VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Pulmonary Arterial Hypertension (PAH): Pulmonary hypertension is high blood pressure in the arteries going to the lung. If the pulmonary arterial pressure exceeds about 40/20 mm Hg or the average pressure exceeds 25 mm Hg, then pulmonary hypertension is present. Since the late 1990s, there has been increasing interest in the causes, consequences and treatment of pulmonary arterial hypertension (PAH). The exact data regarding occurrence of pulmonary arterial hypertension is not available. According to the data published by registry suggested approximately 2-8 cases reported per million populations, in which 1-2 cases per million

populations were reported for the pulmonary arterial hypertension with unknown cause. As per registry, the occurrence of pulmonary arterial hypertension in Czech Republic is around 10-11 cases per million population in 2007.

Digital ulcers: This disease cause excessively reduced blood flow in response to cold or emotional stress, causing discoloration of the fingers, toes, and occasionally other areas.

Internationally, the occurence is varies among different populations, from 3.8-20.1%. It occurs more frequently in women than in men the rate is approximately 4.9%-20.1% in women to 3.8%-13.5% in men. In Europe, This occurs in 5 to 20 % of the population. It is observed four times more often in women than in men. It usually occurs in the second or third decade of life with an average age of 40 years. Attacks are characterized by a paroxysmal white-blue-red or just white and blue discoloration of the fingers and toes; the attacks are induced by cold or stress, usually, cease after no more than some minutes, but can also persist for hours. There is no death however, little serious complication can occur with this disease. In very rare cases, decreased oxygen in a tissue (usually because of decreased blood flow) (ischemia) of the affected body part can result in death of the tissue (necrosis).

VI.2.2 Summary of treatment benefits

Bosentan is used for the treatment of pulmonary arterial hypertension (high blood pressure in the blood vessels (the pulmonary arteries) that carry blood from the heart to the lungs) and digital ulcers (ulcers of the fingers) in people with a condition called scleroderma.

Two studies have been conducted in 32 and 213 adult patients respectively with WHO functional class III–IV pulmonary arterial hypertension. After 4 weeks of bosentan 62.5 mg twice daily, the maintenance doses studied in these studies were 125 mg twice daily in first study and 125 mg twice daily and 250 mg twice daily in the second study. The primary endpoint for each study was change in 6-minute walk distance at 12 weeks for the first study and 16 weeks for the second study. In both studies, treatment with bosentan resulted in significant increases in exercise capacity. The improvement in walk distance was apparent after 4 weeks of treatment, was clearly

evident after 8 weeks of treatment and was maintained for up to 28 weeks of double-blind treatment in a subset of the patient population. A reduction in symptoms of pulmonary arterial hypertension was observed with bosentan treatment. Dyspnoea measurement during walk tests showed an improvement in bosentan-treated patients.

Two other studies have been conducted in 122 and 190 adult patients respectively with systemic sclerosis and digital ulcer disease. After 4 weeks of bosentan 62.5 mg twice daily, the maintenance dose studied in both these studies was 125 mg twice daily. The duration of double-blind therapy was 16 weeks in the first study, and 24 weeks in study the second study. The number of new digital ulcers from baseline to study endpoint was a primary endpoint in both studies. Treatment with bosentan resulted in fewer new digital ulcers for the duration of therapy, compared with placebo. No effect of bosentan on time to healing of digital ulcers was observed in either study.

However, these studies were conducted for Tracleer, by Actelion Registration Ltd, and Accord has not conducted any studies for Bosentan on expected benefit considering its similarity to the currently marketed product.

VI.2.3 Unknowns relating to treatment benefits

Not known

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Hepatotoxicity	Some patients taking Bosentan Accord have been found to have abnormal liver function tests. Elevated liver function tests with	Yes During treatment with bosentan Accord, your doctor will arrange for regular blood tests to check

Risk	What is known	Preventability
	hepatitis (inflammation of the liver) and/or jaundice (yellowing of the skin or the whites of the eyes). Cirrhosis (scarring) of the liver, liver failure (serious disturbance of liver function).	for changes in your liver function. If one experiences any symptoms relating to liver failure, doctor should be immediately contacted.
Teratogenicity	Bosentan Accord may harm unborn babies conceived before starting or during treatment.	Yes If you are a woman who could become pregnant, your doctor will ask you to take a pregnancy test before you start taking bosentan Accord, and regularly while you are taking bosentan Accord. Don't take bosentan Accord if you are pregnant or planning to become pregnant. If it is possible that you could become pregnant, use a reliable form of birth control (contraception) while you are taking bosentan Accord. Your doctor or gynaecologist will advise you about reliable contraceptive methods while taking bosentan Accord. Because bosentan Accord may make

Risk	What is known	Preventability
		hormonal contraception (e.g., oral, injection, implant, or skin patches) ineffective, this method on its own is not reliable. Therefore, if you use hormonal contraceptives you must also use a barrier method (e.g., female condom, diaphragm, contraceptive sponge, or your partner must also use a condom). Inside your pack of Bosentan Accord tablets you will find a Patient Reminder Card. You should complete this card and take it to your doctor at your next visit so that your doctor or gynaecologist can assess whether you need additional or alternative reliable contraceptive methods. Monthly pregnancy tests are recommended while you are taking Bosentan Accord and are of child-bearing age. Tell your doctor immediately if you become pregnant while you are taking Bosentan Accord, or plan to become pregnant in the

