CAMZYOS® (mavacamten) REMS

Education Program
for Healthcare Providers and Pharmacies

Bristol Myers Squibb™

3500-US-2300216 05/23

Welcome to the CAMZYOS® REMS Education Program for Healthcare Providers and Pharmacies

To prescribe CAMZYOS, healthcare providers must become certified in the CAMZYOS Risk Evaluation Mitigation Strategy (REMS), which includes reviewing this education program. Only certified healthcare providers are eligible to prescribe CAMZYOS to patients.

CAMZYOS can only be dispensed by certified pharmacies.

Patients must be enrolled in the CAMZYOS REMS to receive CAMZYOS.

CAMZYOS® Risk Information

Bristol Myers Squibb™

CAMZYOS® Indication and Mechanism of Action

Indication

CAMZYOS is a cardiac myosin inhibitor indicated for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms.

Mechanism of Action

Excess cross-bridge formation between myosin and actin and dysregulation of the super-relaxed state are mechanistic hallmarks of HCM.

CAMZYOS modulates the number of myosin heads that can enter “on actin” (power-generating) states, thus reducing the probability of force-producing (systolic) and residual (diastolic) cross-bridge formation. CAMZYOS shifts the overall myosin population towards an energy-sparing, recruitable, super-relaxed state. In HCM patients, myosin inhibition with CAMZYOS reduces dynamic left ventricular outflow tract (LVOT) obstruction and improves cardiac filling pressures.

BOXED WARNING:
Risk of Heart Failure Due to Systolic Dysfunction

CAMZYOS® reduces left ventricular ejection fraction (LVEF) and can cause heart failure due to systolic dysfunction.

Echocardiogram assessments of LVEF are required prior to and during treatment with CAMZYOS. Initiation of CAMZYOS in patients with LVEF<55% is not recommended.

Interrupt CAMZYOS if LVEF is <50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status.

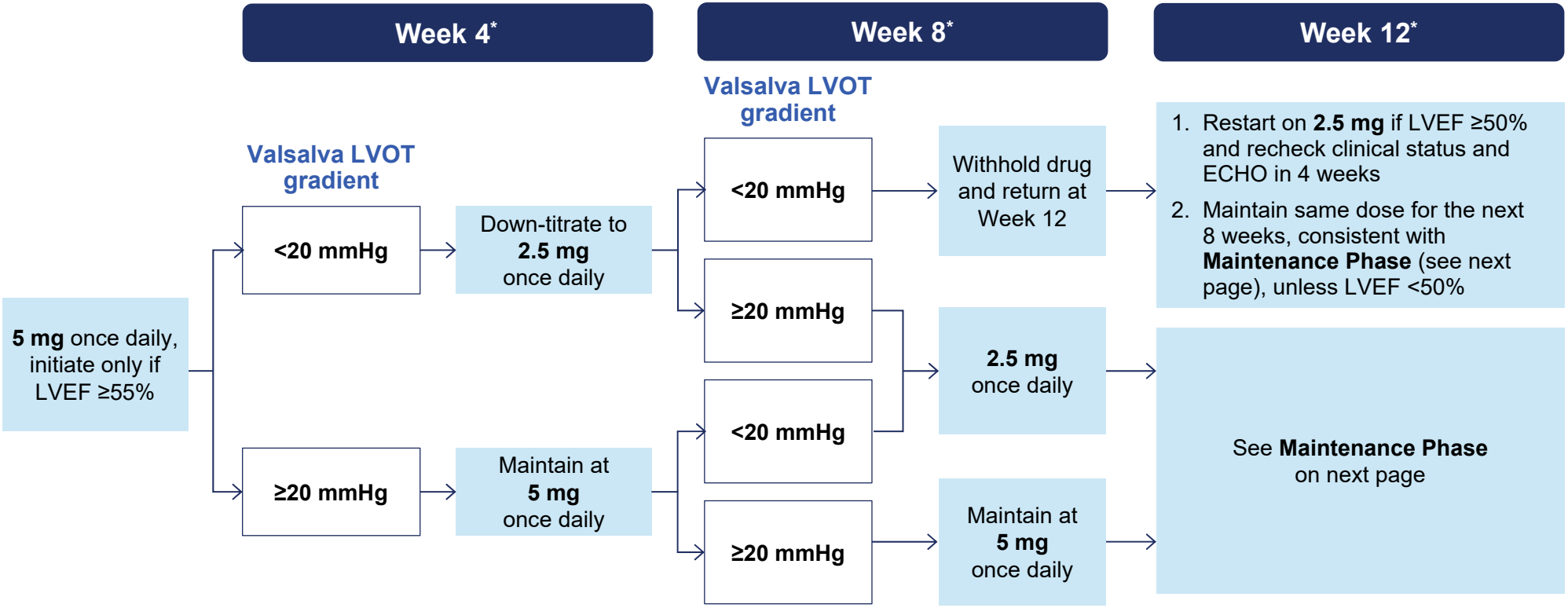
The Use of Echocardiography in CAMZYOS® Dosing and Administration

Regular LVEF and Valsalva LVOT gradient assessment is required for careful titration to achieve an appropriate target Valsalva LVOT gradient, while maintaining LVEF ≥50% and avoiding heart failure symptoms.

