VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

BREVIBLOC belongs to a group of medicines called beta-blockers. It is used to control a rapid heart rate (HR) and to treat heart rate problems when there is an increase in blood pressure (BP) during or immediately after surgery.

Rapid HR that begins in the small heart chambers (the atria) or in the the part of the heart that coordinates contraction between the chambers (atrioventricular node) is known as supraventricular tachycardia (SVT). SVT occurs in all ages; however, the average age of onset is approximately 57 years. SVT is a frequent cause for patients to seek medical help, occurring among 35 individuals for every 100 000 people in the general population each year. SVT is often experienced by patients during or after surgery. Temporary and minor HR changes can occur when a patient is asleep due to anesthesia and are often unpredictable in patients already experiencing heart problems. SVT can occur in 15% to 40% of patients after heart surgery. One risk factor for SVT during or after surgery is older age.

High BP affects around one billion people worldwide, and it occurs more often in elderly and more in men than women. High BP during surgery occurs in about 25% of patients with a history of high BP, but it can also occur in patients with no previous history of high BP. High BP after any type of surgery can occur 4% to 30% of the time. Controlling HR and BP are actual measures that can be taken to reduce the chances of complications after surgery.

VI.2.2 Summary of Treatment Benefits

Almost 1 500 patients were studied in clinical trials for BREVIBLOC. In the over 30 years that BREVIBLOC has been available for use, several additional studies have been published in the literature.

BREVIBLOC lowers rapid heart rate due to SVT and also lowers BP, effectively reducing the strain on the heart. BREVIBLOC works rapidly and has a short half-life. This allows the treating healthcare professional greater control over the patient’s response to BREVIBLOC. If side effects occur, the healthcare professional can adjust the infusion rate as needed.

VI.2.3 Unknowns Relating to Treatment Benefits

The efficacy profile of BREVIBLOC is well-established. However, there are currently insufficient data available to confirm the safety profile of BREVIBLOC in children and

in pregnant women. Therefore, BREVIBLOC is not recommended for use in children or during pregnancy.

VI.2.4 Summary of Safety Concerns

Table 35. Important Identified Risks

Risk	What is Known	Preventability
Side effects affecting the heart such as abnormal heart rhythms, heart failure, or cardiac arrest (Cardiovascular adverse reactions)	BREVIBLOC may reduce the heart rate and/or blood pressure too much. BREVIBLOC can also cause other serious effects on the heart, including abnormal heart rhythms or heart failure.	The BREVIBLOC summary of product characteristics (SmPC) and package leaflet -include information regarding the risk of cardiovascular adverse reactions. Patients with certain conditions should not receive BREVIBLOC. Patients should be carefully monitored while receiving BREVIBLOC.
Local reactions where BREVIBLOC is administered (Infusion site reactions(including extravasation and skin necrosis))	BREVIBLOC is given intravenously (in a vein). Other ingredients in BREVIBLOC were known to cause infusion site reactions. These other ingredients are no longer used in BREVIBLOC products. However, BREVIBLOC may still cause reactions in the area where the medicine enters the vein.	The BREVIBLOC SmPC and package leaflet include information regarding the risks of infusion site reactions, extravasation, and skin necrosis. Healthcare professionals should administer BREVIBLOC into a large, intact vein with good blood flow to help prevent infusion site reactions.
Spasm or constriction of the muscles around the bronchial tubes in the lungs (Reactive airway disease)	BREVIBLOC is a type of beta-blocker. Beta-blockers are known to have the potential to worsen reactive airway diseases in patients with reactive airway disease.	The BREVIBLOC SmPC and package leaflet include information regarding the risk of reactive airway disease. Patients with reactive airway disease should, in general, not receive beta-blockers. If BREVIBLOC must be used in patients with reactive airway disease, it should be used with caution.
Decreased contractility of the heart due to administration of BREVIBLOC and a calcium channel antagonist at the same time (Cardiovascular effects including atrioventricular (AV) conduction abnormalities and myocardial contractility depression with	Beta-blockers (such as BREVIBLOC) and calcium channel blockers (another type of medication for heart problems) both decrease the contractility of the heart. When a beta-blocker is administered at the same time as a calcium channel blocker, fatal outcomes can occur.	The BREVIBLOC SmPC and package leaflet include information regarding the risk of these additive effects. Healthcare professionals should carefully review the patient's medications prior to administering BREVIBLOC. BREVIBLOC must not be administered within

