LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bosentan Accord
(bosentan monohydrate)

SE/H/1906/001–002/E/001

This module reflects the scientific discussion for the approval of Bosentan Accord. The Public Assessment Report was by the previous RMS UK after initial procedure UK/H/5622/001-002/DC and is attached at the end of this document. RMS transfer from UK to SE was completed 2019-02-04. For information on changes after this date please refer to the module 'Update'.

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SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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Public Assessment Report

Decentralised Procedure

Bosentan Accord 62.5 mg film-coated tablets
Bosentan Accord 125 mg film-coated tablets

Procedure No: UK/H/5622/001-002/DC

UK Licence No: PL 20075/0382-0383

Accord Healthcare Limited

Medicines and Healthcare Products Regulatory Agency

Lay Summary

Bosentan Accord 62.5 mg film-coated tablets
Bosentan Accord 125 mg film-coated tablets
(bosentan monohydrate)

This is a summary of the public assessment report (PAR) for Bosentan Accord 62.5 mg and 125 mg film-coated tablets (PL 20075/0382-0383; UK/H/5622/001-002/DC). (Bosentan Accord 62.5 mg and 125 mg film-coated tablets will be referred to as Bosentan 62.5 mg and 125 mg tablets throughout this report, for ease of reading). It explains how Bosentan 62.5 mg and 125 mg tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Bosentan 62.5 mg and 125 mg tablets.

For practical information about using Bosentan 62.5 mg and 125 mg tablets, patients should read the patient information leaflet (PIL) or contact their doctor or pharmacist.

What are Bosentan 62.5 mg and 125 mg tablets and what are they used for?
Bosentan Accord 62.5 mg and 125 mg tablets are 'generic medicines'. This means that they are similar to 'reference medicines', already authorised in the European Union (EU) called Tracleer® 62.5mg and 125 mg film-coated tablets.

Bosentan 62.5 mg and 125 mg tablets are used to treat pulmonary arterial hypertension (PAH). PAH is a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels (the pulmonary arteries) that carry blood from the heart to the lungs. This pressure reduces the amount of oxygen that can get into the blood in the lungs, making physical activity more difficult. The 'class' of PAH reflects the seriousness of the disease. Bosentan 62.5 mg and 125 mg tablets are used to treat class III PAH, which is a condition that involves marked limitation of physical activity. These medicines are also effective in treating class II PAH, which is a condition that involves slight limitation of physical activity. There are several different types of PAH but Bosentan 62.5 mg and 125 mg tablets are used to treat PAH, which is either:

- primary (with no identified cause or familial (i.e. inherited))
- caused by scleroderma (also called systemic sclerosis, a disease where there is abnormal growth of the connective tissue that supports the skin and other organs)

or

- caused by congenital (inborn) heart defects, with shunts (abnormal passageways) causing abnormal flow of blood through the heart and lungs.

Bosentan 62.5 mg and 125 mg tablets can also be used to treat digital ulcers, which are sores on the fingers and toes, in adult patients with a condition called scleroderma. Bosentan reduces the number of new finger and toe ulcers that appear.

How do Bosentan 62.5 mg and 125 mg tablets work?
Bosentan 62.5 mg and 125 mg tablets contain the active substance bosentan (as bosentan monohydrate), which belongs to the class of medicines called "endothelin receptor antagonists". These block a naturally occurring hormone called endothelin-1 (ET-1). ET-1 normally causes blood vessels to narrow and, therefore, the blocking action of bosentan, causes blood vessels to expand.

How are Bosentan 62.5 mg and 125 mg tablets used?
Bosentan 62.5 mg and 125 mg tablets should be swallowed whole with water, morning and evening. These tablets can be taken with or without food.

Please read Section 3 of the PIL for detailed information on dosing recommendations, the route of administration and the duration of treatment.

Treatment with Bosentan 62.5 mg and 125 mg tablets should only be started and monitored by a doctor who has experience in the treatment of PAH or systemic sclerosis. The treatment in adults is usually started for the first 4 weeks with 62.5 mg, twice daily (morning and evening). Depending on how the patient reacts to the 62.5 mg strength tablet, the prescribing doctor will usually advise the patient to take a 125 mg tablet twice daily. The dose recommendation in children is only for PAH. For children 2 years and older, treatment is usually started with 2 mg per kg bodyweight twice daily (morning and evening). The prescribing doctor will advise on the correct dosing.

