CAMZYOS® ▼ (mavacamten)

Healthcare Professional Guide

"Risks associated with the use of the product."

"This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA."

Bristol Myers Squibb™

▼ CAMZYOS is subject to additional monitoring to quickly identify new safety information. Healthcare professionals are asked to report any suspected adverse events.

INTRODUCTION

This guide contains specific information on the safe prescribing and use of CAMZYOS (mavacamten).
This guide contains the following information:

- Details on the mechanism of action of CAMZYOS and dosing information
- Details on the risks of
  - Heart failure due to systolic dysfunction
  - Heart failure due to drug interactions with cytochrome P450 (CYP) 2C19 inhibitors and moderate or strong CYP3A4 inhibitors Embryo-foetal toxicity
- Information about educational materials that healthcare professionals (HCPs) should distribute to patients and/or their caregiver(s)
- Contact details for reporting adverse events and pregnancies in patients receiving CAMZYOS and where to find additional information
- A **Treating and Counseling Checklist** to ensure that HCPs, patients and/or their caregiver(s) are aware of the steps they need to take for safe use of CAMZYOS

07/24
Version 01

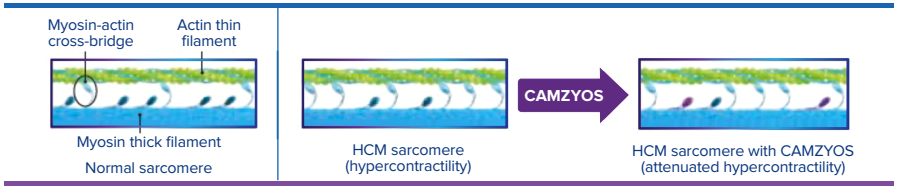
THERAPEUTIC INDICATION

CAMZYOS is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.

MECHANISM OF ACTION OF CAMZYOS

CAMZYOS is a selective, allosteric and reversible cardiac myosin inhibitor. CAMZYOS modulates the number of myosin heads that can enter power-generating states, thus reducing (or in HCM, normalizing) the probability of force-producing systolic and residual diastolic cross-bridge formation. CAMZYOS also shifts the overall myosin population towards an energy-sparing, but recruitable, super-relaxed state (see Figure 1). Excess cross-bridge formation and dysregulation of the super-relaxed state of myosin are mechanistic hallmarks of HCM, which can result in hypercontractility, impaired relaxation, excess energy consumption and myocardial wall stress.

Figure 1: Mechanism of Action



In patients with HCM, myosin inhibition with CAMZYOS normalizes contractility, reduces dynamic left ventricular outflow tract (LVOT) obstruction and improves cardiac filling pressures and biomarkers of cardiac stress, improving symptoms and exercise capacity.

TREATMENT AND DOSING

Before starting treatment

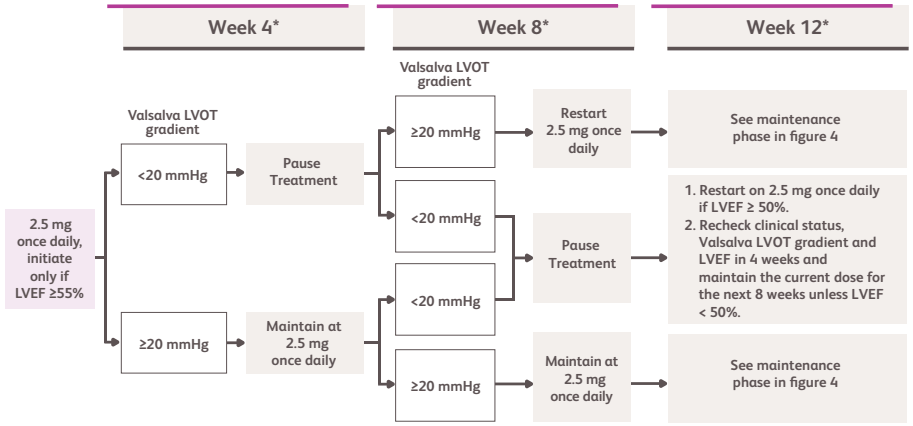
- Confirm a negative pregnancy test and advise patients of reproductive potential to use effective contraception during treatment with CAMZYOS and for 6 months following discontinuation
- Assess left ventricular ejection fraction (LVEF) by echocardiogram. Do not initiate CAMZYOS in patients with LVEF <55%
- Consider contraindications and drug interactions prior to and throughout treatment
- Patients should be genotyped for CYP2C19 phenotype in order to determine appropriate CAMZYOS dose

