present in some tissues and reversibility has not been assessed following longer periods of dosing or recovery.

After approximately 3 months of daily dosing in dogs, venetoclax caused progressive white discoloration of the hair coat, due to loss of melanin pigment in the hair. No changes in the quality of the hair coat or skin were observed, nor in other pigmented tissues examined (e.g., the iris and the ocular fundus of the eye). Reversibility of the hair coat changes has not been assessed in dogs.

CLINICAL TRIALS

The approval for the use of VENCLEXTA in Chronic Lymphocytic Leukaemia (CLL) is based on phase 1 and phase 2 non-randomised trials. The results of a randomised, active-controlled phase 3 study are awaited.

The safety and efficacy of VENCLEXTA were established in 2 open-label, multicentre clinical trials of patients with CLL who had received at least one prior therapy, including those with deletion of the p13 locus on chromosome 17 (17p del).

STUDY M13-982

Study M13-982 was a multicentre, single-arm open-label trial of 107 previously treated patients with CLL with 17p del. Table 1 summarises the baseline demographic and disease characteristics of the study population.

Table 1. Baseline Patient Characteristics in Study M13-982

Characteristics	N = 107[a]
Age, years; median (range)	67 (37 to 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, months; median (range)[b]	81.7 (1.2-385.6)
[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 del were identified using Vysis CLL FISH Probe Kit. Patients received VENCLEXTA via a weekly dose titration schedule starting at 20 mg and titrating to 50

mg, 100 mg, 200 mg and finally 400 mg once daily. Patients continued to receive 400 mg of VENCLEXTA orally once daily until disease progression or unacceptable toxicity. The median time on treatment at the time of evaluation was 12.1 months (range: 0 - 21.5 months).

The primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). Efficacy results for Study M13-982 are shown in Table 2.

Table 2. Efficacy Results in Study M13-982

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

[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.

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

Minimal residual disease (MRD) was evaluated using flow cytometry in 45 of 107 patients who achieved complete remission (CR), complete remission with incomplete marrow recovery (CRi), or partial remission (PR) with limited remaining disease with VENCLEXTA treatment. The cut-off for a negative status was one CLL cell per 10^4 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.

STUDY M12-175

Study M12-175 was a multicentre, open-label trial that enrolled previously treated patients with CLL, including those with 17p del. Efficacy was evaluated in 57 patients who had received a daily dose of 400 mg of VENCLEXTA following a dose titration schedule. Patients continued to receive 400 mg of VENCLEXTA monotherapy orally once daily until disease progression or unacceptable toxicity. The median time on treatment at the time of evaluation was 11.5 months (range: 0.5 - 34.1 months). Table 3 summarises the baseline demographic and disease characteristics of the study population.

Table 3. Baseline Patient Characteristics of Evaluable Patients in Study M12-175

Characteristics	**N=57**
Age, years; median (range)	66 (42 to 84)
White; %	91.2
Male; %	75.4

Characteristics	N=57
ECOG performance status[a]; % 0 1 2	 45.5 52.7 1.8
Tumour burden; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 35.1 66.7
Number of prior therapies; median (range)	3 (1-11)
Time since diagnosis, months; median (range)	108 (13.7-327.6)
[a]Missing for two patients.	

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

Overall response rate (ORR) and duration of response (DOR) were evaluated by both investigators and an IRC according to the IWCLL NCI-WG criteria. Efficacy results are shown in Table 4:

Table 4. Efficacy Results in Study M12-175

	IRC Assessment N=57	Investigator Assessment N=57
ORR, % (95% CI)	73.7 (60.3, 84.5)	80.7 (68.1, 90.0)
CR + CRi (%)	7.0	12.3
nPR (%)	0	3.5
PR (%)	66.7	64.9
DOR, % (95% CI) 12-month estimate	88.8 (67.5, 96.5)	96.6 (77.9, 99.5)
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.		

