CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208573Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VENCLEXTA safely and effectively. See full prescribing information for VENCLEXTA.

VENCLEXTA™ (venetoclax) tablets, for oral use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

VENCLEXTA is a BCL-2 inhibitor indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1)

DOSAGE AND ADMINISTRATION

- Initiate therapy with VENCLEXTA at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule to the recommended daily dose of 400 mg. (2.2)
- VENCLEXTA tablets should be taken orally once daily with a meal and water. Do not chew, crush, or break tablets. (2.2)
- Perform prophylaxis for tumor lysis syndrome. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg, 50 mg, 100 mg (3)

CONTRAINDICATIONS

Concomitant use of VENCLEXTA with strong inhibitors of CYP3A at initiation and during ramp-up phase is contraindicated. (2.5, 4, 7.1)

WARNINGS AND PRECAUTIONS

- Tumor Lysis Syndrome (TLS): Anticipate TLS; assess risk in all patients. Premedicate with anti-hyperuricemics and ensure adequate hydration. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases. (2.3, 5.1)
- Neutropenia: Monitor blood counts and for signs of infection; manage as medically appropriate. (2.4, 5.2)
- Immunization: Do not administer live attenuated vaccines prior to, during, or after VENCLEXTA treatment. (5.3)
- Embryo-Fetal Toxicity: May cause embryo-fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (≥20%) were neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Avoid concomitant use of VENCLEXTA with moderate CYP3A inhibitors, strong or moderate CYP3A inducers, P-gp inhibitors, or narrow therapeutic index P-gp substrates. (2.5, 7.1, 7.2)

- If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the VENCLEXTA dose by at least 50%. (2 5, 7 1)
- If a strong CYP3A inhibitor must be used after the ramp-up phase, reduce the VENCLEXTA dose by at least 75%. (2.5, 7.1)
- If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before VENCLEXTA. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Discontinue breastfeeding. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VENCLEXTA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of relapsed or refractory CLL with VENCLEXTA based on the presence of 17p deletions in blood specimens *[see Indications and Usage (1) and Clinical Studies (14)]*. Patients without 17p deletion at diagnosis should be retested at relapse because acquisition of 17p deletion can occur. Information on FDA-approved tests for the detection of 17p deletions in CLL is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

Assess patient-specific factors for level of risk of tumor lysis syndrome (TLS) and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENCLEXTA to reduce risk of TLS *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*. Administer the VENCLEXTA dose according to a weekly ramp-up schedule over 5 weeks to the recommended daily dose of 400 mg as shown in Table 1. The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS.

Instruct patients 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.

Table 1. Dosing Schedule for Ramp-Up Phase

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

The Starting Pack provides the first 4 weeks of VENCLEXTA according to the ramp-up schedule. Once the ramp-up phase is completed, the 400 mg dose is achieved using 100 mg tablets supplied in bottles *[see How Supplied/Storage and Handling (16)]*.

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

2.3 Risk Assessment and Prophylaxis for Tumor Lysis Syndrome

VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5-week ramp-up phase. Changes in blood chemistries 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 tumor burden and comorbidities. Perform tumor 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. Reduced renal function (creatinine clearance [CrCl] <80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

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

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

Tumor 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 hospitalization 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 (1.5-2 L) 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.

2.4 Dose Modifications Based on Toxicities

Interrupt dosing or reduce dose for toxicities. See Table 3 for dose modifications for hematologic and other toxicities related to VENCLEXTA, and Table 4 for dose. 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 when at the daily dose of 400 mg, reassess for risk of TLS to determine if reinitiation with a reduced dose is necessary (e.g., all or some levels of the dose ramp-up schedule) *[see Dosage and Administration (2.2, 2.3)]*.

Table 3. Recommended Dose Modifications for Toxicities[a]

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 4) *[see Dosage and Administration (2.3)]*.
		For any events of clinical TLS,[b] resume at a reduced dose following resolution (see Table 4) *[see Dosage and Administration (2.3)]*.
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic 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 4 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic Toxicities		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia) *[see Warnings and Precautions (5.2)]*	1st occurrence	Interrupt VENCLEXTA. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (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 4 when resuming treatment with VENCLEXTA after resolution. A larger dose reduction may occur at the discretion of the physician.
Consider discontinuing VENCLEXTA for patients who require dose reductions to less than 100 mg for more than 2 weeks. [a]Adverse reactions were graded using NCI CTCAE version 4.0. [b]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures.		

Table 4. 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]During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.	

