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PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA

Venetoclax–Acalabrutinib Dosing Regimen

This is a medical resource for scientific information and is intended for healthcare providers practicing in the United States

Current as of February 2026

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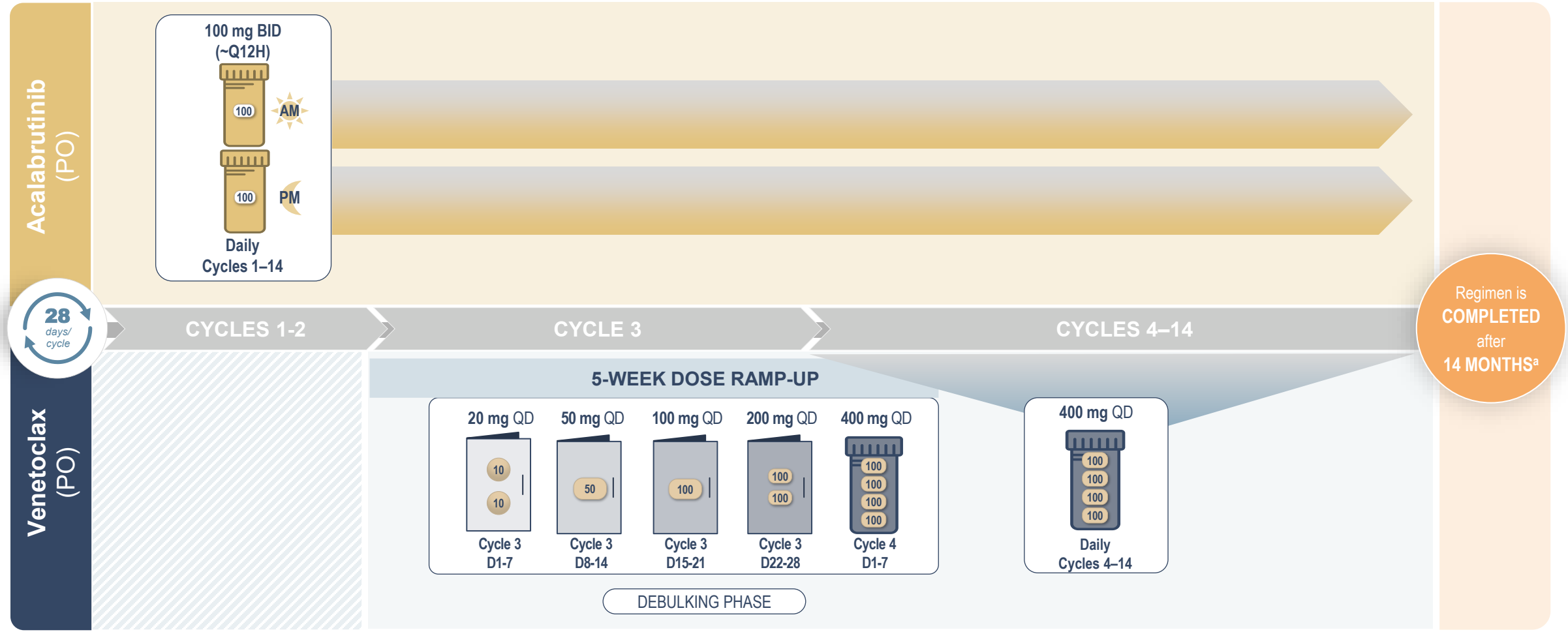
VENETOCLAX–ACALABRUTINIB DOSING SCHEDULE OVERVIEW



Graphic is not to scale. Each cycle is 28 days.
[a]From Cycle 1, Day 1, of acalabrutinib.
BID=twice a day; D=day; PO=oral; QD=once daily; Q12H=every 12 hours.
1.. Acalabrutinib [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2026

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ACALABRUTINIB DOSING

CYCLES 1 THROUGH 14: ACALABRUTINIB DOSING

Recommended dose of acalabrutinib is 100mg orally approximately every 12 hours until disease progression, unacceptable toxicity, or completion of the 14 cycles of treatment

Administration instructions:

- Swallow tablet whole with water. (Do not chew, crush, dissolve or cut the tablets
- May be taken with or without food
- If a dose of acalabrutinib is missed by more than 3 hours, skip and take next dose at the regularly scheduled time
- Do NOT take extra tables of acalabrutinib to make up for a missed dose

See full Acalabrutinib prescribing information for additional information.

[a]From Cycle 1, Day 1, of acalabrutinib. BID=twice a day; PO=oral.

