VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Adenosine Kabi is indicated for rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory by-pass tracts (Wolff-Parkinson-White Syndrome).

AV nodal reentrant tachycardia (AVNRT)

The most common cause of paroxysmal SVT is AV nodal reentrant tachycardia (AVNRT). AVNRT is diagnosed in 50-60% of patients who present with regular narrow QRS tachyarrhythmia[1,2,3,4]. The heart rate is 120-250 bpm and is typically quite regular.

AVNRT may occur in healthy, young individuals, and it occurs most commonly in women[4]. Most patients do not have structural heart disease. However, occasionally these individuals may have an underlying heart condition such as rheumatic heart disease, pericarditis, myocardial infarction, mitral valve prolapse, or preexcitation syndrome (e.g. Wolff-Parkinson-White syndrome)[1,3,4].

AV nodal tissue may have 2 conducting pathways with different electrophysiologic properties. One pathway (alpha) is a relatively slow conducting pathway with a short refractory period, while the second pathway (beta) is a rapid conducting pathway with a long refractory period. The coexistence of these functionally different pathways serves as the substrate for reentrant tachycardia[1,2,3,5].

AV reentrant tachycardia (AVRT)

AVRT is the second most common form of paroxysmal SVT. The incidence rate of AVRT in the general population is 0.1-0.3%. AVRT is more common in males than in females (male-to-female ratio of 2:1), and patients with AVRT commonly present at a younger age than do patients with AVNRT. AVRT is associated with the Ebstein anomaly, although most patients with AVRT do not have evidence of structural heart disease.

AVRT occurs in the presence of accessory pathways, or bypass tracts. Accessory pathways are errant strands of myocardium that bridge the mitral or tricuspid valves[3,5,6,7].

AVRT results from the presence of 2 or more conducting pathways; specifically, the AV node and 1 or more bypass tracts. In a normal heart, only a single route of conduction is present. Conduction begins at the sinus node, progresses to the AV node, and then to the bundle of His and the bundle branches. However, in AVRT, 1 or more accessory pathways connect the atria and the ventricles. The accessory pathways may conduct impulses in an anterograde manner, a retrograde manner, or both[3,5,6,7,8,9,10,11].

Epidemiology

In the US American population, the incidence of paroxysmal SVT is approximately 1-3 cases per 1000 persons. The incidence rate of the WPW pattern on electrocardiographic tracings is 0.1-0.3% in the general population, although not all patients develop SVT [5,7,12,13,14].

In a population-based study, the prevalence of paroxysmal SVT was 2.25 cases per 1000 persons, with an incidence of 35 cases per 100,000 person-years[15.] AVNRT is more common in patients who are middle aged or older, while adolescents are more likely to have SVT mediated by an accessory pathway.

Paroxysmal SVT is observed not only in healthy individuals; it is also common in patients with previous myocardial infarction, mitral valve prolapse, rheumatic heart disease, pericarditis, pneumonia, chronic lung disease, and current alcohol intoxication Digoxin toxicity also may be associated with paroxysmal supraventricular tachycardia[5,7,16]

VI.2.2 Summary of Treatment Benefits

Adenosine is a purine nucleoside which is present in all cells of the body. Animal pharmacology studies have in several species shown that Adenosine has a negative dromotropic effect on the atrioventricular (AV) node.

In man, Adenosine administered by rapid intravenous injection slows conduction through the AV node. This action can interrupt re-entry circuits involving the AV node and restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardias. Once the circuit has been interrupted, the tachycardia stops and normal sinus rhythm is re-established.

One acute interruption of the circuit is usually sufficient to arrest the tachycardia.

Since atrial fibrillation and atrial flutter do not involve the AV node as part of a re-entry circuit, Adenosine will not terminate these arrhythmias.

By transiently slowing AV conduction, atrial activity is easier to evaluate from ECG recordings and therefore the use of Adenosine can aid the diagnosis of broad or narrow complex tachycardias.

Adenosine may be useful during electrophysiological studies to determine the site of AV block or to determine in some cases of pre-excitation, whether conduction is occurring by an accessory pathway or via the AV node.

VI.2.3 Unknowns Relating to Treatment Benefits

Not applicable.