From the CAMZYOS Prescribing Information

- Initiation or up-titration of CAMZYOS in patients with LVEF <55% is not recommended
- When initiating or titrating CAMZYOS, first consider LVEF, then consider the Valsalva LVOT gradient and the patient's clinical status to guide appropriate CAMZYOS dosing. Follow the algorithms for **Initiation** and **Maintenance** (see next pages) for appropriate CAMZYOS dosing and monitoring schedules
- If LVEF <50% while taking CAMZYOS, interrupt treatment. Follow the algorithm for **Treatment Interruption** (see next pages) for guidance on interrupting, restarting, or discontinuing CAMZYOS
- Permanently discontinue treatment if LVEF <50% twice on 2.5 mg daily (the lowest dose level of CAMZYOS)

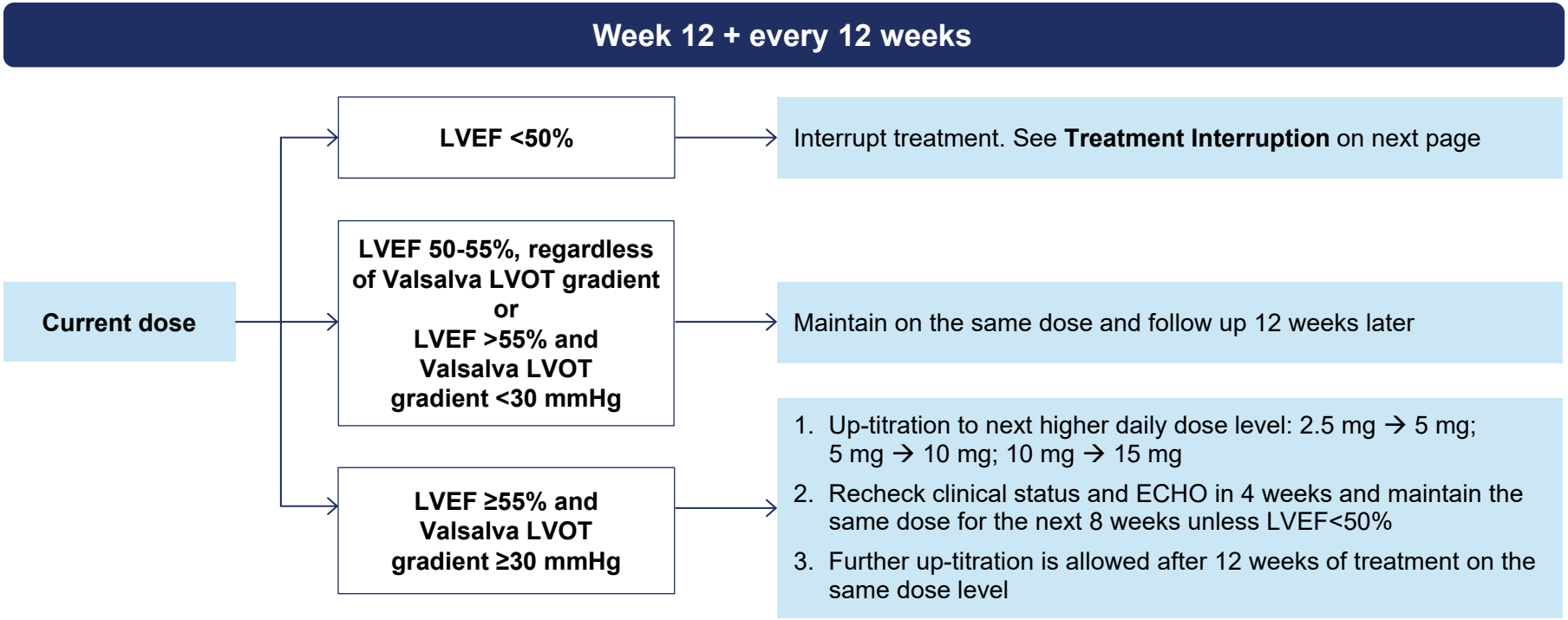
CAMZYOS® Dosing and Administration: Initiation Phase



* Interrupt treatment if LVEF <50% at any clinic visit; restart treatment after 4 weeks if LVEF ≥50%. See **Treatment Interruption.**

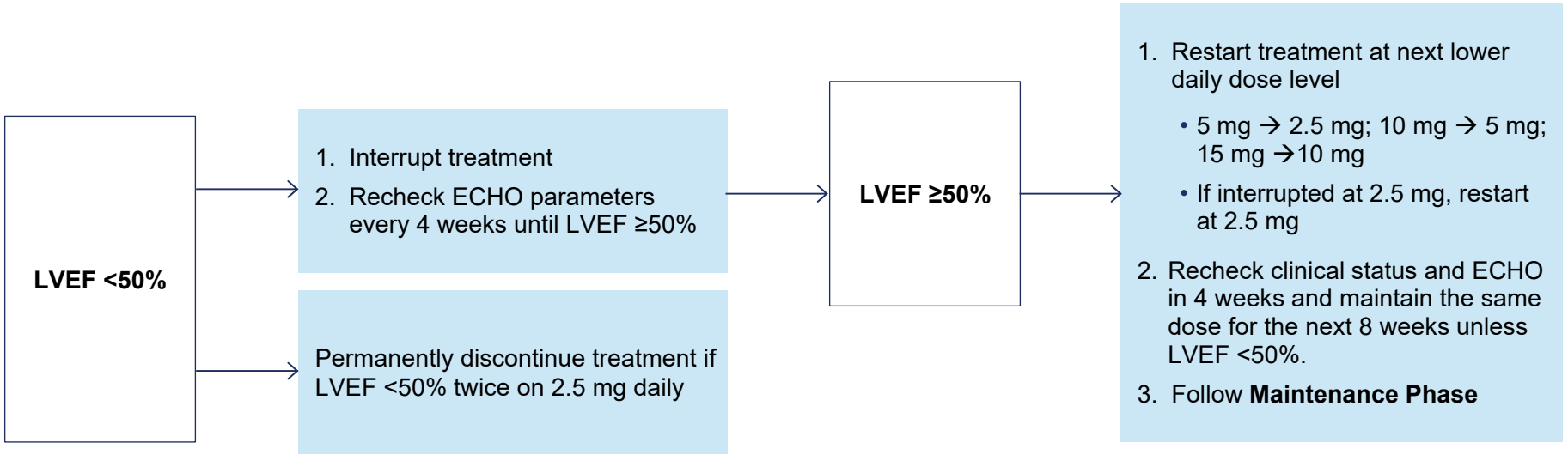
ECHO=echocardiogram; LVEF=left ventricular ejection fraction; LVOT=left ventricular outflow tract.