1. Acalabrutinib [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2026.

WARNINGS AND PRECAUTIONS

INFECTIONS

Fatal and serious infections, including **opportunistic infections**, have occurred in patients with hematological malignancies treated with acalabrutinib.

Management
Consider prophylaxis in patients at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

HEMORRHAGIC EVENTS

Fatal and serious hemorrhagic events have occurred in patients treated with acalabrutinib. Use of **antithrombotic agents concomitantly** with acalabrutinib may further **increase the risk of hemorrhage**.

Management
Consider the **risks and benefits** of antithrombotic agents when co-administered with acalabrutinib. Monitor patients for signs of bleeding.

Consider the benefit-risk of withholding acalabrutinib for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

CYTOPENIAS

Acalabrutinib can cause **Grade 3 or 4 cytopenias**.

Management
Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted.

SECOND PRIMARY MALIGNANCIES

Second primary malignancies, including **skin cancers and other solid tumors**, and fatal events have occurred in patients exposed to acalabrutinib in clinical trials.

Management
Monitor patients for the development of second cancers and advise protection from sun exposure.

CARDIAC ARRHYTHMIAS

Fatal and serious cardiac arrhythmias have occurred in patients treated with acalabrutinib. The risk of arrhythmias may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection.

Management
Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

HEPATOTOXICITY

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of **DILI,** has occurred in patients treated with BTKi's, including acalabrutinib.

Management
Evaluate bilirubin and transaminases at baseline and throughout treatment. For patients who develop abnormal liver tests, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold acalabrutinib. Upon confirmation of DILI, discontinue acalabrutinib.

WARNING AND PRECAUTIONS: See full prescribing information for additional information.

DILI=drug-induced liver injury; HBV=hepatitis B virus; PCP=*Pneumocystis jirovecii* pneumonia.

1. Acalabrutinib [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2026.

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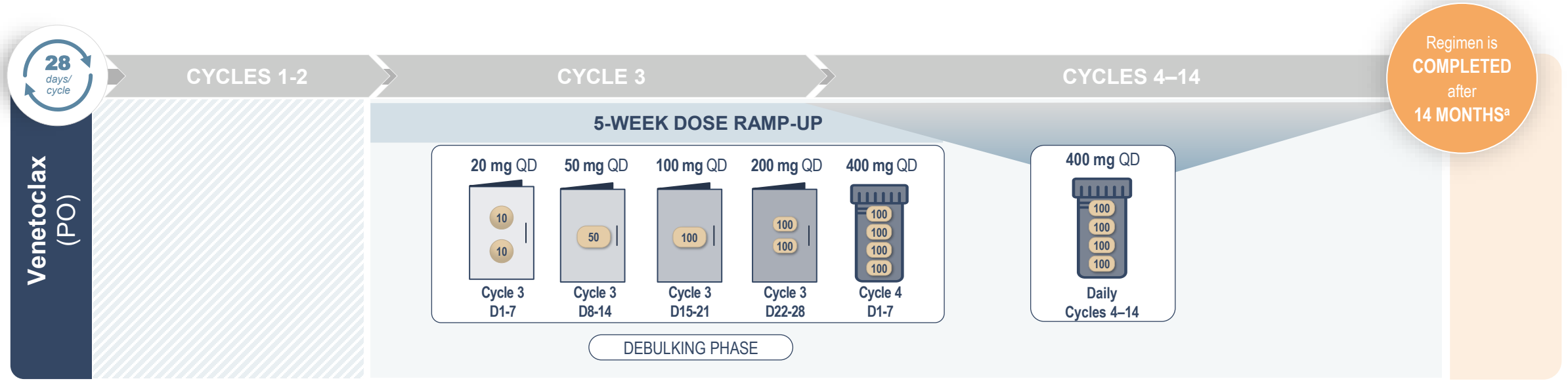
VENETOCLAX DOSING

VENETOCLAX RAMP-UP



Start with the 5-week ramp up on Cycle 3 Day 1. After completing the ramp up, the recommended dose of Venetoclax is 400mg orally once daily until disease progression, unacceptable toxicity or until the last day of Cycle 14

Administration instructions:

- Swallow tablets whole with water (Do not chew, crush, or break tablets prior to swallowing)
- Take with a meal and water
- Take at approximately the same time each day
- If the patient misses a dose within 8 hours of the time it is usually taken, take as soon as possible and resume the normal dosing schedule
- If the patient misses a dose by more than 8 hours, do NOT take the missed dose and resume the normal dosing schedule
- If patient vomits following dosing, do NOT take an additional dose, take the next dose at the usual time