INDICATIONS

VENCLEXTA is indicated for the treatment of:

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

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

CONTRAINDICATIONS

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

Concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during the dose titration phase is contraindicated (see DOSAGE AND ADMINISTRATION and INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

Tumour Lysis Syndrome

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

Interrupt or discontinue VENCLEXTA, as recommended, if this adverse event occurs (see **DOSAGE AND ADMINISTRATION).**

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

The risk of TLS is a continuum based on multiple factors, including tumour burden (see Table 7) and comorbidities. Reduced renal function (CrCl < 80 mL/min) further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricaemics. Blood chemistries should be monitored and abnormalities managed promptly. Dosing should be interrupted, if needed. More intensive measures (intravenous hydration, frequent monitoring, and hospitalisation) should be employed as overall risk increases (see DOSAGE AND ADMINISTRATION).

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk of TLS at initiation and during dose titration phase (see DOSAGE AND ADMINISTRATION and INTERACTIONS WITH OTHER MEDICINES). Inhibitors of P-gp may also increase venetoclax exposure (see INTERACTIONS WITH OTHER MEDICINES).

NEUTROPENIA

Grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L) has occurred in 40.8% (98/240) of patients treated with VENCLEXTA (see **ADVERSE EFFECTS**). Complete blood counts should be monitored throughout the treatment period. Dose interruptions or dose reductions are recommended for severe neutropenia. Supportive measures should be considered, including antimicrobials for any signs of infection, and prophylactic use of growth factors (e.g., granulocyte-colony stimulating factor [G-CSF]) (see DOSAGE AND ADMINISTRATION**,** CONTRAINDICATIONS**,** INTERACTIONS WITH OTHER MEDICINES and PHARMACOLOGY: Pharmacokinetics for further information on potential interactions with CYP3A inhibitors/inducers).

IMMUNISATION

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

HEPATIC IMPAIRMENT

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

RENAL IMPAIRMENT

No specific clinical trials have been conducted in subjects with renal impairment. After a single oral administration of 200 mg radiolabeled [14C]-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 PHARMACOLOGY: Pharmacokinetics).

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 DOSAGE AND ADMINISTRATION). A recommended dose has not been determined for patients with severe renal impairment (CrCl <30 mL/min) or patients on dialysis.

EFFECTS ON FERTILITY

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

Fertility and early embryonic development studies were conducted in male and female mice. These studies evaluated mating, fertilisation, and embryonic development through implantation. There were no effects of venetoclax on oestrus cycles, mating, fertility, corpora lutea, uterine implants or live embryos per litter at dosages up to 600 mg/kg/day (in male and female mice, approximately 3 times the human AUC exposure at the recommended dose). However, a risk to human male fertility exists based on testicular toxicity (germ cell loss) observed in dogs at all dose levels examined (exposures of 0.5 to 18 times the human AUC exposure at the recommend dose). Reversibility of this finding has not been demonstrated.

USE IN PREGNANCY

Pregnancy Category C

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

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

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

In embryo-fetal development studies, venetoclax was administered to pregnant mice and rabbits. These studies evaluated potential effects after implantation and subsequent embryo-fetal development during the respective periods of major organogenesis in mice and rabbits. In mice, venetoclax was associated with increased post-implantation loss and decreased fetal body weight at 150 mg/kg/day (maternal exposures approximately 1.2 times the human AUC exposure at the recommended dose). In rabbits, venetoclax at 300 mg/kg/day produced maternal toxicity, but no fetal toxicity (maternal exposures approximately 0.14 times the human AUC exposure at the recommended dose). No teratogenicity was observed in either the mouse or the rabbit.

USE IN LACTATION

It is not known whether venetoclax or its metabolites are excreted in human breast milk. A risk to newborns/infants cannot be excluded. Because many drugs are excreted in human breast milk and because the potential for serious adverse reactions in breastfed infants from

VENCLEXTA is unknown, nursing women should be advised to discontinue breastfeeding during treatment with VENCLEXTA.

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 164 previously treated patients with CLL evaluated for efficacy by an Independent Review Committee in Studies M13-982 and M12-175, 91 (55.5%) patients were ≥65 years of age and 28 (17.1%) patients were ≥75 years of age. No overall difference in effectiveness was observed between these and younger patients.

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. No overall difference in safety was observed between these patients and younger patients.

