### VI.2 Elements for a Public Summary

#### VI.2.1 Overview of disease epidemiology

**High blood pressure in lung vessels which carry blood away from the heart**

Several studies showed that spontaneous high blood pressure in lungs occur from 6.5 to 25 cases per one million population, high blood pressure in lungs associated with body connective tissue disease between 2.3-15 cases and heart disease associated with high blood pressure in lungs present since birth between 1.7-12 cases per one million population. Of the patients, 25-30% are >60 years old. High blood pressure in lungs occurs approximately two- or three-fold higher in females than in males.

**Skin lesions in fingers**

Scleroderma (hardening, deformity and ulceration of the skin) is a rare disease. Raynaud’s phenomenon (condition causing pain, numbness, coldness and blueness of the fingers), digital ulcers (fingers skin lesions) and calcinosis (calcium deposits) precede the manifestations of this disease. Out of patients with this rare disease, 58% develop at least one finger skin lesion at some point. In 32% of cases, ulcers will become persistent and 25% of patients with scleroderma have more than two digital ulcers.

#### VI.2.2 Summary of treatment benefits

- **High blood pressure in lung vessels**

  A study performed on 213 patients with the mentioned disease showed that after 16 weeks of treatment patients treated with bosentan were able to cover a significantly longer distance by walking six minutes than patients treated with placebo (a fake treatment). This walk test represents a way of measuring patient’s capacity to perform physical exercise. Bosentan also improved the breathing capacity (as measured on a scale that shows how patients perceive breathlessness) and increased the amount of time to the worsening of disease.

  The death rate of 529 patients with high blood pressure in lung vessels (PAH) treated with bosentan in 'real life' was observed in another study. These patients were older and had more advanced disease than patients previously enrolled in experimental studies. Slightly
more than half of patients had PAH of unknown cause while in the remaining patients PAH has a known cause (a connective tissue disease). It was estimated that each year 11.8 in 100 treated patients with unknown cause PAH and 16.6 in 100 treated patients with PAH caused by connective tissue disease die. This was significantly less that the death rate known for patients with the same disease who are not treated. It was also observed that death rates are influenced by age, disease severity and cause of PAH.

- High blood pressure in lung vessels secondary to scleroderma (a disease where connective tissue - the material inside the body that gives tissues their shape and helps keep them strong, gets hard or thick) without significantly scarred lung tissue.

In a review of study results, 66 patients with connective tissue disease, mostly scleroderma or lupus erythematosus who were randomly treated with bosentan or placebo were described. Walking distance was significantly improved in patients treated with bosentan compared to those treated with placebo. 64 patients were followed further as they received bosentan in an extension of the original study. After one year of extended treatment, 85.9 in 100 patients survived and after 2 years 72.4 in 100 survived. Less than a fifth of these patients required additional treatment for their disease. The authors concluded that long term treatment with bosentan was safe and effective.

- High blood pressure in lung vessels associated with certain congenital (that patients are born with) heart disease (such as: systemic-to-lung shunts and intracardiac communication defects).

54 patients with a structural problem of the heart that makes the blood to circulate abnormally in the body (known as Eisenmenger syndrome) were randomly treated with bosentan (37 of them) and with placebo (17 of them) for 16 weeks, in one study. In patients treated with bosentan, the blood pressure in lung vessels decreased and their exercises capacity increased as compared to those treated with placebo. 37 patients who completed this study were further enrolled in an extension where they were treated with bosentan for 24 weeks. At the end of the extension study, the six-minute walking distance increased from where it was at the end of the original study in both patients originally treated with bosentan and in those treated with placebo. This longer follow-up support the efficacy of bosentan for the treatment of Eisenmenger syndrome.

- Reduction of the number of new digital ulcers in patients with scleroderma (a disease where connective tissue - the material inside the body that gives tissues their shape and helps keep them strong, gets hard or thick) and on-going ulceration of the fingers.

188 patients with scleroderma with at least one finger ulcer were randomly treated with bosentan of placebo for 20 weeks in one study. After 24 weeks it was observed that patients treated with bosentan has 30% fewer finger ulcers than patients treated with placebo. The effect was greater in patients with more finger ulcers at the beginning of the study. There was no difference in healing rate or pain felt by the patients. The authors concluded that bosentan is able to reduce the occurrence of new digital ulcers in patients with scleroderma.

