ANNEX

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES

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The Member States shall ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

1. The Member States shall agree details of the implementation of the post-marketing surveillance study in each member state with the MAH and ensure that it is put in place prior to marketing of the product.

2. The Member States shall agree the details of a controlled distribution system with the MAH according to national regulations and healthcare systems and ensure that it is implemented nationally so that prior to prescribing (and at the discretion of the Member State, dispensing) all health care professionals who intend to prescribe (and where appropriate, dispense) Volibris have been provided with the following:

- Product information (Summary of Product Characteristics (SPC) and Package Leaflet)
- Healthcare professional information regarding Volibris
- Pre-prescription checklist for physicians
- Information about the post marketing surveillance study
- Information booklets for patients
- Information booklets for male partners of female patients with childbearing potential
- Patient reminder cards
- Pregnancy reporting forms
- Adverse drug reaction reporting forms

3. The Member States shall ensure that the following key elements are included in the appropriate material and that the material is not promotional.

<u>Health care Professional information</u>

The healthcare professional information regarding Volibris should contain the following key elements:

- Obligations of health care professionals in relation to the prescribing of Volibris:
    - That patients should be capable of complying with the requirements for the safe use of Volibris.
    - The need to provide comprehensive advice and counselling to patients.
    - The need to provide patients with the appropriate information booklet(s) and patient reminder card.
    - Should consider monthly prescription of 30 day supply to ensure that patients and key test results are reviewed prior to further prescription.
    - That the safety database of Volibris is limited and physicians are encouraged to enrol patients in a post marketing surveillance study.
    - To report suspected adverse reactions and pregnancy.

- That Volibris is teratogenic
    - Volibris is contraindicated in pregnancy and in women of child bearing potential who are not using reliable contraception.
    - That women receiving Volibris should be advised of the risk of foetal harm.
    - Guidance for identifying women of child bearing potential and the actions the physician should take if unsure.

For women with childbearing potential

- Exclusion of pregnancy prior to treatment initiation and monthly pregnancy testing during treatment.
- The need to advise women (even if a woman has amenorrhoea) on the use of reliable contraception during treatment and for one month following permanent discontinuation of treatment.
- Definition of reliable contraception and the need to seek expert advice if unsure what is suitable for an individual patient.
- That if a women of childbearing potential needs to change or stop her method of contraception she should inform:
  - The physician prescribing her contraception that she is taking Volibris
  - The physician prescribing Volibris that she has changed or stopped her method of contraception.
- That the patient should contact her doctor immediately if pregnancy is suspected and that alternative therapy should be initiated if pregnancy confirmed.
- The need to refer patients who become pregnant to a physician specialised or experienced in teratology and its diagnosis for evaluation and advice.
- To report all cases of pregnancy occurring during therapy.

- That Volibris is potentially hepatotoxic
  - Contraindication in patients with severe hepatic impairment (with or without cirrhosis) and in patients with baseline values of hepatic aminotransferases (AST and/or ALT) > 3X ULN.
  - Hepatic aminotransferases (ALT and/or AST) should be evaluated prior to initiation of ambrisentan.
  - During therapy, monthly monitoring of ALT and AST is recommended.
  - Discontinuation of ambrisentan therapy if patients develop sustained, unexplained clinically significant ALT and/or AST elevation or if ALT and/or AST elevation is accompanied by signs or symptoms of hepatic injury (e.g. jaundice).
  - In subjects without clinical symptoms of hepatic injury or jaundice, reinitiation of ambrisentan may be considered following resolution of hepatic enzyme abnormalities. The advice of a hepatologist is recommended.

- That treatment with Volibris often causes a decrease in haemoglobin and haematocrit
  - Initiation of Volibris is not recommended for patients with clinically significant anaemia.
  - Patients taking Volibris should have their haemoglobin and/or haematocrit levels measured regularly.
  - If tests show a clinically significant decrease in haemoglobin or haematocrit, and other causes have been excluded, consider reducing the dose of Volibris, or stopping treatment.

- That treatment with Volibris causes peripheral oedema and fluid retention
  - If a patient develops clinically significant peripheral oedema, with or without associated weight gain, carry out further evaluation to determine the cause and if appropriate consider discontinuation of Volibris.

- That chronic administration of Volibris in animals has been linked to testicular tubular atrophy and impaired fertility. The effect of Volibris on human testicular function and male fertility is not known.

- That Volibris should be initiated with caution in patients with severe renal impairment.

- That hypersensitivity reactions, although uncommon, have been reported with Volibris.

Physician checklist

The physician pre-prescription checklist will highlight the contraindications to the use of ambrisentan and important pre-prescription assessments including:

- Liver function tests.
- Determination of child bearing potential in female patients.
- Pregnancy test if female patient with childbearing potential.
- That women of child bearing potential are on reliable contraception.

Patient information

The information for patients should include the following information:

- That Volibris may cause serious birth defects in unborn babies conceived before, during, or within a month after stopping treatment.
- That Volibris cannot be initiated if patient is pregnant.
- Women with childbearing potential must have a pregnancy test immediately prior to the first prescription and at monthly intervals whilst taking Volibris.
- The need to ensure that women of child bearing potential are using reliable contraception and that patients should inform their doctors of any possibility of pregnancy before a new prescription is issued.
- That if a women of childbearing potential needs to change or stop her method of contraception she should inform:
    - The physician prescribing her contraception that she is taking Volibris
    - The physician prescribing Volibris that she has changed or stopped her method of contraception
- The need for female patients to contact their treating doctor immediately if they suspect that they might be pregnant.
- The need for the patient to discuss with her doctor if she is planning to become pregnant.
- That Volibris may cause liver injury.
- That because of the potential for liver injury and anaemia, patients should have regular blood tests and also tell their doctor if experiencing any symptoms of liver injury.
- That the patient should not give Volibris to any other person.
- That the patient should tell their doctor about any adverse event.

Booklet for male partners of women with childbearing potential

The information for male partners of women with childbearing potential should include the following information:

- That Volibris may cause serious birth defects in unborn babies conceived before, during, or within a month after stopping treatment.
- The need to ensure that women of child bearing potential are using reliable contraception.
- That Volibris cannot be taken if a woman is or might become pregnant.

Patient reminder card

- This should include key messages regarding the need for regular blood and pregnancy tests and provide spaces for the dates of appointments and the results of tests.