Preparing for Venetoclax Ramp-Up | Tumor Burden and TLS Risk Assessment | Venetoclax Ramp-Up: Low or Medium Tumor Burden/TLS Risk | Venetoclax Ramp-Up: High Tumor Burden/TLS Risk

[a]Following the 2 cycle acalabrutinib initiation and including the 5-week venetoclax ramp up for a total of 12 cycles of venetoclax + acalabrutinib

1. Venclexta (venetoclax) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2026.

PREPARING FOR VENETOCLAX RAMP-UP

All patients

TLS risk assessment

Reassess tumor burden (repeat ALC) and recategorize TLS risk as appropriate

Hydration

Ensure adequate hydration every day during venetoclax ramp-up and with resumption after an interruption

Blood chemistry

Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities

Drug interactions

Determine if the patient is taking any medications that interact with venetoclax, which may require an alternative medication or venetoclax dose modification

Patients with hepatic impairment (Child-Pugh class C)

Dose modification

Determine if venetoclax daily dose should be reduced by 50% for patients with hepatic impairment

- Low/medium tumor burden/TLS risk
- High tumor burden/TLS risk

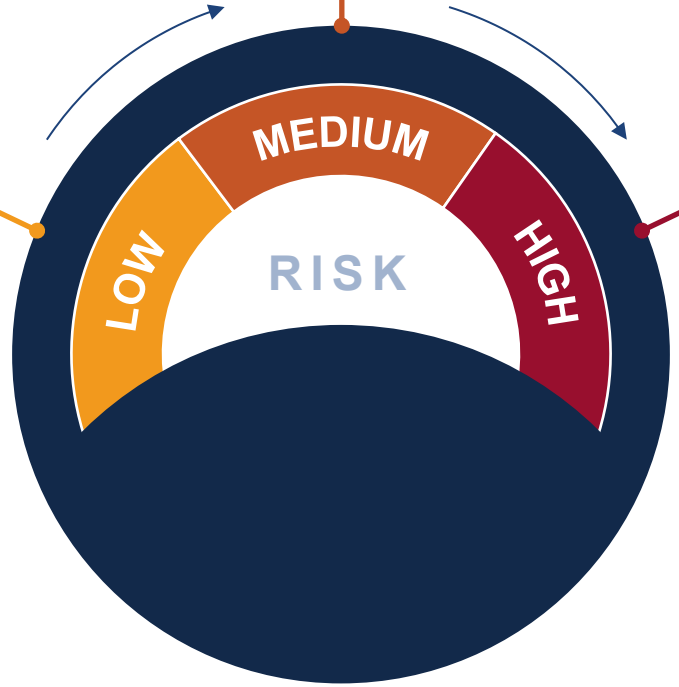
Click for details on prophylaxis and monitoring by tumor burden/TLS risk.

ALC=absolute lymphocyte count; TLS=tumor lysis syndrome.

1. Venclexta (venetoclax) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2026.

TUMOR BURDEN AND TLS RISK ASSESSMENT

Any lymph nodes 5 cm to <10 cm
OR
ALC ≥25×10⁹/L



All lymph nodes <5 cm
AND
ALC <25×10⁹/L

Any lymph node ≥10 cm
OR
Any lymph node ≥5 cm
AND **ALC ≥25×10⁹/L**

1. Venclexta (venetoclax) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2026. 2. Seymour JF, et al. *N Engl J Med.* 2018;378:1107–1120 (protocol).

VENETOCLAX RAMP-UP: LOW OR MEDIUM TUMOR BURDEN/TLS RISK

5-WEEK DOSE RAMP-UP

	Week 1	Week 2	Week 3	Week 4	Week 5
	20 mg QD	50 mg QD	100 mg QD	200 mg QD	400 mg QD
TLS prophylaxis					
Hydration	1.5–2.0 L/d PO[a] throughout the ramp-up phase beginning **at least** 2 days prior to and continuing for at least 24 hours after the first dose of each dose level. **For patients with medium tumor burden:** Consider IV hydration in addition to oral hydration during outpatient stay for the first doses of 20 mg and 50 mg.				
Antihyperuricemic	Allopurinol 300 mg/d beginning **at least** 2 days prior to initiation of venetoclax and continuing until ramp-up is completed.				
Laboratory monitoring on the first day of each dose level					
Setting	Outpatient **For patients with medium tumor burden and CrCl <80 mL/min:** Consider hospitalization for the first venetoclax doses of 20 mg and 50 mg. For these patients, follow the TLS prophylaxis and monitoring plan for high tumor burden.				
Blood chemistry tests	Predose, 6−8 hours, and 24 hours	Predose, 6−8 hours, and 24 hours	Predose	Predose	Predose

[a]Administer IV hydration to any patient who cannot tolerate oral hydration.
CrCl=creatinine clearance.
Venclexta (venetoclax) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2026.