CAMZYOS® Dosing and Administration: Maintenance Phase



ECHO=echocardiogram; LVEF=left ventricular ejection fraction; LVOT=left ventricular outflow tract.

CAMZYOS® Dosing and Administration: Treatment Interruption At Any Clinical Visit If LVEF <50%



ECHO=echocardiogram; LVEF=left ventricular ejection fraction.

BOXED WARNING:
CYP 450 Drug Interactions Leading to Heart Failure or Loss of Effectiveness (I)

CAMZYOS® is primarily metabolized by cytochrome P450 (CYP) enzymes CYP2C19 and (to a lesser extent) CYP3A4.

- Concomitant use of CAMZYOS with **moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors can increase CAMZYOS exposure** and may increase the risk of heart failure due to systolic dysfunction
- **Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers can decrease CAMZYOS exposure** which may reduce CAMZYOS' efficacy
  - The risk of heart failure due to systolic dysfunction may increase when these inducers are discontinued during CAMZYOS treatment, as a result of increased CAMZYOS exposure
- Weak CYP2C19 inhibitors or moderate CYP3A4 inhibitors can increase CAMZYOS exposure, which may increase the risk of adverse drug reactions

BOXED WARNING:
CYP 450 Drug Interactions Leading to Heart Failure or Loss of Effectiveness (II)

CAMZYOS® is **contraindicated** in patients using:

- Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors
- Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers

Patients that intend to initiate a weak CYP2C19 inhibitor or moderate CYP3A4 inhibitor while on CAMZYOS should reduce their dose of CAMZYOS by one level (see table).

- Schedule clinical and echocardiographic assessment 4 weeks after the initiation of an inhibitor, and do not up-titrate CAMZYOS until 12 weeks after initiation
- Avoid initiation of concomitant weak CYP2C19 and moderate CYP3A4 inhibitors in patients who are on stable treatment with 2.5 mg of CAMZYOS because a lower once-daily dose is not available

Stepwise Down-titration For Initiation of a Weak CYP2C19 Inhibitor or Moderate CYP3A4 Inhibitor	
Starting Dose	**New Dose**
15 mg	10 mg
10 mg	5 mg
5 mg	2.5 mg
2.5 mg	0 mg (treatment interruption)

Advise patients of the potential for drug interactions, including with over-the-counter medications (such as omeprazole, esomeprazole, or cimetidine), prior to and during treatment with CAMZYOS

CAMZYOS® REMS Overview

What is the CAMZYOS® REMS?

The CAMZYOS REMS (Risk Evaluation and Mitigation Strategy) program is required by the US Food and Drug Administration (FDA) to ensure that the benefits of CAMZYOS outweigh the risks

Risk

The CAMZYOS REMS is a program to manage the risk of heart failure due to systolic dysfunction

Healthcare Provider Requirements

How Does a Healthcare Provider Become Certified in the CAMZYOS® REMS?

To become certified in the CAMZYOS REMS, healthcare providers must:

1. Review the CAMZYOS Prescribing Information
2. Review the following:
   - **Program Overview**
   - **Education Program for Healthcare Providers and Pharmacies** **(this presentation)**
3. Successfully complete the **Healthcare Provider Knowledge Assessment**
4. Enroll by completing the **Healthcare Provider Enrollment Form**
5. Certification can be completed online at CAMZYOSREMS.com or by printing and faxing the **Healthcare Provider Knowledge Assessment** and the **Healthcare Provider Enrollment Form** to the CAMZYOS REMS at 833-299-9539. Healthcare providers will be notified within 1 business day when they are certified to prescribe CAMZYOS

What are the Requirements of the CAMZYOS® REMS for Certified Healthcare Providers?

To prescribe CAMZYOS, you must:

1. Provide counseling to the patient using the **Patient Brochure** about CAMZYOS prior to initiating treatment and enroll them into the CAMZYOS REMS
2. Assess the patient's cardiovascular status and the appropriateness of initiating treatment by obtaining an echocardiogram
3. Assess the patient's prescription and nonprescription medications and supplements for drug-drug interactions
4. Document and submit the confirmation of an echocardiogram, assessment of drug-drug interactions, and authorization for treatment to the REMS using the **Patient Enrollment Form**
5. For patients who delay treatment initiation up to 90 days from **Patient Enrollment Form** submission: Assess the patient's treatment start date. Document and submit the new start date using the REMS website
    - Healthcare providers can specify an initial treatment start date that falls within 90 days of **Patient Enrollment Form** submission. If a date is not specified, the REMS treatment start date will be based on the initial dispense shipment date of the patient's first dose of CAMZYOS. A REMS-certified healthcare provider, designee, or pharmacy can use the REMS website to submit an updated treatment start date within 90 days of submitting the **Patient Enrollment Form**
6. Counsel the patient, assess drug-drug interactions, and assess the patient's cardiovascular status during treatment, including obtaining echocardiograms at the frequency described in the Prescribing Information
7. Document and submit the **Patient Status Form**, confirming that:
    - The patient has been counseled
    - The echocardiogram for the required time interval based on the Prescribing Information has been performed
    - Assessment of drug-drug interactions has been performed
    - Based on the above, it is appropriate to continue treatment
8. Promptly report adverse events of heart failure due to systolic dysfunction to Bristol Myers Squibb at 833-628-7367