2.5 Dose Modifications for Use with CYP3A and P-gp Inhibitors

Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during ramp-up phase is contraindicated. Concomitant use of VENCLEXTA with strong CYP3A inhibitors increases venetoclax exposure (i.e., C_{max} and AUC) and may increase the risk for TLS at initiation and during ramp-up phase *[see Contraindications (4)]*. For patients who have completed the ramp-up phase and are on a steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by at least 75% when *strong* CYP3A inhibitors must be used concomitantly.

Avoid concomitant use of VENCLEXTA with *moderate* CYP3A inhibitors or P-gp inhibitors. Consider alternative treatments. If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the VENCLEXTA dose by at least 50%. Monitor these patients more closely for signs of toxicities *[see Dosage and Administration (2.4)]*.

Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor *[see Dosage and Administration (2.4) and Drug Interactions (7.1)]*.

The recommendations for managing drug-drug interactions are summarized in Table 5.

Table 5. Management of Potential VENCLEXTA Interactions with CYP3A and P-gp Inhibitors

Inhibitors	Initiation and Ramp-Up Phase	Steady Daily Dose (After Ramp-Up Phase)
Strong CYP3A inhibitor	Contraindicated	Avoid inhibitor use or reduce the VENCLEXTA dose by at least 75%
Moderate CYP3A inhibitor	Avoid inhibitor use or reduce the VENCLEXTA dose by at least 50%	
P-gp inhibitor		

2.6 Missed Dose

If the patient misses a dose of VENCLEXTA within 8 hours of the time it is usually taken, the patient should 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 and should 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.

3 DOSAGE FORMS AND STRENGTHS

Table 6. VENCLEXTA Tablet Strength and Description

Tablet Strength	Description of Tablet
10 mg	Round, biconvex shaped, pale yellow film-coated tablet debossed with “V” on one side and “10” on the other side
50 mg	Oblong, biconvex shaped, beige film-coated tablet debossed with “V” on one side and “50” on the other side
100 mg	Oblong, biconvex shaped, pale yellow film-coated tablet debossed with “V” on one side and “100” on the other side

4 CONTRAINDICATIONS

Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during ramp-up phase is contraindicated *[see Dosage and Administration (2.5) and Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Tumor Lysis Syndrome

Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in previously treated CLL patients with high tumor burden when treated with VENCLEXTA *[see Adverse Reactions (6.1)]*.

VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5-week ramp-up phase. Changes in blood chemistries 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 tumor burden (see Table 2) and comorbidities. Reduced renal function (CrCl <80 mL/min) further increases the risk. Patients

should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases *[see Dosage and Administration (2.3, 2.4) and Use in Specific Populations (8.6)]*.

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors and P-gp inhibitors increases venetoclax exposure, may increase the risk of TLS at initiation and during ramp-up phase and may require VENCLEXTA dose adjustment *[see Dosage and Administration (2.5) and Drug Interactions (7.1)]*.

5.2 Neutropenia

Grade 3 or 4 neutropenia occurred in 41% (98/240) of patients treated with VENCLEXTA *[see Adverse Reactions (6.1)]*. Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for severe neutropenia. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF) *[see Dosage and Administration (2.4)]*.

5.3 Immunization

Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following VENCLEXTA therapy have not been studied. Advise patients that vaccinations may be less effective.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at the recommended dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight. There are no adequate and well-controlled studies in pregnant woman using VENCLEXTA. Advise females of reproductive potential to avoid pregnancy during treatment. If VENCLEXTA is used during pregnancy or if the patient becomes pregnant while taking VENCLEXTA, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following serious adverse events are discussed in greater detail in other sections of the labeling:

- Tumor Lysis Syndrome *[see Warnings and Precautions (5.1)]*
- Neutropenia *[see Warnings and Precautions (5.2)]*

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.

6.1 Clinical Trial Experience

The safety of single agent VENCLEXTA at the 400 mg recommended daily dose following a dose ramp-up schedule is based on pooled data of 240 patients with previously treated CLL from two phase 2 trials and one phase 1 trial. In the pooled dataset, the median age was 66 years (range: 29 to 85 years), 95% were white, and 69% were male. The median number of prior therapies was 3 (range: 1 to 12). The median duration of treatment with VENCLEXTA 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.

The most common adverse reactions (≥20%) of any grade were neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue.

Serious adverse reactions were reported in 43.8% of patients. The most frequent serious adverse reactions (≥2%) were pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia (AIHA), anemia, and TLS.