Table 35. Important Identified Risks

Risk	What is Known	Preventability
concurrent administration of calcium channel blockers)		48 hours of discontinuing verapamil therapy.

Table 36. Important Potential Risks

Risk	What is Known (Including Reason Why it is Considered a Potential Risk)
When BREVIBLOC is used in patients with renal impairment, components of BREVIBLOC may accumulate in the body and/or the blood may have too much potassium in it. (Hyperkalemia in patients with underlying renal insufficiency)	When BREVIBLOC is used in patients with renal impairment, components of BREVIBLOC may accumulate in the body and/or the blood may have too much potassium in it. This has not yet been associated with any significant adverse effects in humans.

Table 37. Missing Information

Risk	What is Known
Pregnant and breastfeeding females were not studied in clinical trials (Lack of data on use in pregnant or lactating females)	Pregnant and breastfeeding females were not studied in clinical trials for BREVIBLOC. BREVIBLOC is not recommended for use during pregnancy or breastfeeding.
Pediatric patients were not studied in clinical trials (Lack of data on safety and efficacy on use in pediatric patients (<18 years of age))	There are not enough data on use of BREVIBLOC in children to confirm the safety and effectiveness on use in this population. BREVIBLOC is not indicated for use in children aged up to 18 years.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a SmPC which provides physicians, pharmacists, and other healthcare professionals with details on how to use the medicine, the risks, and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measures.

VI.2.6 Planned Post-authorization Development Plan

List of Studies in Post-authorization Development Plan

There are currently no plans to initiate any Baxter-sponsored studies to further study the safety or efficacy of BREVIBLOC in the post-authorization setting.

Studies which are a Condition of the Marketing Authorization

There are no studies which are a condition of the marketing authorization.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Table 38. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	08 JUN 2011	Important Identified Risks: Development of cardiac adverse events: hypotension, bradycardia, cardiac arrest, cardiac failure or other arrhythmias Infusion site reactions, extravasation and skin necrosis Hypersensitivity reactions Bronchospasm in patients with pre-existing bronchospastic disease Additive effects on cardiac contractility with concurrent administration of BREVIBLOC and calcium antagonists (i.e. verapamil and to a lesser extent diltiazem and dihydropyridines) Important Potential Risks: Use in patients with underlying renal insufficiency (especially ESRD and chronic renal insufficiency) as a result of decreased excretion of acid metabolite Hypoglycaemia in diabetic patients Overdose Potentiating effect on atrial conduction time and negative inotropic effect with concurrent administration of BREVIBLOC with Class I anti-arrhythmics or amiodarone Use of BREVIBLOC in pregnant and lactating females Missing Information: Paediatric data	None
2.0	20 DEC 2011	Medication errors- use of incorrect product concentration	Added as important potential risk