During treatment

- The recommended starting dose of CAMZYOS is 2.5 mg orally once daily for patients with CYP2C19 poor metaboliser phenotype and 5 mg orally once daily for patients with CYP2C19 intermediate, normal, rapid and ultra-rapid phonotype. Patients should follow dosing instructions for poor metabolisers until CYP2C19 phenotype is determined. CAMZYOS may be taken without regard to food. If a dose is missed, it should be taken as soon as possible, and the next scheduled dose should be taken at the usual time the following day. The exact timing of dosing during the day is not essential, but two doses should not be taken on the same day. Swallow capsules whole. Do not break, open or chew the capsule
- Assess patient response to treatment, including LVOT gradient with Valsalva maneuver and LVEF, at Weeks 4 and 8 after treatment initiation. Once an individualised maintenance dose is achieved, patients should be assessed every 12 weeks. Additional echocardiograms may be required if there is a dose change or treatment interruption, as described in Figures 3, 4 and 5. Adjust the dose based on Figures 2–5
- Patients may develop heart failure while taking CAMZYOS. Regular LVEF and LVOT gradient with Valsalva maneuver assessments are required for careful dose titration to achieve an appropriate target LVOT gradient with Valsalva maneuver while maintaining LVEF ≥50% and avoiding heart failure symptoms (see Figures 2, 3 and 4)
- Dose increases should not occur more frequently than every 12 weeks. Do not up-titrate CAMZYOS in patients with LVEF <55% or those experiencing an intercurrent illness such as infections or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmias) that may impair systolic function. Interrupt treatment if LVEF is <50% at any visit; restart treatment after 4 weeks if LVEF is ≥50% (see Figure 5)

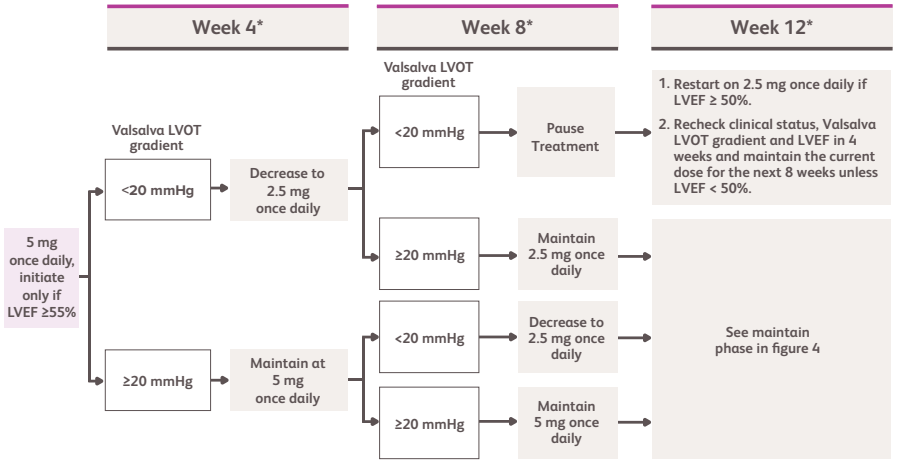
TREATMENT AND DOSING (continued)