Risk	What is known	Preventability
		near future.
Low platelet count (Thrombocytopenia) with decrease in haemoglobin concentration	Bosentan Accord has been found to cause anaemia (low number of red blood cells), lowering of blood platelets (thrombocytopenia) or decrease in haemoglobin.	Yes During treatment with Bosentan Accord, your doctor will arrange for regular blood tests to check haemoglobin level.
An abnormal accumulation of fluid in the circulatory system or within the tissues or cavities of the body (Fluid retention)	Bosentan Accord has been found to cause oedema (swelling of the legs and ankles or other signs of fluid retention)	Yes Inform doctor if there is swelling of the legs and ankles or other signs of fluid retention.
Excess fluid in the lungs (Pulmonary oedema) associated with pulmonary veno-occlusive disease (PVOD)	Bosentan very commonly causes oedema (swelling of the legs and ankles or other signs of fluid retention). Should signs of pulmonary oedema occur when bosentan is administered in patients with PAH, the possibility of associated veno- occlusive disease should be considered.	Yes Inform doctor if there is sign of oedema.

Risk	What is known	Preventability
Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals)	Bosentan Accord when taken along with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals, may result in increase concentrations of Bosentan Accord in the blood or may reduce the efficacy of Bosentan Accord.	Yes Before starting the treatment with bosentan, patient should inform to their doctor for having treatment of hormonal contraceptives, sildenafil and antiretrovirals.

Important potential risks

Risk	What is known
Seminiferous tubule atrophy	None
Vasculitis	None

Missing information

Risk	What is known
Limited information on long term safety and outcomes in paediatric population	There are no data on the safety and efficacy in patients under the age of 18 years.

Risk	What is known
Limited information on use in pregnancy and lactation	Bosentan Accord should be avoided in case of pregnancy or in case the patient is planning pregnancy. The doctor should be informed immediately if the patient is breast-feeding. Breast-feeding should be stopped if Bosentan Accord is prescribed, because it is not known whether this medicine passes into breast milk.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions can be found in Annex II of the product information which will be published in Bosentan Accord's EPAR page.

Hepatotoxicity

Risk minimisation measure(s):
Objective and rationale: Patients and HCPs to understand the risk of occurrence of hepatotoxicity and the appropriate management of this risk
Proposed actions: HCP educational materials to be provided to prescribing physicians warning about this risk and measures to take

Risk minimisation measure(s):
Patient booklet will inform patients what the symptoms of hepatotoxicity are and the importance of seeking medical help immediately. Patient alert card reminding of monthly blood test to check liver function. The MAH after approval of the procedure will get in touch with each Member state and will finalise the contents of educational materials and the distribution plan.

Thrombocytopenia with decrease in haemoglobin concentration

Risk minimisation measure(s):
Objective and rationale: Patients and HCPs to understand the risk of decrease in haemoglobin concentration and the appropriate management of this risk
Proposed actions: HCP educational materials to be provided to prescribing physicians warning about this risk and measures to take Patient booklet will inform patients regarding decrease in haemoglobin concentration and periodic monitoring of hemoglobin concentrations. The MAH after approval of the procedure will get in touch with each Member state and will finalise the contents of educational materials and the distribution plan.

Teratogenicity

Risk minimisation measure(s):
Objective and rationale: Patients and HCPs to understand the risk of occurrence of teratogenicity

Risk minimisation measure(s):
and the appropriate management to avoid this risk
Proposed actions: HCP educational materials to be provided to prescribing physicians warning about this risk and contraceptive measures to take Patient booklet will inform patients what are teratogenic reactions are and the importance of contraception during treatment with bosentan. Patient alert card reminding of pregnancy test before starting and during each month while on treatment with bosentan The MAH after approval of the procedure will get in touch with each Member state and will finalise the contents of educational materials and the distribution plan.

VI.2.6 Planned post authorisation development plan (if applicable)

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Version	**Date**	**Safety Concerns**	**Comment**
4.0	05 November 2014	No changes in safety concerns	As per RMS Day 207 Preliminary Assessment Report of Bosentan 62.5 and 125 mg Film-Coated Tablets (UK/H/5622/01-02/DC) dated 03 November 2014, part III.1 (Safety concerns

Version	Date	Safety Concerns	Comment
			and overview of planned pharmacovigilance actions), part III.5 (Summary of the Pharmacovigilance Plan), part VI.1.2 (Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan) have been updated to include details on additional pharmacovigilance activities.
3.0	15 September 2014	Following important potential risks have been upgraded to important identified risks: • Pulmonary oedema associated with pulmonary veno-occlusive disease (PVOD). • Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals). Section VI.2 *"Elements for a public summary"* has been updated.	Day 120 RMS comments on Bosentan Accord 62.5 mg and 125 mg film-coated tablets (UK/H/5622/001/DC)

Version	Date	Safety Concerns	Comment
2.0	27-May-2014	Following risks were added: *Important Identified Risk:* Fluid retention *Important Potential Risk:* Seminiferous tubule atrophy Vasculitis *Missing Information:* Use in pregnancy and lactation Important identified risk: 'Decrease in haemoglobin concentration' has been modified to 'Thrombocytopenia with decrease in haemoglobin concentration' Important potential risk: 'Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil, and antiretrovirals)' has been modified to 'Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil, lopinavir	