Healthcare Provider Designees

- Certified healthcare providers can designate members of their staff who are **licensed medical professionals** to be their REMS Designee
- The healthcare provider is responsible for all information entered and activities performed in the CAMZYOS® REMS by their designees
- The designee must complete and submit the **Healthcare Provider Designee Enrollment Form** together with the healthcare provider, online through CAMZYOSREMS.com or by fax

Designee Activities

REMS Designees can perform these REMS activities for the certified healthcare provider:

- **Counsel** the patient using the **Patient Brochure** and provide the brochure to the patient
- Assess the patient's prescription and nonprescription medications and supplements for drug-drug interactions
- **Enroll** the patient, **confirm** the initial echocardiogram, and **authorize treatment** by completing and submitting the **Patient Enrollment Form**
- Assess the patient's cardiovascular status and the appropriateness of continuing treatment by echocardiograms
- **Complete and submit the Patient Status Form** during treatment

Initial and subsequent prescriptions can only be written by the certified healthcare provider.

Required Patient Counseling by the Healthcare Provider

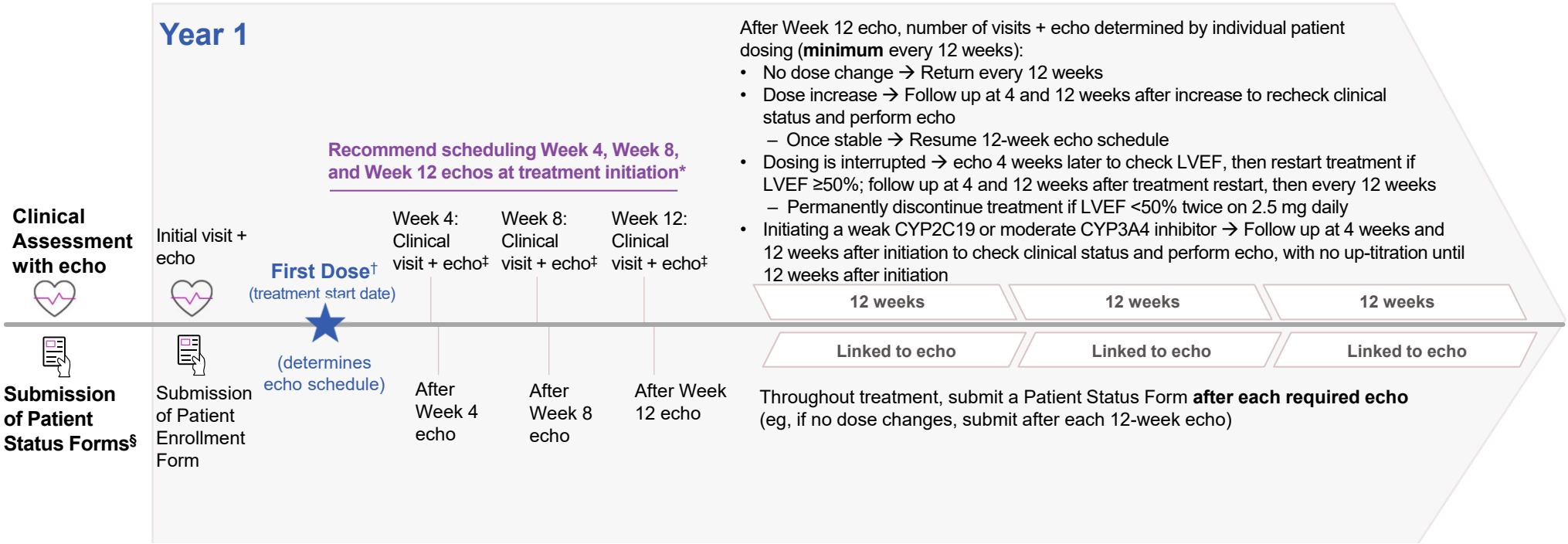
- Before and during treatment, healthcare providers must use the **Patient Brochure** to counsel their patients on:
  - The risk of heart failure due to systolic dysfunction
  - How to recognize and respond to the symptoms of heart failure due to systolic dysfunction
  - Risk of drug-drug interactions with CYP2C19 or CYP3A4 inhibitors and inducers and the need to inform their healthcare provider of all prescription and over-the-counter medications they take
- Provide the patient with a copy of the **Patient Brochure** to take with them
- After the initial patient counseling, complete the **Patient Enrollment Form** with the patient and submit to the REMS

Timing and Completion of Patient Status Forms

Submission of a **Patient Status Form** to the REMS is required after echocardiograms to confirm that the patient has been counseled, the echocardiogram for the required time interval based on the Prescribing Information has been performed, assessment of drug-drug interactions has been performed, and it is appropriate for the patient to continue treatment with CAMZYOS®