VENETOCLAX RAMP-UP: HIGH TUMOR BURDEN/TLS RISK

5-WEEK DOSE RAMP-UP

	20 mg QD Week 1	50 mg QD Week 2	100 mg QD Week 3	200 mg QD Week 4	400 mg QD Week 5
TLS prophylaxis					
Hydration	1.5–2.0 L/d PO[a] throughout the ramp-up phase beginning **at least** 2 days prior to and continuing for at least 24 hours after the first dose of each dose level. *AND* IV hydration 150−200 mL/h as tolerated prior to the first dose of each dose level.				
Antihyperuricemic	Allopurinol 300 mg/d beginning **at least** 2 days prior to initiation of venetoclax and continuing until ramp-up is completed. Consider rasburicase for elevated uric acid (>8 mg/dL).				
Laboratory monitoring on the first day of each dose level					
Setting	Hospital		Outpatient		
Blood chemistry tests	Predose, 4, 8, 12, and 24 hours	Predose, 4, 8, 12, and 24 hours	Predose, 8 hours, and 24 hours	Predose, 8 hours, and 24 hours	Predose, 8 hours, and 24 hours

[a]Administer IV hydration to any patient who cannot tolerate oral hydration.

1. Venclexta (venetoclax) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2026. 2. Seymour JF, et al. *N Engl J Med.* 2018;378:1107–1120 (protocol).

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DOSE MODIFICATIONS FOR DRUG INTERACTIONS AND ADVERSE REACTIONS

ACALABRUTINIB DOSE MODIFICATIONS FOR DRUG INTERACTIONS

COADMINISTERED DRUG	RECOMMENDATION
Strong CYP3A inhibitor	Avoid co-administration If these inhibitors will be used short-term, interrupt acalabrutinib - After discontinuation of inhibitor for at least 24 hours, resume previous dose of acalabrutinib
Moderate CYP3A inhibitor	Reduce acalabrutinib dose to 100 mg once daily
Strong CYP3A inducer	Avoid co-administration If co-administration is unavoidable, increase acalabrutinib dosage to 200 mg every 12 hours

See full Acalabrutinib prescribing information for additional information.

CYP3A=cytochrome P450, family 3, subfamily A.

Acalabrutinib [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2026.

VENETOCLAX DOSE MODIFICATIONS FOR DRUG INTERACTIONS

COADMINISTERED DRUG	INITIATION AND RAMP-UP PHASE	STEADY DAILY DOSE (post ramp-up phase)[a]
Posaconazole	Contraindicated	Reduce to 70 mg
Other strong CYP3A inhibitor	Contraindicated	Reduce to 100 mg
Moderate CYP3A inhibitor	Reduce by at least 50%	Reduce by at least 50% (to 200 mg or less)
P-gp inhibitor	Reduce by at least 50%	Reduce by at least 50% (to 200 mg or less)

[a]Consider alternative medications or reduce the venetoclax dose as described.
CYP3A=cytochrome P450, family 3, subfamily A; P-gp=P-glycoprotein.
Venclexta (venetoclax) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2026.

DOSE MODIFICATIONS FOR NEUTROPENIA[a]

ADVERSE EVENT	ADVERSE REACTION OCCURENCE	DOSE MODIFICATION
Grade 3 or 4 neutropenia with or without fever and/or infection; Grade 4 neutropenia lasting more than 7 days	First	• **Interrupt** venetoclax **and/or** acalabrutinib[b] • Once toxicity resolves to Grade ≤1 or baseline, **restart venetoclax and/or acalabrutinib at same dose**

	Second	• **Interrupt** venetoclax **and/or** acalabrutinib[b]
		• Once toxicity resolves to Grade ≤1 or baseline, **restart**
		  ○ **venetoclax at one lower dose level[c] and**
		  ○ **acalabrutinib at same dose**

	Subsequent	• **Withhold** venetoclax **and/or** acalabrutinib until toxicity resolves to Grade ≤1 or baseline[b] • **Clinical judgement of the treating physician should guide the management plan** of each patient based on the individual benefit/risk assessment

[a]For patients receiving venetoclax in combination with acalabrutinib.
[b]Growth factor may be used at physician discretion.
[c]See venetoclax USPI for dose level reductions details. (here)
Venclexta (venetoclax) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2026.