Table 38. Major Changes to the Risk Management Plan Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
		Off-label use of BREVIBLOC in paediatric patients	Added as important potential risk
		Use of BREVIBLOC in pregnant and lactating females	Re-categorized from important potential risk to missing information
3.0	27 FEB 2012	"Hypoglycaemia in diabetic patients" was revised to "Use of BREVIBLOC in diabetic patients or in the case of suspected or actual hypoglycaemia: -Increased blood glucose-lowering effect of antidiabetic agents when used concomitantly with BREVIBLOC -Brevibloc may mask tachycardia occurring with hypoglycaemia"	None
4.0	01 JUN 2012	No changes to the safety concerns	None
5.0	05 JUL 2012	No changes to the safety concerns	None
6.0	25 JUL 2014	"Development of cardiac adverse events: hypotension, bradycardia, cardiac arrest, cardiac failure or other arrhythmias" was revised to "Cardiovascular adverse reactions, including dysrhythmias, cardiac failure, and cardiac arrest"	None
		"Bronchospasm in patients with pre-existing bronchospastic disease" was revised to "Reactive airway disease"	None
		"Additive effects on cardiac contractility with concurrent administration of BREVIBLOC and calcium antagonists (i.e. verapamil and to a lesser extent diltiazem and dihydropyridines)" was revised to "Additive effects on cardiac contractility with concurrent administration of calcium channel antagonists"	None
		"Use in patients with underlying renal insufficiency (especially ESRD and chronic renal insufficiency) as a result of decreased excretion of acid metabolite" was revised to "Decreased acid metabolite excretion and hyperkalemia in patients with underlying renal insufficiency"	None
		"Use of BREVIBLOC in diabetic patients or in the case of suspected or actual hypoglycaemia:	None

Table 38. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
		-Increased blood glucose-lowering effect of antidiabetic agents when used concomitantly with BREVIBLOC -Brevibloc may mask tachycardia occurring with hypoglycaemia" was revised to "Masking of tachycardia occurring with hypoglycemia and increased glucose-lowering effect of concomitantly used antidiabetic agents in diabetic patients"	
		The important potential risk of "Overdose" was removed as a safety concern.	The formulation of BREVIBLOC to which this safety concern applied is no longer available on the market.
		"Medication errors- use of incorrect product concentration" was revised to "Medication errors"	None
		"Off-label use of BREVIBLOC in paediatric patients" was revised to "Lack of data on safety and efficacy in pediatric patients (<18 years of age) and re-categorized as missing information	Per Good Pharmacovigilance Practice definitions
		"Use of BREVIBLOC in pregnant and lactating females" was revised to "Lack of data in pregnant or lactating females"	None
Version 7.0	22 NOV 2017	The important identified risk "Cardiovascular adverse reactions, including dysrhythmias, cardiac failure, and cardiac arrest" was revised to "Cardiovascular adverse reactions"	The safety concern was broadened to be inclusive of all cardiovascular adverse reactions.
		The important identified risk "Infusion site reactions, extravasation, and skin necrosis" was revised to "Infusion site reactions (including extravasation and skin necrosis)"	None
		The important identified risk "Hypersensitivity reactions" was revised to "Hypersensitivity"	None
		The important identified risk "Additive effects on cardiac contractility with concurrent administration of calcium channel antagonists" was revised to "Cardiovascular effects including atrioventricular (AV) conduction abnormalities and myocardial	None

Table 38. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
		contractility depression with concurrent administration of calcium channel blockers"	
		The important potential risk "Decreased acid metabolite excretion and hyperkalemia in patients with underlying renal insufficiency" was revised to "Hyperkalaemia in patients with underlying renal insufficiency"	None
		The important potential risk "Masking of tachycardia occurring with hypoglycemia and increased glucose-lowering effect of concomitantly used antidiabetic agents in diabetic patients" was removed	The important potential risk was omitted.
		The important potential risk "Potentiating effect on atrial conduction time and negative inotropic effect with concurrent administration of BREVIBLOC with Class I anti-arrhythmics or amiodarone" was removed	The important potential risk was omitted.
		The important potential risk "Medication errors" was removed	The formulation of BREVIBLOC to which this safety concern applied (BREVIBLOC 20 mg/ml) is not available on the market in the EU.
		The missing information "Lack of data in pregnant or lactating females" was revised to "Lack of data on use in pregnant or lactating females"	None
		The missing information "Lack of data on safety and efficacy in pediatric patients (<18 years of age) was revised to "Lack of data on safety and efficacy on use in pediatric patients (<18 years of age)"	None
7.1	15 MAY 2018	The important identified risk "Hypersensitivity" was removed	None