- **Patient Status Forms** include:
  - Confirmation that you have completed the required steps with each submission (see above)
  - The date on which the associated echocardiogram was performed
  - An indication of whether the patient has experienced LVEF <50%
  - An indication of what action was taken with the patient's dose based on this clinical visit
  - An indication of whether the patient has experienced a clinical heart failure event requiring hospitalization
- Submit a **Patient Status Form** as soon as possible but no later than **3 calendar days after the last day of the week that the echocardiogram was due**
- Failure to submit the **Patient Status Form** according to the required schedule may result in dispensing holds and potentially treatment interruptions

Echo Assessments and Patient Status Form Submissions: Year 1



*If a patient is transitioning from a CAMZYOS® clinical trial and is on a stable dose, follow the monitoring schedule on Slide 27.
†The REMS treatment start date will be based on the initial dispense shipment date of the patient's first dose of CAMZYOS. A REMS-certified healthcare provider, designee, or pharmacy can use the REMS website to submit an updated treatment start date within 90 days of submitting the **Patient Enrollment Form**. If treatment initiation is delayed for greater than 90 days from submission of the **Patient Enrollment Form**, a new **Patient Enrollment Form** must be submitted.
‡For early clinical response.
§Required by the CAMZYOS REMS; failure to complete and submit **Patient Status Forms** may lead to interruptions in dosing.

Echo=echocardiogram; LVEF=left ventricular ejection fraction.

Echo Assessments and Patient Status Form Submissions: Year 2 and Beyond

Year 2+

Number of visits + echo determined by individual patient dosing (**minimum** every 12 weeks):

- No dose change → Return every 12 weeks
- Dose increase → Follow up at 4 and 12 weeks after increase to recheck clinical status and perform echo
  - Once stable → resume 12-week echo schedule
- Dosing is interrupted → echo 4 weeks later to check LVEF, then restart treatment if LVEF ≥50%; follow up at 4 and 12 weeks after treatment restart, then every 12 weeks
  - Permanently discontinue treatment if LVEF <50% twice on 2.5 mg daily
- Initiating a weak CYP2C19 or moderate CYP3A4 inhibitor → Follow up at 4 weeks and 12 weeks after initiation to check clinical status and perform echo, with no up-titration until 12 weeks after initiation

Clinical Assessment with echo

12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
Linked to echo	Linked to echo	Linked to echo	Linked to echo	Linked to echo

Submission of Patient Status Forms*

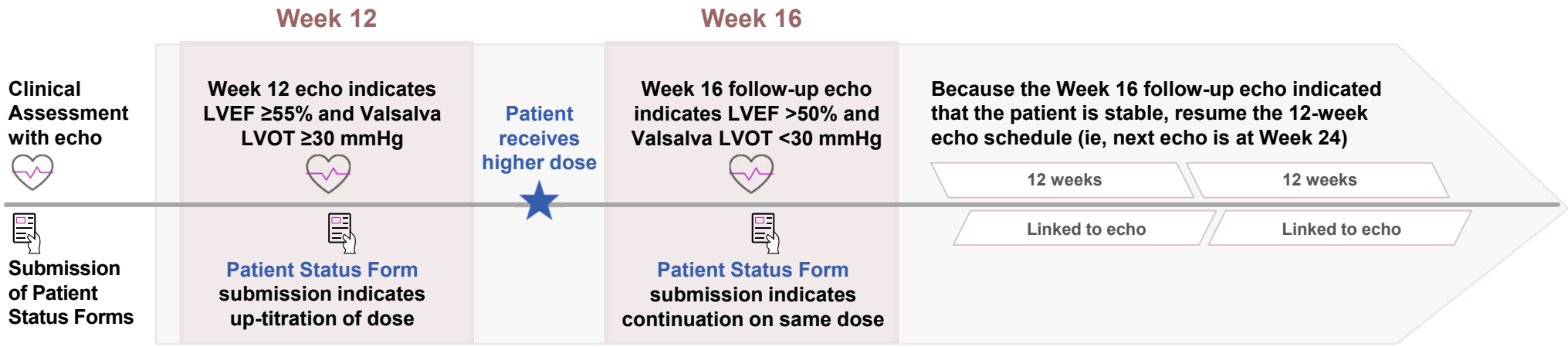
Throughout treatment, submit a Patient Status Form **after each required echo** (eg, if no dose changes, submit after each 12-week echo)

*Required by REMS; failure to complete and submit **Patient Status Forms** may lead to interruptions in dosing.

Echo=echocardiogram; LVEF=left ventricular ejection fraction.

Echo Assessments and Patient Status Form Submissions: Case Scenarios (I)

Scenario 1: Dose increase after Initiation Phase monitoring*

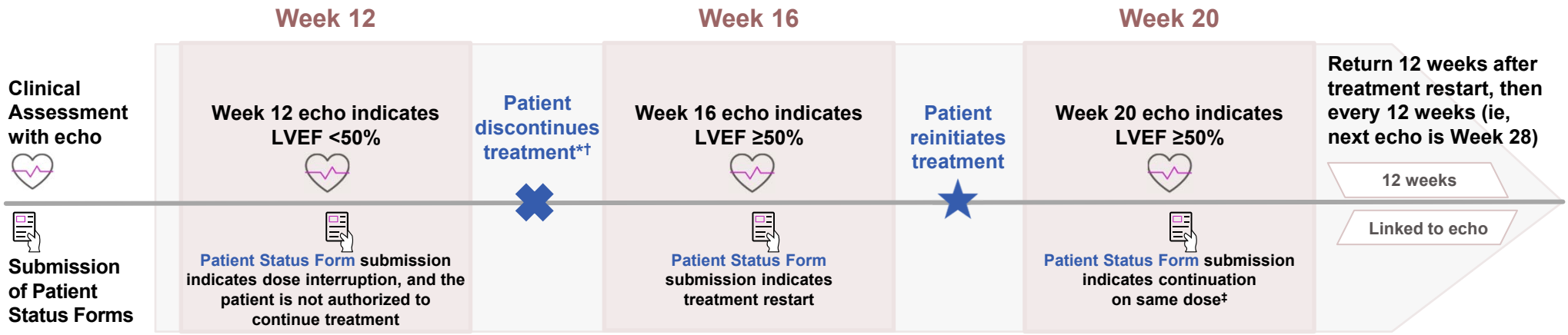


*The dosing algorithm described in the CAMZYOS® Prescribing Information does not include dose increases until the Maintenance Phase (see Slide 8).