Figure 2: Treatment initiation in CYP2C19 poor metaboliser phenotype



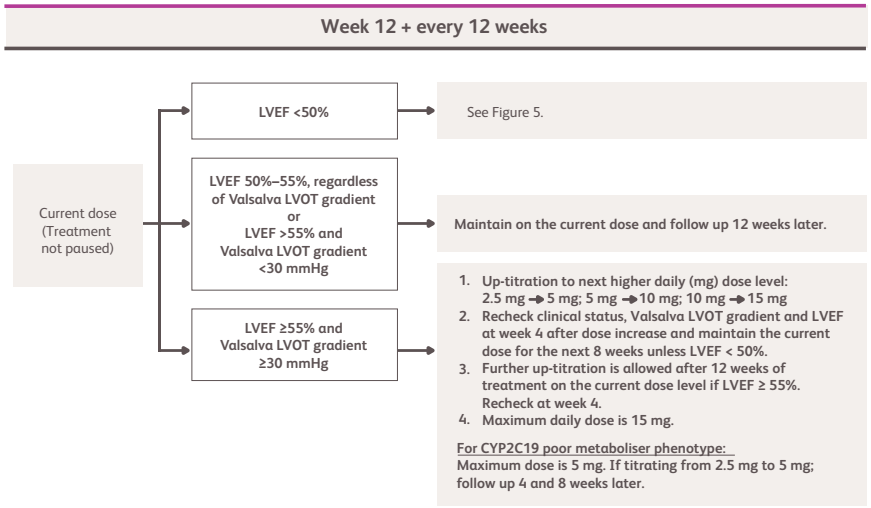
*Interrupt treatment if LVEF <50% at any clinical visit; restart treatment after 4 weeks if LVEF ≥50%. (see Figure 5.)
LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

Figure 3: Treatment initiation in CYP2C19 intermediate, normal, rapid and ultra-rapid metaboliser phenotypes



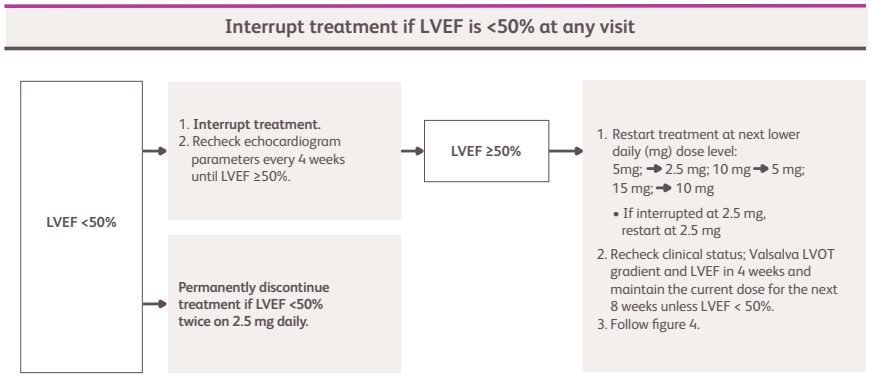
*Interrupt treatment if LVEF <50% at any clinical visit; restart treatment after 4 weeks if LVEF ≥50%. (see Figure 5.)
LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

Figure 4: Maintenance phase



LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

Figure 5: Treatment Interruption at any clinic visit if LVEF <50%



LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

TREATMENT AND DOSING (continued)

Dose modification with concomitant medicinal products

For concomitant treatment with inhibitors of CYP2C19 or CYP3A4, follow the steps shown in Table 1.

Table 1: Dose modification with concomitant medicinal products (refer to the Approved SmPC Sections 4.3 and 4.5 for further details)

Concomitant medicine/product	CYP2C19 poor metaboliser phenotype*	CYP2C19 intermediate, normal, rapid and ultra rapid phenotype
Inhibitors		
Combined use of a strong CYP2C19 inhibitor and a strong CYP3A4 inhibitor	Contra-indicated.	Contra-indicated.
Strong CYP2C19 inhibitor	No dose adjustment. If CYP2C19 phenotype has not yet been determined: No adjustment of the starting dose of 2.5 mg is needed. The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg.	Initiate mavacamten at a dose of 2.5 mg. The dose should be reduced from 15 mg to 5 mg and from 10 mg and 5 mg to 2.5 mg or pause treatment if on 2.5 mg.
Strong CYP3A4 inhibitor	Contra-indicated.	No dose adjustment.
Moderate CYP2C19 inhibitor	No dose adjustment. **If CYP2C19 phenotype has not yet been determined:** No adjustment of the starting dose of 2.5 mg is needed. The dose should be reduced from 5 mg to 2.5 mg or pause treatment if on 2.5 mg.	No adjustment of the starting dose of 5 mg is needed. The dose should be reduced by one dose level or pause treatment if on 2.5 mg.
Moderate or weak CYP3A4 inhibitor	No adjustment of the starting dose of 2.5 mg is needed. If patients are receiving a 5 mg dose of mavacamten, their dose should be reduced to 2.5 mg.	No dose adjustment.