DOSE MODIFICATIONS FOR THROMBOCYTOPENIA[a]

ADVERSE EVENT	ADVERSE REACTION OCCURENCE	DOSE MODIFICATION
Grade 3 or 4 thrombocytopenia and/or bleeding[b]	First	• **Interrupt** venetoclax **and/or** acalabrutinib • When bleeding resolves and thrombocytopenia is Grade ≤1 or baseline without transfusion support for 5 consecutive days, **restart venetoclax and/or acalabrutinib at same dose**

	Second	• **Interrupt** acalabrutinib **and** venetoclax
		• When bleeding resolves and thrombocytopenia is Grade ≤1 or baseline, **restart**
		  ○ **venetoclax at one lower dose level[c] and**
		  ○ **acalabrutinib at same dose**

	Subsequent	• **Interrupt** venetoclax **and** acalabrutinib until resolution of bleeding and thrombocytopenia resolves to Grade ≤1 or baseline • **Restart venetoclax at one lower dose level and resume acalabrutinib at a reduced frequency of 100 mg once daily[c,d,e]**

[a]For patients receiving venetoclax in combination with acalabrutinib. [b]Platelets may be used at physician discretion.
[c]See venetoclax USPI for dose level reductions details. (here) [d]Acalabrutinib dose may be re-escalated at the discretion of the physician if patient tolerates a reduced dose for ≥4 weeks.
[e]Clinical judgment of the treating physician should guide the management plan of each patient based on the individual benefit/risk assessment for treatment with venetoclax in combination with acalabrutinib.
Venclexta (venetoclax) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2026.

DOSE MODIFICATIONS FOR TUMOR LYSIS SYNDROME (TLS)[a]

ADVERSE EVENT	ADVERSE REACTION OCCURENCE	DOSE MODIFICATION
Grade 3 or 4 tumor lysis syndrome (TLS)	First and Subsequent	• **If a subject experiences blood chemistry changes suggestive of TLS**, the following day's venetoclax and acalabrutinib dose should be withheld • **If resolved within 24 - 48 hours of last dose**, treatment can be resumed at the same dose • **For events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve**, venetoclax should be resumed at one lower dose level[b] ○ when resuming treatment after interruption due to TLS, monitor for TLS and provide prophylaxis

[a]For patients receiving venetoclax in combination with acalabrutinib.
[b]See venetoclax USPI for dose level reductions details.
Venclexta (venetoclax) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2026.

DOSE MODIFICATIONS FOR NON-HEMATOLOGIC EVENTS[a]

ADVERSE EVENT	ADVERSE REACTION OCCURENCE	DOSE MODIFICATION
Grade 3 other non-hematologic events[b]	First	• **Interrupt** venetoclax **and/or** acalabrutinib until toxicity resolves to Grade ≤1 • **Restart venetoclax and/or acalabrutinib at the same dose**
	Second	• **Interrupt** venetoclax **and/or** acalabrutinib until toxicity resolves to Grade ≤1 • **Clinical judgment of the treating physician should guide the management plan** of each patient based on the individual benefit/risk assessment
Grade 4 other non-hematologic events[b]	First	• **Interrupt** venetoclax **and/or** acalabrutinib until toxicity resolves to Grade ≤1 • **Restart venetoclax at one lower dose level[d] and restart acalabrutinib[c] at a reduced frequency of 100 mg once daily**
	Second	• **Interrupt** venetoclax **and/or** acalabrutinib until toxicity resolves to Grade ≤1 • **Clinical judgment of the treating physician should guide the management plan** of each patient based on the individual benefit/risk assessment

[a]For patients receiving acalabrutinib in combination with venetoclax.
[b]Certain treatment-emergent non-hematologic AEs (e.g., venous thromboembolic events) may be managed and become clinically stable following medical intervention but may not improve to Grade ≤1 according to the NCI CTCAE definitions; in such cases, if a subject is clinically stable, resumption of acalabrutinib may be possible based on clinical judgement of the treating physician. [c]Acalabrutinib dose may be re-escalated at the discretion of the physician if patient tolerates a reduced dose for ≥4 weeks. [d]See venetoclax USPI for dose level reductions details.
AE=adverse event.
Venclexta (venetoclax) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2026.

VENETOCLAX DOSE MODIFICATIONS FOR ADVERSE REACTIONS

Venetoclax dose at interruption, mg	Venetoclax restart dose, mg
400	300
300	200
200	100
100	50
50	20
20	10

- During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.
- If a dosage interruption lasts more than 1 week during the ramp-up phase or more than 2 weeks after completion of ramp-up, reassess the risk of TLS and determine whether reinitiation at a reduced dosage is necessary.

1. Venclexta (venetoclax) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2026.