Echo=echocardiogram; LVEF=left ventricular ejection fraction; LVOT=left ventricular outflow tract.

Echo Assessments and Patient Status Form Submissions: Case Scenarios (II)

Scenario 2: Discontinuation due to LVEF <50% or any discontinuation for 8 weeks or less



*Permanently discontinue treatment if LVEF <50% twice on 2.5 mg daily (the lowest dose level of CAMZYOS®).

†For discontinuation due to LVEF <50%, recheck echo parameters every 4 weeks until LVEF ≥50%, as described on Slide 9. If treatment is discontinued for >8 weeks, please refer to Slide 24.

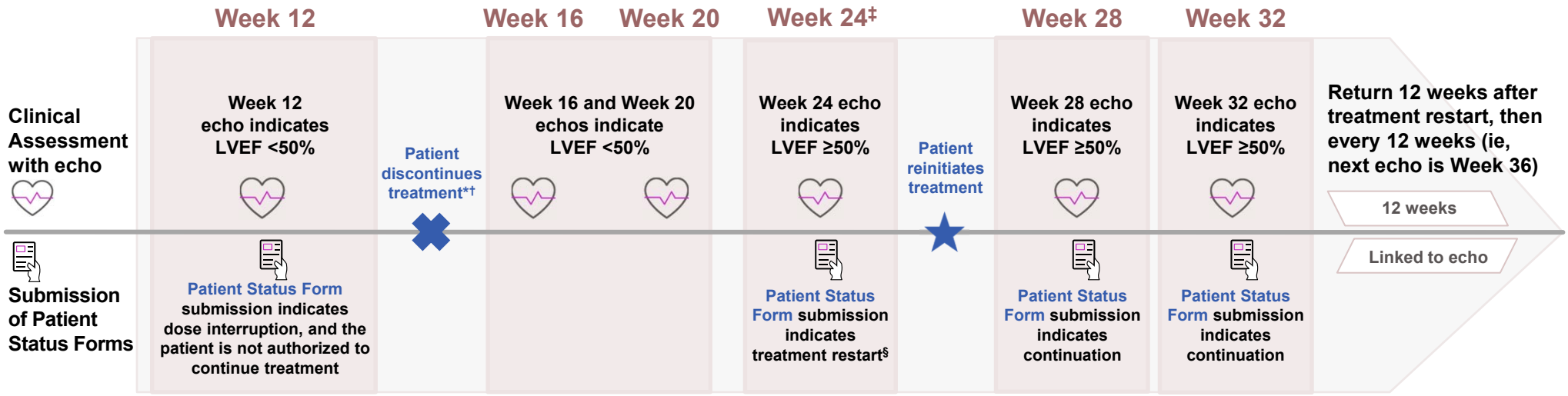
‡Maintain the same dose for the next 8 weeks unless LVEF <50%.

Echo=echocardiogram; LVEF=left ventricular ejection fraction.

Echo Assessments and Patient Status Form Submissions: Case Scenarios (III)

Scenario 3: Discontinuation for longer than 8 weeks after Initiation Phase due to LVEF <50%

If the patient is discontinued from treatment for longer than 8 weeks (except for patients who permanently discontinue due to repeated LVEF <50%) and treatment is reinitiated, the Patient Status Form submission schedule will be at Week 4, Week 8, Week 12, and at minimum every 12 weeks thereafter.



*Permanently discontinue treatment if LVEF <50% twice on 2.5 mg daily (the lowest dose level of CAMZYOS®).

†For discontinuation due to LVEF <50%, recheck echo parameters every 4 weeks until LVEF ≥50%, as described on Slide 9.

‡Reinitiation is shown here at Week 24 to illustrate a treatment interruption longer than 8 weeks.