Discontinuations due to adverse reactions occurred in 8.3% of patients. The most frequent adverse reactions leading to drug discontinuation were thrombocytopenia and AIHA.

Dosage adjustments due to adverse reactions occurred in 9.6% of patients. The most frequent adverse reactions leading to dose adjustments were neutropenia, febrile neutropenia, and thrombocytopenia.

Adverse reactions reported in 3 trials of patients with previously treated CLL using single agent VENCLEXTA are presented in Table 7.

Table 7. Adverse Reactions Reported in ≥10% (Any Grade) or ≥5% (Grade 3 or 4) of Patients with CLL

Body System	Adverse Reaction	Any Grade (%) N=240	Grade 3 or 4 (%) N=240
Blood and lymphatic system disorders	Neutropenia[a]	45	41
	Anemia[b]	29	18
	Thrombocytopenia[c]	22	15
	Febrile neutropenia	5	5
Gastrointestinal disorders	Diarrhea	35	<1
	Nausea	33	<1
	Vomiting	15	<1
	Constipation	14	0
General disorders and administration site conditions	Fatigue	21	2
	Pyrexia	16	<1
	Peripheral edema	11	<1
Infections and infestations	Upper respiratory tract infection	22	1
	Pneumonia	8	5
Metabolic and nutrition disorders	Hypokalemia	12	4

Body System	Adverse Reaction	Any Grade (%) N=240	Grade 3 or 4 (%) N=240
Musculoskeletal and connective tissue disorders	Back pain	10	<1
Nervous system disorders	Headache	15	<1
Respiratory, thoracic, and mediastinal disorders	Cough	13	0
Adverse Reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0. [a]Neutropenia/neutrophil count decreased. [b]Anemia/hemoglobin decreased. [c]Thrombocytopenia/platelet count decreased.			

Tumor Lysis Syndrome

Tumor lysis syndrome is an important identified risk when initiating VENCLEXTA. In the initial Phase 1 dose-finding trials, which had shorter (2-3 week) ramp-up phase and higher starting dose, the incidence of TLS was 12% (9/77; 4 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 (2.2, 2.3)]*. 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 hospitalized 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 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 either met laboratory TLS criteria (laboratory abnormalities that met ≥2 of the following 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. The events 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.

Laboratory abnormalities relevant to TLS observed in 66 patients with CLL who followed the dose ramp-up schedule and TLS prophylaxis measures are presented in Table 8.

Table 8. Adverse Reactions of TLS and Relevant Laboratory Abnormalities Reported in Patients with CLL

Parameter	All Grades (%) N=66	Grade ≥3 (%) N=66
Laboratory TLS[a]	6	6

Parameter	All Grades (%) N=66	Grade ≥3 (%) N=66
Hyperkalemia[b]	20	2
Hyperphosphatemia[c]	15	3
Hypocalcemia[d]	9	3
Hyperuricemia[e]	6	2

[a]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.
[b]Hyperkalemia/blood potassium increased.
[c]Hyperphosphatemia/blood phosphorus increased.
[d]Hypocalcemia/blood calcium decreased.
[e]Hyperuricemia/blood uric acid increased.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on VENCLEXTA

Venetoclax is predominantly metabolized by CYP3A4/5.

Strong CYP3A Inhibitors

Concomitant use of VENCLEXTA with strong CYP3A inhibitors (e.g., ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole and voriconazole) at initiation and during ramp-up phase is contraindicated *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

For patients who have completed the ramp-up phase and are on a steady daily dose of VENCLEXTA, reduce the VENCLEXTA dose by at least 75% when used concomitantly with strong CYP3A inhibitors. Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor *[see Dosage and Administration (2.4, 2.5) and Clinical Pharmacology (12.3)]*.

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

Moderate CYP3A Inhibitors and P-gp Inhibitors

Avoid concomitant use of moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil) or P-gp inhibitors (e.g., amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor) with VENCLEXTA. Consider alternative treatments. If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the VENCLEXTA dose by at least 50%. Monitor patients more closely for signs of VENCLEXTA toxicities *[see Dosage and Administration (2.4, 2.5) and Clinical Pharmacology (12.3)]*.

Resume the VENCLEXTA dose that was used prior to initiating the CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

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

Co-administration of a single dose of rifampin, a P-gp inhibitor, increased venetoclax C_{max} by 106% and AUC_{∞} by 78%.

CYP3A Inducers

Avoid concomitant use of VENCLEXTA with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin). Consider alternative treatments with less CYP3A induction *[see Clinical Pharmacology (12.3)]*.