- Some improvements have also been shown in patients with class II pulmonary arterial hypertension. ‘Class II’ involves slight limitation of physical activity.

A 6-month study involving 185 patients with class II pulmonary arterial hypertension was conducted. Patients received either treatment with bosentan or placebo (a fake treatment). Compared with placebo, patients treated with bosentan had an improved six-minutes walking distance.

**VI.2.3 Unknowns relating to treatment benefits**

Pulmonary arterial hypertension
Based on the currently available data an important gap in knowledge was identified in relation to bosentan efficacy in children. For paediatric patients aged 2 years or older, the optimal maintenance dose has not been defined in well-controlled studies. In addition, there is only limited clinical experience in paediatric patients under 2 years of age.

**Systemic sclerosis with on-going digital ulcer disease**
Based on the currently available data an important gap in knowledge was identified in relation to bosentan efficacy in children (no data on the safety and efficacy in patients under the age of 18 years is available) and long-term use (controlled clinical study experience in this indication is limited to 6 months).

**Severe pulmonary arterial hypertension**
**Use in patients with severe pulmonary arterial hypertension**
Based on the currently available data an important gap in knowledge was identified in relation to bosentan use in patients with severe pulmonary arterial hypertension. The efficacy in this category has not been established.

**Use in children with renal function impairment**
Based on the currently available data an important gap in knowledge was identified in relation to bosentan use in children with renal function impairment. The efficacy in this category has not been established.

**VI.2.4 Summary of safety concerns**

**Important identified risks**

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
<th>Preventability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver toxicity (hepatotoxicity)</td>
<td>Increase in liver enzymes associated with bosentan is dose dependent. Liver enzyme changes typically occur within the first months of treatment but may also occur late in treatment. In case the liver enzymes levels are greater than 3 times of the upper limit of normal (ULN), bosentan dose should be reduced or the treatment should be dis-continued, in which case, re-introduction of bosentan is made after the return of enzymes levels to pre-treatment values. In case of symptoms of liver injury occur, bosentan treatment must be stopped and not re-introduced.</td>
<td>Yes, by monitoring for early symptoms of liver injury. Liver enzymes levels must be measured prior to initiation of treatment and regularly during the bosentan treatment.</td>
</tr>
<tr>
<td>Malformation development in foetus (teratogenicity)</td>
<td>Studies in animals have shown reproductive toxicity (malformations in foetus and embryo). Bosentan is contra-indicated in pregnant women and child-bearing potential women who do not use reliable contraception. Bosentan decrease the effectiveness of hormonal contraceptives (including oral, injectable, transdermal or implantable forms) and an additional or an alternative reliable method of con-</td>
<td>Yes, by taking regularly pregnancy tests and by using adequate contraception method during bosentan treatment.</td>
</tr>
</tbody>
</table>
## Risk

<table>
<thead>
<tr>
<th>What is known</th>
<th>Preventability</th>
</tr>
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</table>
| **Decrease of the oxygen carries in the blood**  
(decrease in haemoglobin concentration) | Treatment with bosentan has been associated with dose-related decreases in oxygen carries concentration in the blood. These decreases stabilise after the first weeks of treatment. The oxygen carries in the blood should be checked before the initiation of treatment and regularly during the treatment. In addition, the decrease of red blood cells in the blood that may require red blood cell transfusion can occur. | Yes, by regularly monitoring of the oxygen carries concentrations levels in the blood. |
| **Decrease of sperm count** | A study described the effects of bosentan on testicular function in male PAH patients. Detrimental effects on the production of sperm were noted. In male children, a long-term impact on fertility after bosentan treatment can occur.  
A slightly increased incidence of testicular tubular atrophy was observed during bosentan administration. | Yes, by notifying prescribers if this safety concern occurs. |