* includes patients for whom the CYP2C19 phenotype has not yet been determined

RISKS ASSOCIATED WITH CAMZYOS

Risk of heart failure due to systolic dysfunction

A reduction in LVEF is an expected on-target effect of CAMZYOS. This LVEF effect is generally small (mean reduction of 4% in a pivotal Phase 3 trial of CAMZYOS [N=251]) and contributes to the efficacy of treatment with CAMZYOS. Some patients may see a decrease in their LVEF to <50% due to an excess medicinal effect of CAMZYOS, which may lead to heart failure.

Risk factors and groups

Patients with a serious intercurrent illness such as serious infection or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia) or those undergoing major cardiac surgery may be at greater risk of developing systolic dysfunction and heart failure.

Risk mitigation

Assess patients presenting with signs and symptoms of systolic dysfunction, including new or worsening dyspnoea, chest pain, fatigue, palpitations, leg oedema or elevations in N-terminal pro hormone B-type natriuretic peptide (NT proBNP), and promptly evaluate cardiac function.
Advise patients to report any signs or symptoms of heart failure (described above) **immediately** to their HCP or seek medical attention. Regular echo-cardiograms must be performed, as described in the **Treatment and Dosing** section of this guide, in order to mitigate the risk of heart failure. Please see the Approved Summary of Product Characteristics for additional information. In the presence of intercurrent illnesses, such as infections or arrhythmias that may impair systolic function, dose increases are not recommended.

Risk of heart failure due to drug interactions with CYP2C19 inhibitors and moderate or strong CYP3A4 inhibitors

CAMZYOS is primarily metabolized by CYP2C19 and (to a lesser extent) CYP3A4. Coadministration or discontinuation of CYP2C19 inhibitors or moderate or strong CYP3A4 inhibitors may alter the plasma concentration of CAMZYOS. Starting or increasing the dose of any CYP2C19 inhibitor or a moderate or strong CYP3A4 inhibitor may increase the risk of heart failure due to systolic dysfunction; conversely, discontinuation or decreasing the dose of these inhibitor types may lead to loss of response to CAMZYOS.

RISKS ASSOCIATED WITH CAMZYOS

Risk factors and groups

Patients treated with CYP2C19 inhibitors or moderate or strong CYP3A4 inhibitors.

Risk mitigation

HCPs should consider, **prior to and throughout treatment,** the potential for drug interactions involving CAMZYOS, including those arising from coadministration with over-the-counter medications (such as omeprazole or esomeprazole) and herbal supplements. Refer to Table 1 for guidance on CAMZYOS dose adjustment and LVEF monitoring recommendations when initiating or changing the dose of a CYP2C19 inhibitor or a moderate or strong CYP3A4 inhibitor.

Examples of CYP2C19 inhibitors and moderate/strong CYP3A4 inhibitors are shown in Table 2. Please be aware that **this is not an exhaustive list** of CYP2C19 inhibitors or moderate/strong CYP3A4 inhibitors nor their indications. Intermittent use of products that might interact with CAMZYOS, including prescription and over-the-counter medications, herbal supplements and grapefruit juice, is not recommended.

RISKS ASSOCIATED WITH CAMZYOS

Table 2: Examples of CYP2C19 inhibitors and moderate/strong CYP3A4 inhibitors

Inhibitor	Medicines/products	Condition treated
CYP2C19 inhibitors	Felbamate	Epilepsy
	Chloramphenicol	Bacterial infections
	Fluoxetine, fluvoxamine	Depression and OCD
	Fluconazole	Fungal infections
	Omeprazole, esomeprazole, cimetidine	Gastric ulcers and acid reflux
Moderate CYP3A4 inhibitors	Verapamil, diltiazem	Heart conditions
	Erythromycin	Bacterial infections
	Grapefruit juice	
Strong CYP3A4 inhibitors	Clarithromycin	Bacterial infections
	Itraconazole, ketoconazole, posaconazole, voriconazole	Fungal infection
	Paritaprevir	Hepatitis C
	Ritonavir (usually given in combination with other anti-HIV or anti-hepatitis C drugs)	Hepatitis C and HIV
	Cobicistat, elvitegravir, lopinavir, saquinavir, tipranavir	HIV

CYP=cytochrome P450; HIV=human immunodeficiency virus; OCD=obsessive compulsive disorder.
Information adapted from the Food and Drug Administration, 2020; Park, 2003; Orlando, 2003; and the SmPC Section 4.5.