Co-administration of multiple doses of rifampin, a strong CYP3A inducer, decreased venetoclax C_{max} by 42% and AUC_{∞} by 71%.

7.2 Effects of VENCLEXTA on Other Drugs

Warfarin

In a drug-drug interaction study in healthy subjects, administration of a single dose of venetoclax with 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 normalized ratio (INR) be monitored closely in patients receiving warfarin.

P-gp substrates

In vitro data suggest venetoclax has inhibition potential on P-gp substrates at therapeutic dose levels in the gut. 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data on the use of VENCLEXTA in pregnant women. Based on toxicity observed in mice, VENCLEXTA may cause fetal harm when administered to pregnant women. In mice, venetoclax was fetotoxic at exposures 1.2 times the human clinical exposure based on AUC at the recommended human dose of 400 mg daily. If VENCLEXTA is used during pregnancy or if the patient becomes pregnant while taking VENCLEXTA, the patient should be apprised of the potential risk to a fetus.

The background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal data

In embryo-fetal development studies, venetoclax was administered to pregnant mice and rabbits during the period of organogenesis. 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 of 400 mg daily). No teratogenicity was observed in either the mouse or the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of VENCLEXTA in human milk, the effects of VENCLEXTA on the breastfed child, or the effects of VENCLEXTA on milk production. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in breastfed infants from VENCLEXTA is unknown, advise nursing women to discontinue breastfeeding during treatment with VENCLEXTA.

8.3 Females and Males of Reproductive Potential

VENCLEXTA may cause fetal harm *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)]*.

Pregnancy Testing

Females of reproductive potential should undergo pregnancy testing before initiation of VENCLEXTA *[see Use in Specific Populations (8.1)]*.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last dose *[see Use in Specific Populations (8.1)]*.

Infertility

Based on findings in animals, male fertility may be compromised by treatment with VENCLEXTA *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

Of the 106 patients with previously treated CLL with 17p deletion who were evaluated for efficacy, 57% were ≥65 years of age and 17% were ≥75 years of age.

Of the 240 patients with previously treated CLL evaluated for safety from 3 open-label trials, 58% were ≥65 years of age and 17% were ≥75 years of age.

No overall differences in safety and effectiveness were observed between older and younger patients.

8.6 Renal Impairment

Patients with reduced renal function (CrCl <80 mL/min) are at increased risk of TLS. These patients may require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with VENCLEXTA *[see Dosage and Administration (2.3, 2.4)]*.

No specific clinical trials have been conducted in subjects with renal impairment. 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 results of the population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been determined for patients with severe renal impairment (CrCl <30 mL/min) or patients on dialysis.

8.7 Hepatic Impairment

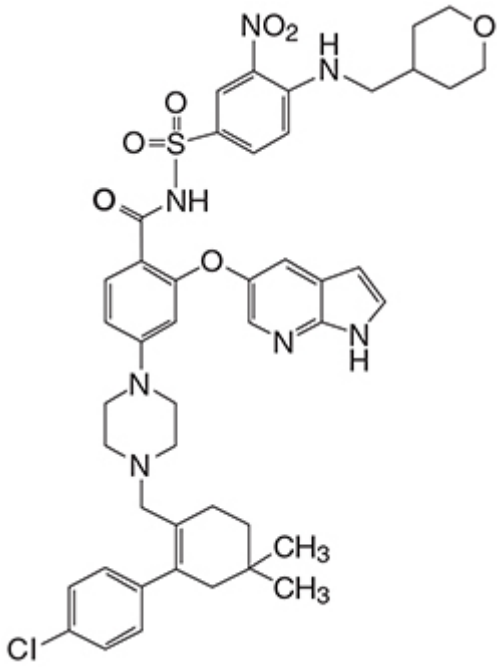
No specific clinical trials have been conducted in subjects with hepatic impairment, however human mass balance study showed that venetoclax undergoes hepatic elimination. Although no dose adjustment is recommended in patients with mild or moderate hepatic impairment based on results of the population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*, a trend for increased adverse events was observed in patients with moderate hepatic impairment; monitor these patients more closely for signs of toxicity during the initiation and dose ramp-up phase. A recommended dose has not been determined for patients with severe hepatic impairment.

10 OVERDOSAGE

There is no specific antidote for VENCLEXTA. For patients who experience overdose, closely monitor and provide appropriate supportive treatment; during ramp-up phase interrupt VENCLEXTA and monitor carefully for signs and symptoms of TLS along with other toxicities *[see Dosage and Administration (2.3, 2.4)]*. Based on venetoclax large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax.