### Important potential risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known (Including reason why it is considered a potential risk)</th>
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</thead>
</table>
| **Lung fluid retention associated with contraction and/or obstruction of lung veins disease**  
(pulmonary oedema associated with pulmonary veno-occlusive disease) | Lung fluid retention has been observed with medications that widen blood vessels and help prevent high blood pressure when used in patients with contraction and/or obstruction of lung veins disease. Consequently, if signs of lung fluid retention occur during bosentan treatment in patients with pulmonary arterial hypertension, the possibility of associated contraction and/or obstruction of lung veins disease should be considered. |
| **Interaction with medicines that are bio-transformed by body enzymes known as CYP3A4 and CYP2C9, increase or decrease the activity of these enzymes (including hormonal contraceptives, sildenafil and antiretrovirals)** | Bosentan increases the activity of the body enzymes known as CYP3A4 and CYP2C9. Therefore, the medicines bio-transformed by these enzymes will have a decreased concentration in blood when co-administrated with bosentan. The dosages of these medicines may be adjusted or discontinued. For this reason, the concomitant administration of bosentan with medicines such as cyclosporine A, tacrolimus, sirolimus, glibenclamide, hormonal contraceptives, warfarin, simvastatin and sildenafil should not be used. |
RMP version 5.0  Bosentan

<table>
<thead>
<tr>
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<th>What is known (Including reason why it is considered a potential risk)</th>
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</thead>
<tbody>
<tr>
<td>Bosentan</td>
<td>Bosentan is bio-transformed by the body enzymes known as CYP3A4 and CYP2C9. The decreased activity of these enzymes may increase the blood concentration of bosentan. For this reason, co-administration with fluconazole, ketoconazole, voriconazole and medicines for the treatment of HIV infection is contraindicated. As rifampicin increases the activity of body enzymes known as CYP3A4 and CYP2C0 and decrease the blood concentration of bosentan, this combination should not be used.</td>
</tr>
<tr>
<td>Testicular disorders and male infertility</td>
<td>A study described the effects of bosentan on testicular function in male PAH patients. Detrimental effects on the production of sperm were noted. In male children, a long-term impact on fertility after bosentan treatment can occur. A slightly increased incidence of testicular tubular atrophy was observed during bosentan administration.</td>
</tr>
<tr>
<td>Respiratory tract infection in children</td>
<td>A study conducted on paediatric patients showed that among the most frequent adverse events experienced with bosentan, infections occurred with an increased incidence of 33%.</td>
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</table>

**Missing information**

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
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</thead>
<tbody>
<tr>
<td>Use of bosentan with addition of sildenafil</td>
<td>Co-administration of bosentan with sildenafil resulted in increased body concentration of bosentan.</td>
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<tr>
<td>Use in children with renal function impairment</td>
<td>No information is available for use in children with renal function impairment.</td>
</tr>
</tbody>
</table>

**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). How they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities. These additional risk minimisation measures are for the following risks:

**Liver toxicity (hepatotoxicity)**

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**Prescriber Kit containing a**
- Prescriber brochure
- Patient brochure
- Patient Alert Card

**Objective and rationale**

Prescribers and patients to understand the risk of hepatotoxicity and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.

**Proposed action:**
- Prescriber brochure to be provided to prescribers including advice on:
  - Contraindication in patients with moderate to severe hepatic impairment.
### Decrease of the oxygen carries in the blood (decrease in haemoglobin concentration)

**Prescriber Kit containing a prescriber brochure**

- Patient brochure
- Patient Alert Card

- Importance of liver function tests to be measured.
- Importance of close monitoring and dosage adjustment if levels rise above 3 x upper limit normal (ULN).

- Patient brochure to be provided to patients including advice on:
  - Importance for regular monitoring of liver function.

- Patient Alert Card including advice on:
  - Importance of regular blood tests for liver function.
  - Importance of an addition blood test for liver function after an increase in dose.

### Decrease of sperm count

**Prescriber Kit containing a prescriber brochure**

- Patient brochure

**Objective and rationale**

Prescribers to understand the risk of decrease in sperm count and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.

**Proposed action:**

- Prescriber brochure to be provided to prescribers including advice on:
  - Importance for regular blood tests

### Interaction with medicines that are bio-transformed by body enzymes known as CYP3A4 and CYP2C9, increase or decrease the activity of these enzymes (including hormonal contraceptives, sildenafil and antiretrovirals)

**Prescriber Kit containing a prescriber brochure**

- Patient brochure
- Patient Alert Card (only applicable for interaction with hormonal contraceptives)

**Objective and rationale**

Prescribers and patients to understand the risk of interaction with the mentioned medicinal products and importance of this risk to minimise its occurrence and its severity.