VI.2.4 Summary of safety concerns

Safety Concern	What is known	Preventability
Important Identified Risks		
Cardiac arrhythmias (potentially life-threatening)	Cardiac arrhythmias (bradycardia or tachyarrhythmia due to increased conduction) may occur	Risk minimization: Administration in hospital setting, monitoring and cardio-respiratory resuscitation equipment
Significant hypotension (in particular in patients with left main coronary stenosis, uncorrected hypovolemia, stenotic valvular heart disease, left to right shunt, pericarditis or pericardial effusion, autonomic dysfunction, stenotic carotid artery disease with cerebrovascular insufficiency)	Significant hypotension may occur in patients with heart diseases with reduced cardiac output.	Yes, contraindicated in patients with severe hypotension, continuous monitoring of blood pressure for early symptoms in other patients
Patients with myocardial infarction, severe heart failure, or in patients with minor conduction defects (first degree AV block, bundle branch block)	Transient aggravation during infusion may occur	Yes, contraindicated in patients with decompensated states of heart failure, continuous ECG monitoring for early symptoms in other patients
Severe bradycardia (early post heart transplantation patients, patients with occult sino-atrial disease, patients with long QT syndrome)	Increased sensitivity to Adenosine in patients with recent heart transplantation	Yes, contraindicated in patients with long QT syndrome, continuous ECG monitoring for early symptoms in other patients
Patients with atrial fibrillation or flutter and accessory bypass tract	Increased conduction, in particular down the anomalous pathway may occur in patients with accessory bypass tract	Risk minimization: Administration in hospital setting, monitoring and cardio-respiratory resuscitation equipment

Safety Concern	What is known	Preventability
Patients with a history of convulsions/seizures	Adenosine may trigger convulsions in patients who are susceptible to convulsions	Risk minimization: Administration in hospital setting, continuous monitoring
Interaction with dipyridamole	Dipyridamole is a known inhibitor of adenosine uptake, it may potentiate the action of Adenosine Kabi up tot he 4-fold	Yes, Adenosine Kabi is contraindicated in patients receiving dipyridamole, otherwise, dipyridamole should be stopped 24 hrs before hand, or the adenosine dose should be greatly reduced
Interaction with aminophylline, theophylline and other xanthines	Aminophylline, theophylline and other xanthines are competitive adenosine antagonists	Yes, Aminophylline, theophylline and other xanthines should be avoided for 24 hrs prior to the use of adenosine; Foods and drinks containing xanthines (tea, coffee, chocolate and cola) should be avoided for at least 12 hrs prior to the use of adensosine
Drugs tending to impair cardiac conduction	Drugs tending to impair cardiac conduction may lead to bradycardia in combination with adenosine	Yes, drugs tending to impair cardiac conduction should be avoided in combination with adenosine
Transient and spontaneously rapidly reversible worsening of intracranial hypertension	Incidence: very rare	Risk minimization: Administration in hospital setting, monitoring and cardio-respiratory resuscitation equipment
Loss of consciousness/syncope	Incidence: not known	Risk minimization: Administration in hospital setting, monitoring and cardio-respiratory resuscitation equipment

Safety Concern	**What is known**	**Preventability**
Respiratory failure (bronchospasm, apnea, respiratory arrest) with fatal outcome	Incidence bronchospasm: very rare Incidence respiratory failure/arrest: Not known	Risk minimization: Administration in hospital setting, monitoring and cardio-respiratory resuscitation equipment
Important Missing Information		
Use in breast-feeding and pregnant women	There are no or limited amount of data from the use of adenosine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. It is unknown whether adenosine metabolites are excreted in human milk. Adenosine Kabi should not be used during breast-feeding.	Yes, adenosine is not recommended during pregnancy and breast-feeding unless the physician considers the benefits to outweigh the potential risks.
Important Missing Information		
Use in children (0 – 18 years)	The safety and efficacy of Adenosine in children aged 0-18 years old have not been established. No data are available. No controlled pediatric study has been undertaken. Published uncontrolled studies show similar effects of adenosine in adults and children: effective doses for children were between 0.0375 and 0.25mg/kg.	Yes, adenosine is not recommended for use in children (0 – 18 years) unless the physician considers the benefits to outweigh the potential risks

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

The Summary of Product Characteristics and the Package Leaflet for Adenosine Kabi contain information about routine risk minimisation measures. Refer to **Dossier Module 1, Section 1.3.1.** for the same.

VI.2.6 Planned Post Authorisation Development Plan

Refer to table-2, section III.1.

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

Not applicable.