CAMZYOS® (mavacamten)

How It Works — A Guide for the Scientifically Curious

CAMZYOS is the first drug of its kind to treat **obstructive hypertrophic cardiomyopathy (oHCM)** — a genetic heart condition in which the muscle squeezes too hard, the walls thicken over time, and blood struggles to flow out with each beat. Rather than masking symptoms, CAMZYOS corrects the underlying molecular over-contraction. Here is how.

The Molecular Motor Inside Every Heartbeat

Your heart muscle contracts because of a protein machine called **myosin**. Think of it as a microscopic rowing oar. Millions of these oars grab a parallel protein track called **actin**, pull, release, and reset — hundreds of times per second. Each grab-and-pull cycle burns one molecule of **ATP** (adenosine triphosphate, the cell's universal energy currency). The enzyme that splits ATP to power this stroke is called **myosin ATPase**.

In a healthy heart, the number of myosin oars actively rowing at any instant is precisely regulated. In oHCM, a genetic mutation — usually in the myosin heavy-chain gene — disrupts this regulation. Too many oars row simultaneously, the muscle squeezes too forcefully, and the walls of the left ventricle (the heart's main pumping chamber) gradually thicken from chronic overwork.

Myosin's Hidden Off-Switch: The Super-Relaxed State

Myosin does not exist in just two states — on (rowing) and off (released). A third configuration discovered in the 2010s, called the **super-relaxed state (SRX)**, is the key to how CAMZYOS works.

In SRX, pairs of myosin molecules fold back on each other in a compact head-to-tail arrangement, tucking their ATP-splitting heads against the myosin tail. ATP hydrolysis slows by roughly **10-fold**. The oars are not just idle — they are physically stowed. Stowed oars cannot grab actin, cannot generate force, and the heart conserves energy. In oHCM, the mutation destabilizes SRX: too few oars remain stowed, too many remain active. CAMZYOS was designed to push the equilibrium back toward SRX.

How Mavacamten Binds the Myosin Motor

Mavacamten is a small organic molecule (molecular formula $C_{21}H_{25}FN_2O_3$, ~376 daltons) that fits into a specific binding pocket on the myosin head domain, near — but not inside — the ATP-binding site. This is **allosteric binding**: rather than blocking the active site, the drug changes the three-dimensional shape of the myosin head in a way that strongly stabilizes the SRX folded configuration.

The net result: a larger fraction of myosin heads remain stowed per heartbeat. Fewer myosin–actin contacts form, less force is generated, and the heart squeezes with appropriate — not excessive —

strength.

Step	What Happens
1. Binding	Drug docks on myosin head; reshapes it toward SRX geometry.
2. SRX stabilization	More myosin pairs fold into compact, stowed configuration.
3. Fewer cross-bridges	Less myosin grabs actin per contraction cycle.
4. Force reduction	Heart pumps strongly but no longer excessively.
5. Obstruction clears	Blood exits the left ventricle freely each beat.

The Disease: Why the Heart Fights Itself

> **In oHCM, a genetic mutation causes too many myosin motors to be active at once. The heart squeezes too hard, the exit channel narrows, and the walls thicken from years of overwork — like a repeatedly clenched fist developing a callus.**

The direct consequence is narrowing of the channel through which blood exits the left ventricle on its way to the rest of the body. Cardiologists measure this as the **left ventricular outflow tract gradient** — the pressure difference across the outflow channel. A healthy value is under 30 mmHg (millimeters of mercury, the same pressure unit used in blood pressure readings). In oHCM patients this can exceed 100 mmHg, meaning the heart must generate enormous extra pressure just to push blood through its own narrowed exit.

Over years, patients experience breathlessness on exertion, chest pain, fatigue, fainting episodes, and in severe cases, sudden cardiac arrest. The thickened walls also become stiff, filling poorly between beats and compounding the problem.

What Patients Actually Experience

The landmark clinical trial — **EXPLORER-HCM** — enrolled 251 adults with symptomatic oHCM in a randomized, double-blind, placebo-controlled study (the gold standard for drug evidence). Results after 30 weeks:

- **Outflow pressure dropped dramatically.** Most patients saw gradients fall from symptomatic levels (>50 mmHg) to near-normal (<30 mmHg).
- **Exercise capacity improved.** Peak oxygen consumption on a treadmill test — a direct measure of cardiovascular fitness — increased significantly.
- **Heart stress markers fell.** NT-proBNP and cardiac troponin I — proteins the heart releases into the blood when under mechanical strain — decreased substantially, indicating less wall stress at the

molecular level.

- **Symptoms improved.** Patients reported less breathlessness and better quality of life.

A second trial, **VALOR-HCM**, tested mavacamten in patients scheduled for septal reduction therapy — an invasive procedure to physically remove or destroy the obstructing muscle by open-heart surgery or catheter-based alcohol injection. After 16 weeks on mavacamten, **82% of those patients no longer met the criteria for intervention.** The drug had achieved what surgery was going to do, non-invasively.

How the Drug Is Dosed

Mavacamten is taken once daily as an oral capsule, starting at 2.5 mg/day. Dose is adjusted every four to eight weeks based on echocardiogram measurements of the heart. Because the drug reduces pumping force, physicians track **ejection fraction (EF)** — the percentage of blood the heart ejects with each beat. Normal EF is roughly 55–70%. The dose is increased only as long as EF stays safely above 50%.