11 DESCRIPTION

Venetoclax is a selective inhibitor of BCL-2 protein. It is a light yellow to dark yellow solid with the empirical formula $C_{45}H_{50}ClN_7O_7S$ and a molecular weight of 868.44. Venetoclax has very low aqueous solubility. 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) and has the following chemical structure:



VENCLEXTA tablets for oral administration are supplied as pale yellow or beige tablets that contain 10, 50, or 100 mg venetoclax as the active ingredient. Each tablet also contains the following inactive ingredients: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic. In addition, the 10 mg and 100 mg coated tablets include the following: iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide. The 50 mg coated tablets also include the following: iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, talc, polyethylene glycol and titanium dioxide. Each tablet is debossed with “V” on one side and “10”, “50” or “100” corresponding to the tablet strength on the other side.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Venetoclax is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics. 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 permeabilization and the activation of caspases. In nonclinical studies, venetoclax has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2.

12.2 Pharmacodynamics

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 hematologic

malignancies. VENCLEXTA had no large effect on QTc interval (i.e., > 20 ms) and there was no relationship between venetoclax exposure and change in QTc interval.

12.3 Pharmacokinetics

Absorption

Following multiple oral administrations under fed conditions, maximum plasma concentration of venetoclax was reached 5-8 hours after dose. Venetoclax steady state AUC increased proportionally over the dose range of 150-800 mg. Under low-fat meal conditions, venetoclax mean (± standard deviation) steady state C_{max} was 2.1 ± 1.1 µg/mL and AUC_{0-24} was 32.8 ± 16.9 µg•h/mL at the 400 mg once daily dose.

Food Effect

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 (2.2)]*.

Distribution

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

Elimination

The population estimate for the terminal elimination half-life of venetoclax was approximately 26 hours. The pharmacokinetics of venetoclax does not change over time.

Metabolism

In vitro studies demonstrated that venetoclax is predominantly metabolized by CYP3A4/5. 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*.

Excretion

After single oral administration of 200 mg radiolabeled [^{14}C]-venetoclax dose to healthy subjects, >99.9% of the dose was recovered in feces and <0.1% of the dose was excreted in urine within 9 days, indicating that hepatic elimination is responsible for the clearance of venetoclax from the systemic circulation. Unchanged venetoclax accounted for 20.8% of the administered radioactive dose excreted in feces.

Special Populations

Age, Race, Sex, and Weight

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

Renal Impairment

Based on a population pharmacokinetic analysis that included 211 subjects with mild renal impairment (CrCl ≥60 and <90 mL/min, calculated by Cockcroft-Gault equation), 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 Use in Specific Populations (8.6)]*.

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 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 times ULN. The pharmacokinetics of venetoclax has not been studied in subjects with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

Drug Interactions

Ketoconazole

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 *[see Drug Interactions (7.1)]*.

Rifampin multiple doses

Co-administration of 600 mg once daily rifampin, a strong CYP3A inducer, for 13 days in 10 healthy subjects decreased venetoclax C_{max} by 42% and AUC_{∞} by 71% *[see Drug Interactions (7.1)]*.

Rifampin single dose

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% *[see Drug Interactions (7.1)]*.

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.

Warfarin

In a drug-drug interaction study in three healthy subjects, administration of a single 400 mg dose of venetoclax with 5 mg warfarin resulted in 18% to 28% increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin *[see Drug Interactions (7.2)]*.

In vitro Studies

In vitro studies indicated that venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations. Venetoclax is a weak inhibitor of CYP2C8, CYP2C9, and UGT1A1 *in vitro*, but it is not predicted to cause clinically relevant inhibition due to high plasma protein binding. Venetoclax is not an inhibitor of UGT1A4, UGT1A6, UGT1A9, or 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, co-administration of narrow therapeutic index P-gp substrates such as digoxin 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. Venetoclax is not expected to inhibit OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with venetoclax.

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 doses up to 835 mg/kg. The M27 metabolite was negative for genotoxic activity in *in vitro* Ames and chromosome aberration assays.

Fertility and early embryonic development studies were conducted in male and female mice. These studies evaluate mating, fertilization, and embryonic development through implantation. There were no effects of venetoclax on estrus cycles, mating, fertility, corpora lutea, uterine implants or live embryos per litter at dosages up to 600 mg/kg/day. However, a risk to human male fertility exists based on testicular toxicity (germ cell loss) observed in dogs at exposures as low as 0.5 times the human AUC exposure at the recommend dose.

