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 PAH. The exact data regarding occurrence of pulmonary arterial hypertension is not available. According to the data published by registry, approximately 2-8 cases reported per million population, of which 1-2 cases per million are of unknown cause. The occurrence of pulmonary arterial hypertension in the Czech Republic was 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 occurrence varies among different populations, from 3.8-20.1%. It occurs more frequently in women than in men with a rate of approximately 4.9%-20.1% in women 3.8%-13.5% in men. In Europe, digital ulcer occur in 5 to 20 % of the population and 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 onset 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 and usually cease after no more than some minutes, but can also persist for hours. Digital ulcers are not fatal and few serious complications occur with this disease.

VI.2.2 Summary of treatment benefits

In an analysis based on change in walking distance, 95 patients randomly assigned to bosentan 125 mg twice daily in the dummy drug controlled (placebo-controlled) studies, it was found that at week 8, 66 patients had improvement in breathlessness, 22 were stable and 7 had deteriorated. Of the 22 patients stable at week 8, 6 improved at week 12/16 and 4 deteriorated compared with baseline. Of the 7 patients who deteriorated at week 8, 3

improved at week 12/16 and 4 deteriorated compared with baseline. A reduction in symptoms of pulmonary arterial hypertension was observed with bosentan treatment.
In a clinical study, 185 PAH patients received bosentan 62.5 mg twice daily for 4 weeks followed by 125 mg twice daily (n = 93), or dummy treatment (n = 92) for 6 months. Treatment with bosentan was associated with a reduction in the rate of clinical worsening. There was one hospitalisation related to PAH worsening in the bosentan group and three hospitalisations in the placebo group. Only one death occurred in each treatment group during the 6-month double-blind study period, therefore no conclusion can be drawn on survival.
A randomized, double-blind, placebo-controlled study with bosentan on healing and revention of Ischemic Digital ulcers (DU) in patients with systemic Sclerosis (SSc) was conducted to evaluate the effects of bosentan treatment on DUs associated with SSc. This double-blind, placebo-controlled trial conducted at 41 centres in Europe and North America randomised 188 patients with SSc with at least 1 active DU ('cardinal ulcer') to bosentan 62.5 mg twice daily for 4 weeks and 125 mg twice daily thereafter for 20 weeks (n=98) or matching placebo (n=90; total 24 weeks). The two primary end points were the number of new DUs and the time to healing of the cardinal ulcer. Secondary end points included pain, disability and safety. Bosentan treatment reduced the occurrence of new DUs in patients with SSc but had no effect on DU healing. Bosentan was well tolerated and may be a useful adjunct in the management of patients with SSc with recurrent DUs.

VI.2.3 Unknowns relating to treatment benefits

There are no important unknowns relating to the treatment benefits of bosentan in the populations for which it is approved.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	**What is known**	**Preventability**
Hepatotoxicity	There is no specific recommendation for the use of bosentan with other available	This combination is not recommended. Blood tests should be performed monthly during treatment to monitor liver function.

Risk	What is known	Preventability
	antiretroviral agents due to the lack of data. Due to the marked hepatotoxicity of nevirapine, which could add to bosentan liver toxicity.	
Teratogenicity	Studies in animals have shown reproductive toxicity (teratogenicity, embryotoxicity). There are no reliable data on the use of bosentan in pregnant women. The potential risk for humans is still unknown. Bosentan is contraindicated in pregnancy.	Studies in animals have shown reproductive toxicity (teratogenicity, embryotoxicity). There are no reliable data on the use of bosentan in pregnant women. The potential risk for humans is still unknown. Bosentan is contraindicated in pregnancy.
Decrease in haemoglobin concentration	Treatment with bosentan has been associated with dose-related decreases in haemoglobin concentration. It is recommended that haemoglobin concentrations be checked prior to initiation of treatment, every month during the first 4 months, and quarterly thereafter. If a clinically relevant decrease in haemoglobin concentration occurs, further evaluation and investigation should be undertaken to determine the cause and need for specific treatment.	Treatment with bosentan has been associated with dose-related decreases in haemoglobin concentration. It is recommended that haemoglobin concentrations be checked prior to initiation of treatment, every month during the first 4 months, and quarterly thereafter.
Decrease of sperm count	Animal studies showed testicular effects. In a study investigating the effects of bosentan on testicular function in male PAH patients, 8	Animal studies showed testicular effects. In a study investigating the effects of bosentan on testicular function in male PAH patients, 8 out of 24 patients showed a decreased sperm