The Chemistry of Mavacamten

Mavacamten belongs to a class called **pyrimidinediones** — a six-membered ring containing two nitrogen atoms flanked by carbonyl (C=O) groups, similar in backbone to the pyrimidine bases found in DNA. Several structural features explain its behavior:

- **Fluorine substitution:** A single fluorine atom on the aromatic ring increases metabolic stability. Fluorine-carbon bonds are among the strongest in organic chemistry and resist enzymatic attack, helping the drug persist long enough between once-daily doses to maintain therapeutic blood levels.
- **Moderate lipophilicity:** The molecule partitions readily into fatty membranes and muscle tissue, achieving good penetration into heart-muscle cells — which are packed with lipid-rich membranes surrounding the contractile machinery.
- **Cardiac myosin selectivity:** The binding pocket on the myosin head that mavacamten fits into exists in a subtly different geometry in cardiac myosin versus skeletal or smooth muscle myosin. This structural selectivity means the drug preferentially targets the heart rather than causing widespread relaxation of all muscles.
- **Reversible, non-covalent binding:** Mavacamten is not covalently bonded to myosin — it can diffuse in and out of the binding pocket. The effect is dose-dependent and fully reversible: stopping the drug allows the heart to recover its full contractile force within weeks.

How the Body Processes the Drug

Mavacamten is absorbed through the small intestine. It is highly protein-bound in the bloodstream — roughly 97–98% is attached to albumin and other plasma proteins, with only the unbound fraction active in tissue. This high binding contributes to its unusually long **plasma half-life of**

approximately 6–9 days. (Half-life is the time for blood concentration to fall by 50% after stopping the drug; this long half-life means it takes several weeks to reach steady-state and several weeks to fully clear after stopping.)

The drug is eliminated almost entirely by **CYP2C19** — a cytochrome P450 enzyme in the liver that performs oxidative metabolism. Individual genetics matter here:

- **Normal/rapid metabolizers (most people):** CYP2C19 works at full capacity. Standard doses produce safe therapeutic levels.
- **Poor metabolizers (2–3% of people, more common in East Asian ancestry):** CYP2C19 is nearly non-functional due to inherited gene variants. Mavacamten accumulates to much higher blood levels at the same dose, requiring lower starting doses and more frequent monitoring. A simple genetic test (cheek swab or blood draw) identifies poor metabolizers before treatment begins.
- **CYP2C19-inhibiting drugs:** Common medications — including omeprazole (Prilosec, a heartburn drug), fluconazole (Diflucan, an antifungal), and several antidepressants — slow CYP2C19 activity. Co-administering these with mavacamten is like being a poor metabolizer: drug levels rise dangerously. These combinations are contraindicated.

The REMS Program: Built-In Safety Net

Because reducing heart muscle force too much is a predictable risk, the FDA required a mandatory safety program called a **REMS (Risk Evaluation and Mitigation Strategy)**. Think of it as a protocol-enforced feedback loop between drug dose and echocardiogram results:

When	Requirement
Before starting	Echocardiogram: confirms ejection fraction ≥55% and measures baseline outflow gradient.
Week 4	Echocardiogram: dose increased, held, or reduced based on results.
Week 8	Echocardiogram: further titration if appropriate.
Week 12	Final check before long-term maintenance dose is set.
Every 12 wks	Ongoing monitoring for duration of treatment.
EF drops <50%	Drug interrupted immediately; resumed only after recovery to ≥55%.

Why Ejection Fraction Is the Key Safety Signal

If the left ventricle holds 100 mL at the start of a beat and pumps out 60 mL, the ejection fraction is 60%. It is measured in real time by echocardiogram — an ultrasound probe placed on the chest gives a live image of the contracting heart, with software calculating volumes from the image. No radiation, no invasive procedure.

An EF below 50% means the heart is not pumping enough blood — the definition of **systolic dysfunction** ("systolic" refers to the pumping phase of each heartbeat). At that point, mavacamten has reduced myosin activity too far. The fix is straightforward: stop or reduce the dose, wait 2–4 weeks for the drug to clear, and EF typically recovers fully to baseline — a consequence of the drug's reversible, non-covalent binding.

Why This Drug Matters

Before mavacamten, treatment of oHCM was limited to drugs that slow the heart (beta blockers, calcium channel blockers) — none of which address the underlying molecular overactivity. For patients who did not respond, the only option was septal reduction surgery or catheter-based alcohol ablation, both irreversible and carrying procedural risk.

Mavacamten is the first drug that targets the actual molecular defect — too many myosin cross-bridges — derived directly from structural biology research into the SRX state. It represents a shift from symptom management to mechanism-targeted therapy, and its success has opened a pipeline of cardiac myosin modulators for related conditions including non-obstructive HCM and heart failure with preserved ejection fraction.

> ⚠ **Key Safety Note**
>
> The primary risk is reducing ejection fraction below 50% (heart pumps too weakly). CAMZYOS is also contraindicated in pregnancy. Common CYP2C19-inhibiting drugs — omeprazole, fluconazole, many antidepressants — can dangerously raise drug levels and must be avoided or substituted. Your cardiologist will review every medication before prescribing.