**Proposed action:**

- Prescriber brochure to be provided to prescribers including advice on the:
  - Interaction with hormonal contraceptives
  - Contraindication of co-administration of bosentan with cyclosporine.
Prescriber Kit containing a prescriber brochure

Patient brochure

Patient Alert Card (only applicable for interaction with hormonal contraceptives)

- Patient brochure to be provided to patients including advice on:
  - Hormonal contraceptives which are not effective on their own.

Only applicable for interaction with hormonal contraceptives:

- Patient Alert Card including advice on:
  - Importance to avoid pregnancy and to ensure effective contraceptives measures while using this medicine.

Malformation development in foetus (teratogenicity)

Prescriber Kit containing a prescriber brochure

Patient brochure

Patient Alert Card

Objective and rationale

Prescribers and patients to understand the risk of teratogenicity and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.

Proposed action:

- Prescriber brochure to be provided to prescribers including advice on:
  - Contraindication in pregnant women.
  - The need for effective contraception.
  - Importance of regular pregnancy tests.
  - Importance of reporting pregnancy cases.

- Patient brochure to be provided to patients including advice on:
  - The need for regular pregnancy tests
  - The need for effective contraception
  - Importance to know that pregnant women must not take this medicine.

- Patient Alert Card including advice on:
  - Importance of absence of a pregnancy before bosentan treatment initiation and pregnancy avoidance during the treatment.
  - Importance of additional or alternative contraceptive methods.
  - Importance of a pre-treatment pregnancy test and regular pregnancy tests during the treatment.

Testicular disorders and male infertility

Prescriber Kit containing a prescriber brochure

Objective and rationale

Prescribers to understand the risk of testicular disorders and male infertility and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.

Proposed action:

- Prescriber brochure to be provided to prescribers including advice that treatment with bosentan might be associated with the occurrence of testicular disorders and male infertility.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are on-going or are planned to be conducted for bosentan.
VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Safety Concerns</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>23/05/2014</td>
<td><strong>Important identified risks</strong>: Hepatotoxicity; Decrease in haemoglobin concentration; Fluid retention; Interaction with substrates, inducers or inhibitors of cytochrome (CYP) P450 isoenzymes CYP3A4 and CYP2C9 <strong>Important potential risks</strong>: Teratogenicity; Pulmonary oedema associated with veno-occlusive disease (PVOD) <strong>Missing information</strong>: Long term safety and efficacy in digital ulcer population; Use in children</td>
<td>The RMP was updated in relation to Day 70 Preliminary Assessment Report received for procedure: IS/H/0236-0237/001-002/DC from RMS Iceland.</td>
</tr>
<tr>
<td>2.0</td>
<td>30/03/2015</td>
<td><strong>Important identified risks</strong>: Hepatotoxicity; Teratogenicity; Decrease in haemoglobin concentration; Decrease of sperm count; <strong>Important potential risks</strong>: Pulmonary oedema associated with pulmonary veno-occlusive disease (PVOD); Interaction with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals); Testicular disorders and male infertility; Respiratory tract infection in children; <strong>Missing information</strong>: Use of bosentan with addition of sildenafil; Use in children with renal function impairment.</td>
<td>The RMP was updated in relation to Day 120 Draft Assessment Report received for procedure: IS/H/0236-0237/001-002/DC from RMS Iceland.</td>
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<tr>
<td>3.0</td>
<td>08-06-2015</td>
<td>No changes</td>
<td>The RMP was updated in relation to Day 180 Draft Assessment Report received for procedure: IS/H/0236-0237/001-002/DC from RMS Iceland.</td>
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<tr>
<td>4.0</td>
<td>17-07-2015</td>
<td>No changes to the list of safety concerns</td>
<td>The RMP was updated in relation to Day 180 Draft Assessment Report received for procedure: IS/H/0236-0237/001-002/DC from RMS Iceland.</td>
</tr>
<tr>
<td>5.0</td>
<td>27-07-2016</td>
<td>No changes to the list of safety concerns</td>
<td>Serbian product added</td>
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</tbody>
</table>