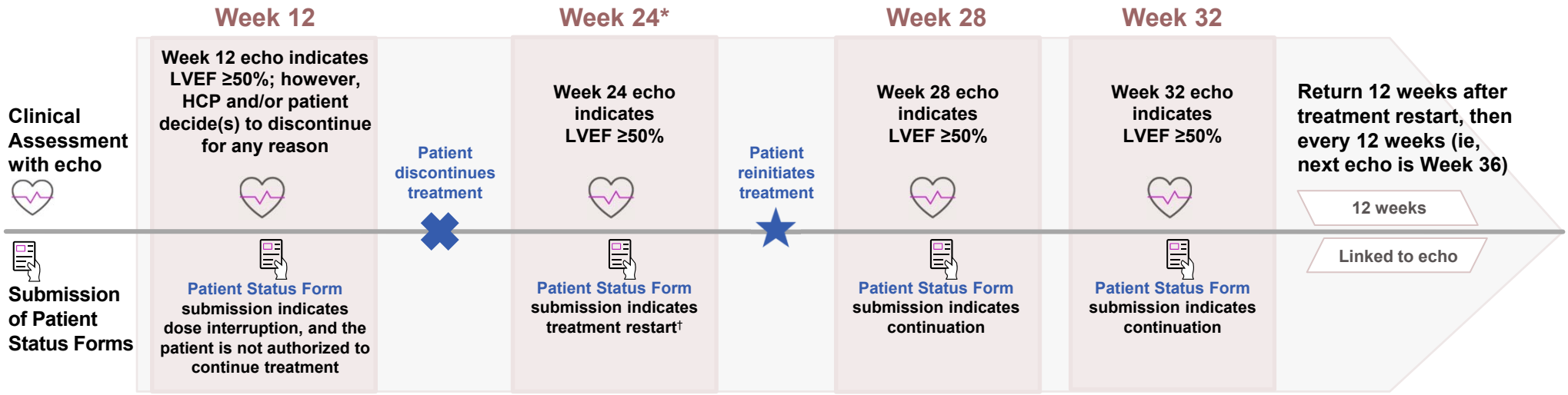
§If reinitiating treatment for a patient who has discontinued treatment for >1 year, an HCP or Designee must submit a new **Patient Enrollment Form** indicating an echo was performed within 12 weeks of reinitiation. If treatment has been discontinued for ≤1 year, either a **Patient Status Form** or **Patient Enrollment Form** must be submitted indicating an echo was performed within 12 weeks of reinitiation.

Echo=echocardiogram; HCP=healthcare provider; LVEF=left ventricular ejection fraction.

Echo Assessments and Patient Status Form Submissions: Case Scenarios (IV)

Scenario 4: Discontinuation for longer than 8 weeks after Initiation Phase due to any reason with LVEF ≥50%

If the patient is discontinued from treatment for longer than 8 weeks (except for patients who permanently discontinue due to repeated LVEF <50%) and treatment is reinitiated, the Patient Status Form submission schedule will be at Week 4, Week 8, Week 12, and at minimum every 12 weeks thereafter.



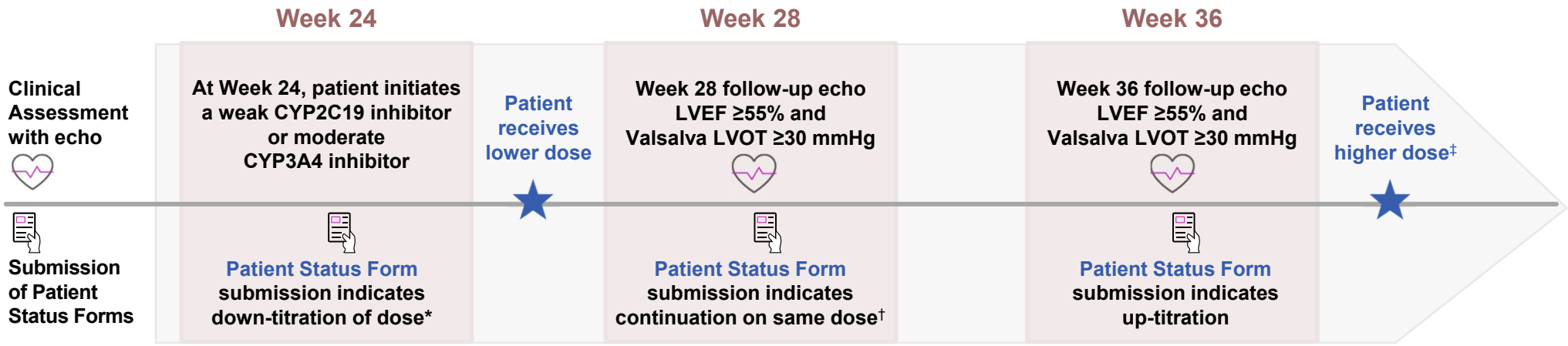
*Reinitiation is shown here at Week 24 to illustrate a treatment interruption longer than 8 weeks.

†If reinitiating treatment for a patient who has discontinued treatment for >1 year, an HCP or Designee must submit a new **Patient Enrollment Form** indicating an echo was performed within 12 weeks of reinitiation. If treatment has been discontinued for ≤1 year, either a **Patient Status Form** or **Patient Enrollment Form** must be submitted indicating an echo was performed within 12 weeks of reinitiation.

Echo=echocardiogram; HCP=healthcare provider; LVEF=left ventricular ejection fraction.

Echo Assessments and Patient Status Form Submissions: Case Scenarios (V)

Scenario 5: Dose decrease after Initiation Phase monitoring
(including initiation of a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor)