GENOTOXICITY

Venetoclax was not mutagenic in an *in vitro* bacterial mutagenicity (Ames) assay, did not induce numerical or structural aberrations in an *in vitro* chromosome aberration assay using human peripheral blood lymphocytes, and was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay at a single oral dose up to 835 mg/kg (~3 times the clinical C_{max} at the maximum recommended dose of 400 mg/day). The M27 metabolite was negative for genotoxic activity in *in vitro* Ames and chromosome aberration assays.

CARCINOGENICITY

Carcinogenicity studies have not been conducted with venetoclax.

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.

INTERACTIONS WITH OTHER MEDICINES

POTENTIAL EFFECTS OF OTHER MEDICINES ON VENCLEXTA

Venetoclax is predominantly metabolised by CYP3A4.

<u>CYP3A Inhibitors</u>

Co-administration of 400 mg once daily ketoconazole, a strong CYP3A, P-gp and BCRP inhibitor, for 7 days in 11 previously treated NHL patients increased venetoclax C_{max} by 2.3-fold and AUC_{∞} by 6.4-fold. Concomitant use of VENCLEXTA with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole, posaconazole) at initiation and during the ramp-up phase is contraindicated (see **Contraindications**).

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

Initiation and Dose Titration Phase

Concomitant use of moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil) should be avoided with VENCLEXTA at initiation and during the dose titration phase. Alternative treatments should be considered. If a moderate CYP3A inhibitor must be used, the initiation and dose titration doses of VENCLEXTA should be reduced by at

least 2-fold. Patients should be monitored more closely for signs of VENCLEXTA toxicities (see DOSAGE AND ADMINISTRATION).

After Dose Titration Phase

For patients who have completed the dose titration phase and are on a steady daily dose of VENCLEXTA, VENCLEXTA dose should be reduced by at least 2-fold when used concomitantly with moderate CYP3A inhibitors and by at least 4-fold when used concomitantly with strong CYP3A inhibitors. VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor can be resumed 2 to 3 days after discontinuation of the inhibitor (see DOSAGE AND ADMINISTRATION).

OATP1B1/1B3 and P-gp Inhibitors

Co-administration of a 600 mg single dose of rifampin, 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 at initiation and during the dose titration phase should be avoided; if a P-gp inhibitor must be used, patients should be monitored closely for signs of toxicities.

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 PHARMACOLOGY: Pharmacokinetics).

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 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.

ADVERSE EFFECTS

CLINICAL TRIAL EXPERIENCE

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

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

approximately 10.3 months (range: 0 to 34.1 months); approximately 46% of patients received VENCLEXTA for more than 48 weeks.

Tabulated list of adverse reactions

The frequencies of adverse drug reactions (ADRs) reported with VENCLEXTA are summarised in Table 5. Adverse reactions are listed below by MedDRA body system organ class and by frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 5. Adverse drug reactions reported in patients with CLL treated with VENCLEXTA

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

[a]Neutropenia/neutrophil count decreased.
[b]Anaemia/haemoglobin decreased.
[c]Lymphopenia/lymphocyte count decreased
[d]Hyperphosphataemia/blood phosphorus increased.
[e]Hyperkalaemia/blood potassium increased.
[f]Hyperuricaemia/blood uric acid increased.
[g]Hypocalcaemia/blood calcium decreased.

Summary of the safety profile

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

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

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

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

Tumour Lysis Syndrome

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

The risk of TLS was reduced after revision of the dosing regimen and modification to prophylaxis and monitoring measures (see DOSAGE AND 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 dose titration phase.

In 66 patients with CLL starting with a daily dose of 20 mg and increasing over 5 weeks to a daily dose of 400 mg, the rate of TLS was 6%. All events were laboratory TLS (laboratory abnormalities that met ≥2 of the following criteria within 24 hours of each other: potassium >6 mmol/L, uric acid >476 µmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L; or were reported as TLS events) and occurred in patients who had a lymph node(s) ≥5 cm or ALC ≥25 x 10^9/L. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias or sudden death and/or seizures was observed in these patients. All patients had CrCl ≥50 mL/min.