Risk	What is known	Preventability
	out of 24 patients showed a decreased sperm concentration from baseline of at least 42% after 3 or 6 months of treatment with bosentan. Based on these findings and preclinical data, it cannot be excluded that bosentan may have a detrimental effect on spermatogenesis in men. In male children, a long-term impact on fertility after treatment with bosentan cannot be excluded.	concentration from baseline of at least 42% after 3 or 6 months of treatment with bosentan. Based on these findings and preclinical data, it cannot be excluded that bosentan may have a detrimental effect on spermatogenesis in men. In male children, a long-term impact on fertility after treatment with bosentan cannot be excluded.

Important potential risks:

Risk	What is known (Including reason why it is considered a potential risk)
Pulmonary oedema associated with PVOD	Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, should signs of pulmonary oedema occur when Bosentan Cipla is administered in patients with PAH, the possibility of associated veno-occlusive disease should be considered. In the post-marketing period there have been rare reports of pulmonary oedema in patients treated with bosentan who had a suspected diagnosis of pulmonary veno-occlusive disease.
Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and	Bosentan is an inducer of the cytochrome P450 (CYP) isoenzymes CYP2C9 and CYP3A4. In vitro data also suggest an induction of CYP2C19. Consequently, plasma concentrations of substances metabolised by these isoenzymes will be decreased when bosentan is co-administered. The possibility of altered efficacy of medicinal products metabolised by these isoenzymes should be considered. The

Risk	**What is known (Including reason why it is considered a potential risk)**
antiretrovirals)	dosage of these products may need to be adjusted after initiation, dose change or discontinuation of concomitant bosentan treatment.
Testicular disorders and male infertility	Animal studies showed testicular effects. In a study investigating the effects of bosentan on testicular function in male PAH patients, 8 out of 24 patients showed a decreased sperm concentration from baseline of at least 42% after 3 or 6 months of treatment with bosentan. Based on these findings and preclinical data, it cannot be excluded that bosentan may have a detrimental effect on spermatogenesis in men. In male children, a long-term impact on fertility after treatment with bosentan cannot be excluded.
Respiratory tract infection in children	The safety profile in this pooled analysis of uncontrolled paediatric studies was similar to that observed in the pivotal trials in adult patients with PAH except for infections, which were more frequently reported than in adults (69.0% vs 41.3%). This difference in infection frequency may in part be due to the longer median treatment exposure in the paediatric set (median 71.8 weeks) compared to the adult set (median 17.4 weeks). In this study respiratory infection (25%) in children was one of the most frequent adverse event reported.

Missing information:

Risk	**What is known**
Use of bosentan with addition of sildenafil in children	Co-administration of bosentan 125 mg twice daily (steady state) with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63% decrease in the sildenafil AUC and a 50% increase in the bosentan AUC. Caution is recommended in the case of co-administration.
Use in children with renal function impairment	There are no data on the safety and efficacy in children. Pharmacokinetic data are not available for bosentan in young children

Risk	What is known
	with renal function impairment.

VI.2.5 Summary of additional 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.

The Summary of Product Characteristics and the Package leaflet for Bosentan can be found on the national authority's home page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). These additional risk minimisation measures are for the following risks:

Hepatotoxicity
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. Patient booklet will inform patients about the symptoms of hepatotoxicity and the importance of seeking medical help immediately. Patient alert card reminding of monthly blood test to check liver function (available in product package). Also a specific "follow-up questionnaire" will be distributed to optimise the clinical information available for safety reports concerning liver function test abnormalities, hepatitis or liver failure (available in Company website).

Teratogenicity

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Objective and rationale: Patients and HCPs to understand the risk of occurrence of teratogenicity 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 about the teratogenic reactions 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 (available in product package). Also a specific "follow-up questionnaire" will be distributed to optimise the clinical information available for safety reports concerning use in women of child-bearing potential, if the method of contraception is not mentioned in the ADR report (available in Company website).

Decrease in haemoglobin concentration
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 haemoglobin concentrations.

Decrease of sperm count
Objective and rationale: Patients and HCPs to understand the risk of decrease of sperm count 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 of sperm count and periodic

monitoring on this risk.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.