Inform the patient that they **must** consult their prescribing HCP and pharmacist prior to taking any new medications or herbal supplements, changing the dose or stopping any medications or herbal supplements they may currently be taking.

RISKS ASSOCIATED WITH CAMZYOS (continued)

Embryo-foetal toxicity

CAMZYOS may cause embryo-foetal harm when administered to a pregnant patient based on pregnancy data from animal studies. There are no data on the use of CAMZYOS in pregnant patients. CAMZYOS should **not** be used during pregnancy.

Risk factors and groups

Pregnant patients and patients of childbearing potential not using effective contraception.

Risk mitigation

Prior to treatment initiation, confirm a negative pregnancy test in patients of childbearing potential. Inform the patient about the risk of embryo-foetal toxicity associated with CAMZYOS and counsel the patient on the need to avoid pregnancy. Recommend use of effective form of contraception during treatment and for 6 months after the last dose is administered.
Please instruct the patient to inform you if they are pregnant or suspect they are pregnant **immediately**. If, at any point, a patient becomes pregnant while receiving CAMZYOS, inform the patient of the potential risk to the fetus.

ADDITIONAL INFORMATION

A **Patient Guide** and **Patient Card** are available for you to aid in counseling of, and to provide to, patients and/or their caregiver(s).

Please ensure patients and/or their caregiver(s) are counseled appropriately, including on the following key safety messages:

- The risks associated with CAMZYOS and when to seek medical attention
- The importance of and requirements for echocardiogram assessment prior to and during treatment
- The importance of informing their HCPs of all medications and herbal supplements the patient is taking

Please inform patients to carry the **Patient Card** with them at all times. A copy of this card is embedded in the **Patient Guide**. Advise patients to tell any HCP that sees them that they are taking CAMZYOS.

A checklist is provided at the end of this guide to support HCPs in treating patients receiving CAMZYOS and counseling patients and/or their caregiver(s).

REPORTING ADVERSE EVENTS

The safe use of CAMZYOS is of paramount importance. As part of our ongoing safety monitoring, Bristol Myers Squibb wishes to be informed of adverse events that have occurred during use of CAMZYOS. Please report any adverse events and pregnancies to:

Bristol Myers Squibb International Corporation, Saudi Arabia:
At: medinfo.saudiarabia@bms.com
or call: 800 844 7710

The National Pharmacovigilance Centre (NPC) Saudi Food and Drug Authority (SFDA):
SFDA call center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa

CONTACT DETAILS

If you have any questions regarding CAMZYOS or require more information, please contact Bristol Myers Squibb.

Telephone: 800 844 7710

Email: medinfo.saudiarabia@bms.com

REFERENCE LIST

1. Drug development and drug interactions: table of substrates, inhibitors and inducers. U.S. Food and Drug Administration. Updated March 10, 2020. Accessed July 7, 2022. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.
2. Park JY, Kim KA, Kim SL. Chloramphenicol is a potent inhibitor of cytochrome P450 isoforms CYP2C19 and CYP3A4 in human liver microsomes. *Antimicrob Agents Chemother.* 2003;47(11):3463-3469.
3. Orlando R, Piccoli P, De Martin S, Padrini R, Palatini P. Effect of the CYP3A4 inhibitor erythromycin on the pharmacokinetics of lignocaine and its pharmacologically active metabolites in subjects with normal and impaired liver function. Br J *Clin Pharmacol.* 2003;55(1):86-93.

HEALTHCARE PROFESSIONAL CHECKLIST

The checklist below includes information to consider when treating patients receiving CAMZYOS and counseling patients and/or their caregiver(s).
Please note that this checklist is not meant to be all-inclusive.