DOSAGE AND ADMINISTRATION

VENCLEXTA should be taken orally once daily until disease progression or unacceptable toxicity is observed. Patients should be instructed to take VENCLEXTA tablets with a meal and water at approximately the same time each day. VENCLEXTA tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

RECOMMENDED DOSAGE REGIMEN

The starting dose of VENCLEXTA is 20 mg once daily for 7 days. The VENCLEXTA dose must be administered according to a weekly dose titration schedule to the recommended daily dose of 400 mg over a period of 5 weeks as shown in Table 6.

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

Table 6. Dosing Schedule for Dose Titration Phase

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

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

RISK ASSESSMENT AND PROPHYLAXIS FOR TUMOUR LYSIS SYNDROME

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

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

Table 7 below describes the recommended TLS prophylaxis and monitoring during VENCLEXTA treatment based on tumour burden determination from clinical trial data.

Table 7. Recommended TLS Prophylaxis Based on Tumour Burden From Clinical Trial Data (consider all patient co-morbidities before final determination of prophylaxis and monitoring schedule)

Tumour Burden		Prophylaxis		Blood Chemistry Monitoring[c,d]
		Hydration[a]	Anti-hyperuricemics	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
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

Tumour Burden		Prophylaxis		Blood Chemistry Monitoring[c,d]
		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments
				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.

DOSE MODIFICATIONS BASED ON TOXICITIES

Dosing interruption and/or dose reduction may be required. See Table 8 for dose modifications for haematologic and other toxicities related to VENCLEXTA. For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of dose titration phase or greater than 2 weeks when at the daily dose of 400 mg, the risk of TLS is to be reassessed to determine if re-initiation with a reduced dose is necessary (e.g., all or some levels of the dose titration schedule) (see DOSAGE AND ADMINISTRATION Recommended Dosage Regimen and Risk Assessment and Prophylaxis for Tumour Lysis Syndrome).

Table 8. Recommended Dose Modifications for Toxicities

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 9) (see **DOSAGE AND ADMINISTRATION**; *Risk Assessment and Prophylaxis for Tumour Lysis Syndrome*).
		For any events of clinical TLS, resume at a reduced dose following resolution (see Table 9) (see **DOSAGE AND ADMINISTRATION**; *Risk Assessment and Prophylaxis for Tumour Lysis Syndrome*).
Non-Haematologic Toxicities		
Grade 3 or 4 non-haematologic 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 9 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion

Event	Occurrence	Action
		of the physician.
Haematologic Toxicities		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 haematologic toxicities (except lymphopaenia) *(*see **Precautions;** ***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 9 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 9. Dose Modification for Toxicity During VENCLEXTA Treatment

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.	

DOSE MODIFICATIONS FOR USE WITH CYP3A INHIBITORS

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during dose titration phase. Concomitant use of VENCLEXTA with strong CYP3A inhibitors at initiation and during dose titration phase is contraindicated (see CONTRAINDICATIONS).

Concomitant use of VENCLEXTA with moderate CYP3A inhibitors should be avoided at initiation and during dose titration phase. Consider alternative treatments. If a moderate CYP3A inhibitor must be used, the initiation and dose titration doses of VENCLEXTA should be reduced by at least 2-fold.

Patients should be monitored more closely for signs of toxicities (see DOSAGE AND ADMINISTRATION: Dose Modifications Based on Toxicities).

For patients who have completed the dose titration phase and are on a steady daily dose of VENCLEXTA, the VENCLEXTA dose should be reduced by at least 2-fold when used concomitantly with moderate CYP3A inhibitors and by at least 4-fold when used concomitantly with strong CYP3A inhibitors. Patients should be monitored more closely for signs of toxicities. The VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor can be resumed 2

to 3 days after discontinuation of the inhibitor (see DOSAGE AND ADMINISTRATION: Dose Modifications Based on Toxicities and INTERACTIONS WITH OTHER MEDICINES).

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.

OVERDOSAGE

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

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

PRESENTATION AND STORAGE CONDITIONS

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

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

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

VENCLEXTA is dispensed as follows:

Packaging Presentation	Number of Tablets
Starting Pack	Each pack contains four weekly wallets containing blister packs: · 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)
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 x 100 mg tablets

Not all presentations may be marketed.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

AbbVie Pty Ltd
241 O’Riordan Street
Mascot NSW 2020

Australia

POISONS SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

05 January 2017