13.2 Animal Toxicology and/or Pharmacology

In dogs, venetoclax caused single-cell necrosis in various tissues, including the gallbladder, exocrine pancreas, and stomach 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.

In addition, after approximately 3 months of daily dosing in dogs, venetoclax caused progressive white discoloration of the hair coat, due to loss of melanin pigment.

14 CLINICAL STUDIES

The efficacy of VENCLEXTA was established in an open-label, single-arm, multicenter clinical trial of 106 patients with CLL with 17p deletion who had received at least one prior therapy. In the study, 17p deletion was confirmed in peripheral blood specimens from patients using Vysis CLL FISH Probe Kit, which is FDA approved for selection of patients for VENCLEXTA treatment. Patients received VENCLEXTA via a weekly ramp-up schedule starting at 20 mg and ramping 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 efficacy of VENCLEXTA was evaluated by overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008).

Table 9 summarizes the baseline demographic and disease characteristics of the study population.

Table 9. Baseline Patient Characteristics

Characteristics	N=106
Age, years; median (range)	67 (37-83)
White; %	97.1
Male; %	65.1
ECOG performance status; % 0 1 2	 39.6 51.9 8.5
Tumor burden; % Absolute lymphocyte count ≥25 x 10^9/L One or more nodes ≥5 cm	 50.0 52.8
Number of prior therapies; median (range)	2.5 (1-10)
Time since diagnosis, months; median (range)[a]	79.4 (1.2-385.6)
[a]N=105.	

The median time on treatment at the time of evaluation was 12.1 months (range: 0 to 21.5 months). Efficacy results are shown in Table 10.

Table 10. Efficacy Results for Patients with Previously Treated CLL with 17p Deletion by IRC

	VENCLEXTA N=106
ORR, n (%) (95% CI)	85 (80.2) (71.3, 87.3)
CR + CRi, n (%) CR, n (%) CRi, n (%)	8 (7.5) 6 (5.7) 2 (1.9)

	VENCLEXTA N=106
nPR, n (%)	3 (2.8)
PR, n (%)	74 (69.8)
CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete marrow recovery; IRC = independent review committee; nPR = nodular partial remission; ORR = overall response rate (CR + CRi + nPR + PR); PR = partial remission.	

The median time to first response was 0.8 months (range: 0.1 to 8.1 months). Median duration of response (DOR) has not been reached with approximately 12 months median follow-up. The DOR ranged from 2.9 to 19.0+ months.

Minimal residual disease (MRD) was evaluated in peripheral blood and bone marrow for patients who achieved CR or CRi, following treatment with VENCLEXTA. Three percent (3/106) were MRD negative in the peripheral blood and bone marrow (less than one CLL cell per 10^4 leukocytes).

16 HOW SUPPLIED/STORAGE AND HANDLING

VENCLEXTA is dispensed as follows:

Packaging Presentation	Number of Tablets	National Drug Code (NDC)
Starting Pack	Each pack contains four weekly wallet 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)	0074-0579-28
10 mg Wallet	14 x 10 mg tablets	0074-0561-14
50 mg Wallet	7 x 50 mg tablets	0074-0566-07
10 mg Unit Dose	2 x 10 mg tablets	0074-0561-11
50 mg Unit Dose	1 x 50 mg tablet	0074-0566-11
100 mg Unit Dose	1 x 100 mg tablet	0074-0576-11
100 mg Bottle	120 x 100 mg tablets	0074-0576-22

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

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

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

Store at or below 86°F (30°C).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- **Tumor Lysis Syndrome**
  Advise patients of the potential risk of TLS, particularly at treatment initiation and during ramp-up phase, and to immediately report any signs and symptoms associated with this event (fever, chills, nausea, vomiting, confusion, shortness of breath, seizure, irregular heartbeat, dark or cloudy urine, unusual tiredness, muscle pain, and/or joint discomfort) to their doctor for evaluation *[see Warnings and Precautions (5.1)]*.

  Advise patients to be adequately hydrated every day when taking VENCLEXTA to reduce the risk of TLS. The recommended volume is 6 to 8 glasses (approximately 56 ounces total) of water each day. Patients should drink water starting 2 days before and on the day of the first dose, and every time the dose is increased *[see Dosage and Administration (2.3)]*.

  Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Dosage and Administration (2.3)]*.