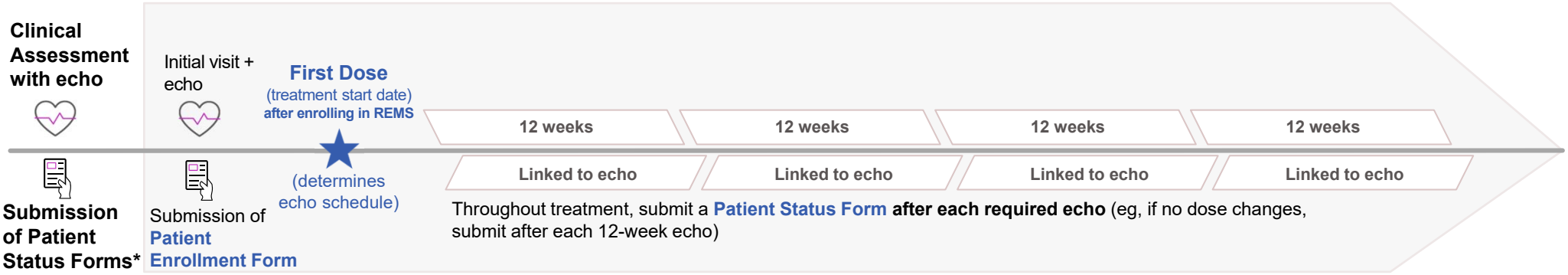
*Patients who are on CAMZYOS® therapy and intend to initiate a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor should reduce dose of CAMZYOS by one level (ie, 15 mg → 10 mg; 10 mg → 5 mg; or 5 mg → 2.5 mg). Avoid initiation of concomitant weak CYP2C19 and moderate CYP3A4 inhibitors in patients who are on stable therapy with 2.5 mg of CAMZYOS because a lower dose is not available.
†The patient cannot be up-titrated until 12 weeks after inhibitor initiation.
‡Following up-titration, the patient requires a Week 40 follow-up echo; if the patient is stable, resume 12-week echo schedule (ie, next echo is Week 48).

Echo=echocardiogram; LVEF=left ventricular ejection fraction; LVOT=left ventricular outflow tract.

Echo Assessments and Patient Status Form Submissions: Case Scenarios (VI)

Scenario 6: Patient is transitioning from a clinical trial

- If a patient is transitioning from a CAMZYOS® clinical trial and is on a stable dose, the patient can continue to take the same dose and follow the **Maintenance Phase** schedule starting at Week 12 (shown on Slide 8)
  - Ensure completion of the questions related to CAMZYOS clinical trial participation in the **Patient Enrollment Form**
- A patient is on a stable dose if they are on the same dose of CAMZYOS for the last 12 weeks of their clinical trial dosing and if there are 8 weeks or less between exit from the clinical trial and enrollment into the REMS
- If the patient is not on a stable dose and/or it has been longer than 8 weeks between clinical trial exit and **Patient Enrollment Form** submission, the **Patient Status Form** submission schedule will be at Week 4, Week 8, and Week 12, and at minimum every 12 weeks thereafter (please see Slides 7 and 20)



*Required by the CAMZYOS REMS; failure to complete and submit **Patient Status Forms** may lead to interruptions in dosing.
Echo=echocardiogram.

Pharmacy Requirements

How Does a Pharmacy Become Certified in the CAMZYOS® REMS?

CAMZYOS can only be dispensed by certified pharmacies.

To become certified to dispense, pharmacies must designate an authorized representative to complete the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy.

1. Have the authorized representative review the Prescribing Information, the **Program Overview**, and this presentation
2. Have the authorized representative successfully complete the **Pharmacy Authorized Representative Knowledge Assessment**
3. Have the authorized representative enroll in the REMS on behalf of the pharmacy by completing the **Pharmacy Enrollment Form**
4. Submit both the **Knowledge Assessment** and **Enrollment Form** to the CAMZYOS REMS.

Certification can be completed online at CAMZYOSREMS.com or by faxing the **Pharmacy Authorized Representative Knowledge Assessment** and the **Pharmacy Enrollment Form** to the CAMZYOS REMS.

Pharmacies will be notified within 1 business day if they are certified to dispense CAMZYOS.

What Are the Pharmacy Responsibilities?

Authorized Representatives must:

- Train all relevant staff involved in dispensing CAMZYOS® using the **Program Overview** and this presentation

Pharmacies must:

- Report any adverse events of heart failure due to systolic dysfunction to Bristol Myers Squibb at 833-628-7367
- Not distribute, transfer, loan or sell CAMZYOS except to a certified pharmacy
- Maintain records of dispensing information
- Maintain records documenting completion of the REMS training by relevant staff
- Maintain records that all processes and procedures are in place and being followed
- Have any new representatives enroll in the REMS by successfully completing the **Pharmacy Authorized Representative Knowledge Assessment** and completing the **Pharmacy Enrollment Form**

What are the Dispensing Requirements for Pharmacies?

Before dispensing CAMZYOS®, the certified pharmacy will:

1. Counsel the patient on drug-drug interactions
2. Assess the patient's prescription and nonprescription medications and supplements for drug-drug interactions. Complete and submit the **Drug Interaction and Counseling Checklist for Pharmacies** to the CAMZYOS REMS
3. Document the prescribed dose
4. Obtain authorization to dispense CAMZYOS by contacting the REMS to verify that the:
   - Prescriber is certified and the patient is enrolled
   - Healthcare provider has authorized the patient to receive the drug, the patient was counseled, and the pharmacy identified and resolved any drug-drug interactions

With each dispense of CAMZYOS:

1. Provide a **Patient Brochure** with each shipment of CAMZYOS
2. Dispense no more than a 35-day supply of CAMZYOS
3. For patients who delay treatment initiation up to 90 days from **Patient Enrollment Form** submission: Assess the patient's treatment start date. Document and submit the new start date using the REMS website

CAMZYOS must be shipped overnight or dispensed, as applicable within 24 hours of logging a dispense for a patient. All product shipments must ship for next business day or next calendar day delivery.

This concludes the CAMZYOS® REMS Education Program for Healthcare Providers and Pharmacies

If you are a potential healthcare provider or pharmacist, you will need to successfully complete your respective **Knowledge Assessment** and complete your **Enrollment Form** to become certified in the CAMZYOS REMS.

For more information or to obtain any REMS materials,
visit **CAMZYOSREMS.com** or call **833-628-7367.**

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