Prior to starting treatment

- ☐ Obtain a medical history from the patient to determine risk factors for heart failure.
- ☐ Complete an echocardiogram to confirm that the patient's LVEF is ≥55% prior to initiating CAMZYOS.
- ☐ Patients should be genotyped for CYP2C19 phenotype in order to determine appropriate CAMZYOS dose.
- ☐ Assess for potential drug interactions involving CAMZYOS and any drug (including prescription and over-the-counter medications), herbal supplements and grapefruit juice. Detailed guidance on dose modifications/contraindications with concomitant medicines, based on the patient's CYP2C19 phenotype status, is included in the Approved Summary of Product Characteristics.
- ☐ Inform the patient of the risk of heart failure associated with CAMZYOS and that they must consult their HCP or seek medical attention immediately if they experience worsening, persistent or new shortness of breath, chest pain, fatigue, palpitations or leg swelling.
- ☐ Counsel the patient on the risks of potential drug interactions involving CAMZYOS and to not start or stop taking any medications or change the dose of any medication they are taking without talking to you first.
- ☐ Confirm a negative pregnancy test in patients of childbearing potential.
- ☐ Educate patients of childbearing potential on the risk of embryo-foetal toxicity associated with CAMZYOS. Counsel on the need to avoid pregnancy and the need for an effective form of contraception during treatment with CAMZYOS and for 6 months following discontinuation.
- ☐ Instruct patients of childbearing potential to contact you or another member of your healthcare team **immediately** if they become pregnant or suspect they may be pregnant.
- ☐ Provide the patient with the **Patient Guide** and highlight the **Patient Card** within the guide.
- ☐ Schedule the next echocardiogram 4 weeks after initiation of treatment.

During treatment at each clinical visit (as described in the Approved Summary of Product Characteristics)

- ☐ Confirm LVEF is ≥50% by echocardiogram assessment. If at any visit LVEF is <50%, interrupt treatment for 4 weeks and until LVEF is ≥50%.
- ☐ Assess the LVOT gradient with the Valsalva maneuver and adjust the dose per the guidance provided in the Approved Summary of Product Characteristics .
- ☐ Assess the patient for signs and symptoms of heart failure.
- ☐ Assess for intercurrent illnesses such as infections or arrhythmia (e.g., atrial fibrillation or other uncontrolled tachyarrhythmia).
- ☐ Assess for drug interactions involving CAMZYOS and any drug (including prescription and over-the-counter medications), herbal supplements and grapefruit juice that the patient has newly started, has changed the dose of or plans on taking in the future. Detailed guidance on dose modifications/contraindications with concomitant medicines, based on the patient's CYP2C19 phenotype status, is included in the Approved Summary of Product Characteristics.
- ☐ Counsel the patient on the risks of potential drug interactions involving CAMZYOS.
- ☐ Remind the patient of the risks associated with CAMZYOS and that they must consult their HCP or seek medical attention immediately if they experience worsening, persistent or new shortness of breath, chest pain, fatigue, palpitations or leg swelling.
- ☐ Counsel the patient on actions to take in case of an overdose and missed or delayed doses.
- ☐ Remind patients of childbearing potential of the risk of embryo-foetal toxicity associated with CAMZYOS. Counsel on the need to avoid pregnancy and the need for an effective form of contraception during treatment and for 6 months following discontinuation.
- ☐ Periodically check pregnancy status throughout treatment in patients of childbearing potential.
- ☐ Instruct patients of childbearing potential to contact you or another member of your healthcare team **immediately** if they become pregnant or suspect they may be pregnant.
- ☐ Provide the patient with the **Patient Guide** and **Patient Card** if needed.
- ☐ Schedule the next echocardiogram per the instructions provided in the Approved Summary of Product Characteristics.

After treatment

- ☐ Counsel patients of childbearing potential on the need to avoid pregnancy and the need for an effective form of contraception for 6 months following discontinuation of CAMZYOS.

NOTES

For reporting any suspected adverse reactions via the national reporting system :

Bristol Myers Squibb™

Bristol Myers Squibb International Corporation,
Saudi Arabia:
At: medinfo.saudiarabia@bms.com
or call: 800 844 7710

The National Pharmacovigilance Centre (NPC)
Saudi Food and Drug Authority (SFDA):
SFDA call center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa

07/24
Version 01