  Advise patients that it may be necessary to take VENCLEXTA in the presence of a doctor to allow monitoring for TLS.
- **Neutropenia**
  Advise patients to contact their doctor immediately if they develop a fever or any signs of infection. Advise patients of the need for periodic monitoring of blood counts *[see Warnings and Precautions (5.2)]*.
- **Drug Interactions**
  Advise patients to avoid consuming grapefruit products, Seville oranges, or starfruit during treatment with VENCLEXTA. Advise patients that VENCLEXTA may interact with some drugs; therefore, advise patients to inform their doctor of the use of any prescription medication, over-the-counter drugs, vitamins and herbal products *[see Contraindications (4) and Drug Interactions (7.1)]*.
- **Immunizations**
  Advise patients to avoid vaccination with live vaccines because they may not be safe or effective during treatment with VENCLEXTA *[see Warnings and Precautions (5.3)]*.
- **Pregnancy and Lactation**
  Advise women of the potential risk to the fetus and to avoid pregnancy during treatment with VENCLEXTA. Advise female patients of reproductive potential to use effective contraception during therapy and for at least 30 days after completing of therapy. Advise females to contact their doctor if they become pregnant, or if pregnancy is suspected, during treatment with VENCLEXTA. Also advise patients not to breastfeed while taking

VENCLEXTA *[see Warnings and Precautions (5.4), and Use in Specific Populations (8.1, 8.2, and 8.3)]*.

- **Male Infertility**
  Advise patients of the possibility of infertility and possible use of sperm banking for males of reproductive potential *[see Use in Specific Populations (8.3)]*.

Instructions for Taking VENCLEXTA

Advise patients to take VENCLEXTA exactly as prescribed and not to change their dose or to stop taking VENCLEXTA unless they are told to do so by their doctor. Advise patients to take VENCLEXTA orally once daily, at approximately the same time each day, according to their doctor's instructions and that the tablets should be swallowed whole with a meal and water without being chewed, crushed, or broken *[see Dosage and Administration (2.2)]*.

Advise patients to keep VENCLEXTA in the original packaging during the first 4 weeks of treatment, and not to transfer the tablets to a different container.

Advise patients that if a dose of VENCLEXTA is missed by less than 8 hours, to take the missed dose right away and take the next dose as usual. If a dose of VENCLEXTA is missed by more than 8 hours, advise patients to wait and take the next dose at the usual time *[see Dosage and Administration (2.6)]*.

Advise patients not to take any additional dose that day if they vomit after taking VENCLEXTA, and to take the next dose at the usual time the following day.

Manufactured and Marketed by:
AbbVie Inc.
North Chicago, IL 60064

and

Marketed by:
Genentech USA, Inc.

A Member of the Roche Group
South San Francisco, CA 94080-4990

03-B232 April 2016

MEDICATION GUIDE
VENCLEXTA™ (ven-KLEKS-tuh)
(venetoclax)
tablets

What is the most important information I should know about VENCLEXTA?

VENCLEXTA can cause serious side effects, including:

Tumor lysis syndrome (TLS). TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure, the need for dialysis treatment, and may lead to death. Your doctor will do tests to check your risk of getting TLS before you start taking VENCLEXTA. You will receive other medicines before starting and during treatment with VENCLEXTA to help reduce your risk of TLS. You may also need to receive intravenous (IV) fluids into your vein. Your doctor will do blood tests in your first 5 weeks of treatment to check you for TLS during treatment with VENCLEXTA. It is important to keep your appointments for blood tests. Tell your doctor right away if you have any symptoms of TLS during treatment with VENCLEXTA, including:

- fever
- chills
- nausea
- vomiting
- confusion
- shortness of breath
- seizures
- irregular heartbeat
- dark or cloudy urine
- unusual tiredness
- muscle or joint pain

Drink plenty of water when taking VENCLEXTA to help reduce your risk of getting TLS. Drink 6 to 8 glasses (about 56 ounces total) of water each day, starting 2 days before your first dose, on the day of your first dose of VENCLEXTA, and each time your dose is increased.

Your doctor may delay, decrease your dose, or stop treatment with VENCLEXTA if you have side effects.

See "**What are the possible side effects of VENCLEXTA?**" for more information about side effects.

What is VENCLEXTA?

VENCLEXTA is a prescription medicine used to treat people with chronic lymphocytic leukemia (CLL) with 17p deletion, who have received at least one prior treatment.

It is not known if VENCLEXTA is safe and effective in children.

Who should not take VENCLEXTA?

Certain medicines must not be taken when you first start taking VENCLEXTA and while your dose is being slowly increased.

- **Tell your doctor about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. VENCLEXTA and other medicines may affect each other causing serious side effects.
- Do not start new medicines during treatment with VENCLEXTA without first talking with your doctor.

What should I tell my doctor before taking VENCLEXTA?

Before taking VENCLEXTA, tell your doctor about all of your medical conditions, including if you:

- have kidney or liver problems
- have problems with your body salts or electrolytes, such as potassium, phosphorus, or calcium
- have a history of high uric acid levels in your blood or gout
- are scheduled to receive a vaccine. You should not receive a “live vaccine” before, during, or after treatment with VENCLEXTA, until your doctor tells you it is okay. If you are not sure about the type of immunization or vaccine, ask your doctor. These vaccines may not be safe or may not work as well during treatment with VENCLEXTA.
- are pregnant or plan to become pregnant. VENCLEXTA may harm your unborn baby. If you are able to become pregnant, your doctor should do a pregnancy test before you start treatment with VENCLEXTA. Females who are able to become pregnant should use effective birth control during treatment and for 30 days after the last dose of VENCLEXTA. If you become pregnant or think you are pregnant, tell your doctor right away.
- are breastfeeding or plan to breastfeed. It is not known if VENCLEXTA passes into your breast milk. Do not breastfeed during treatment with VENCLEXTA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. VENCLEXTA and other medicines may affect each other causing serious side effects. See **"Who should not take VENCLEXTA?"**

How should I take VENCLEXTA?

- Take VENCLEXTA exactly as your doctor tells you to take it. Do not change your dose of VENCLEXTA or stop taking VENCLEXTA unless your doctor tells you to.
- When you first take VENCLEXTA:
  - You may need to take VENCLEXTA at the hospital or clinic to monitor for TLS.
  - Your doctor will start VENCLEXTA at a low dose. Your dose will be slowly increased weekly over 5 weeks up to the full dose. Read the Quick Start Guide that comes with VENCLEXTA before your first dose.
- Follow the instructions about drinking water described in the section of this Medication Guide about TLS called **"What is the most important information I should know about VENCLEXTA?"** and also in the Quick Start Guide.
- Take VENCLEXTA 1 time a day with a meal and water at about the same time each day.
- Swallow VENCLEXTA tablets whole. Do not chew, crush, or break the tablets.
- If you miss a dose of VENCLEXTA and it has been less than 8 hours, take your dose as soon as possible. If you miss a dose of VENCLEXTA and it has been more than 8 hours, skip the missed dose and take the next dose at your usual time.
- If you vomit after taking VENCLEXTA, do not take an extra dose. Take the next dose at your usual time the next day.

What should I avoid while taking VENCLEXTA?

- You should not drink grapefruit juice, eat grapefruit, Seville oranges (often used in marmalades), or starfruit while you are taking VENCLEXTA. These products may increase the amount of VENCLEXTA in your blood.

What are the possible side effects of VENCLEXTA?

VENCLEXTA can cause serious side effects, including:

- **See "What is the most important information I should know about VENCLEXTA?"**
- **Low white blood cell count (neutropenia).** Low white blood cell counts are common with VENCLEXTA, but can also be severe. Your doctor will do blood tests to check your blood counts during treatment with VENCLEXTA. Tell your doctor right away if you have a fever or any signs of an infection while taking VENCLEXTA.

The most common side effects of VENCLEXTA include:

- diarrhea
- nausea
- low red blood cell count
- upper respiratory tract infection
- low platelet count
- feeling tired

VENCLEXTA may cause fertility problems in males. This may affect your ability to father a child. Talk to your doctor if you have concerns about fertility.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of VENCLEXTA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VENCLEXTA?

- Store VENCLEXTA at or below 86°F (30°C).
- Keep VENCLEXTA tablets in the original package during the first 4 weeks of treatment. **Do not** transfer the tablets to a pillbox or other container.

Keep VENCLEXTA and all medicines out of reach of children.

General information about the safe and effective use of VENCLEXTA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VENCLEXTA for a condition for which it was not prescribed. Do not give VENCLEXTA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about VENCLEXTA that is written for health professionals.

What are the ingredients in VENCLEXTA?

Active ingredient: venetoclax

Inactive ingredients: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic. The 10 mg and 100 mg coated tablets also include the following: iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide. The 50 mg coated tablets also include the following: iron oxide yellow, iron oxide red, iron oxide black, polyvinvyl alcohol, talc, polyethylene glycol, and titanium dioxide.

Manufactured and Marketed by: AbbVie Inc. North Chicago, IL 60064

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A member of the Roche Group South San Francisco, CA 94080-4990

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 04/2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
04/11/2016