These medicines can only be obtained with a prescription.

How have Bosentan 62.5 mg and 125 mg tablets been studied?
Because Bosentan 62.5 mg and 125 mg tablets are generic medicines, studies in patients have been limited to tests to determine that the highest strength medicine, Bosentan 125 mg tablets, are bioequivalent to the reference medicine, Tracleer® 125mg film-coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

It was deduced from these tests that Bosentan 62.5 mg and 125 mg tablets are comparable to equivalent strengths of the reference medicines Tracleer® 62.5 mg and 125mg film-coated tablets.

What are the possible side effects of Bosentan 62.5 mg and 125 mg tablets?
Because Bosentan 62.5 mg and 125 mg tablets are generic medicines, their benefits and possible side effects are taken as being the same as those of the reference medicines, Tracleer® 62.5 mg and 125mg film-coated tablets.

For further information, please see the PIL.

Why are Bosentan 62.5 mg and 125 mg tablets approved?
It was concluded that, in accordance with EU requirements, Bosentan 62.5 mg and 125 mg tablets have been shown to have comparable quality and be comparable to Tracleer® 62.5 mg and 125 mg film-coated tablets. Therefore, the view was that, as for Tracleer® 62.5 mg and 125 mg film-coated tablets, the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Bosentan 62.5 mg and 125 mg tablets?
A risk management plan has been developed to ensure that Bosentan 62.5 mg and 125 mg tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the PIL for Bosentan 62.5 mg and 125 mg tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Bosentan 62.5 mg and 125 mg tablets
Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Iceland, Italy, Lithuania, Malta, the Netherlands, Norway, Portugal, Sweden, Slovakia and the UK agreed to grant marketing authorisations to Accord Healthcare Limited for Bosentan 62.5 mg and 125 mg tablets on 06 November 2014. The marketing authorisations in the UK were granted on 08 December 2014.

The full PAR for Bosentan 62.5 mg and 125 mg tablets follows this summary.

For more information about treatment with Bosentan 62.5 mg and 125 mg tablets, read the PIL or contact your doctor or pharmacist.

This summary was last updated in February 2015.

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I Introduction

Based on the review of the data on quality, safety and efficacy, the member states have granted marketing authorisations (MAs) to Accord Healthcare Limited for the medicinal products Bosentan 62.5 mg and 125 mg tablets.

These products are prescription-only medicines (POM), indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in:

- Primary (idiopathic and heritable) pulmonary arterial hypertension
- Pulmonary arterial hypertension secondary to scleroderma without significant interstitial pulmonary disease
- Pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology

Some improvements have also been shown in patients with pulmonary arterial hypertension WHO functional class II.

Bosentan tablets are also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Iceland, Italy, Lithuania, Malta, Netherlands, Norway, Portugal, Sweden and Slovakia as Concerned Member States (CMSs).

These applications were made under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products. The reference medicinal products, which have been authorised in accordance with Community provisions in force for not less than 10 years in the European Economic Area are Tracleer® 62.5 mg and 125mg film-coated tablets. Tracleer® 62.5 mg and 125mg film-coated tablets have been registered in the EU (via a centralised authorisation) since 15 May 2002, and have been marketed by Actelion Registration Limited in the United Kingdom.

Bosentan 62.5 mg and 125 mg tablets contain the active ingredient bosentan (as bosentan monohydrate). Bosentan is a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (ET_A and ET_B) receptors. The neurohormone endothelin-1 (ET-1) is one of the most potent vasoconstrictors known and can also promote fibrosis, cell proliferation, cardiac hypertrophy and remodelling, and is pro-inflammatory.

In the pathological state of pulmonary arterial hypertension (PAH) the endothelins are thought to contribute to the underlying pathology causing raised pulmonary vascular resistance (PVR), reduced cardiac indices, reduced exercise capacity (6MWD) and symptoms (dyspnoea, cyanosis). ET_A receptors are expressed in vascular smooth muscle cells, mediating vasoconstriction, cellular proliferation and fibrosis, and are the main receptors found in the heart. ET_B receptors are expressed in brain, lung, kidney, aorta and vascular smooth muscle cells, where they mediate vasodilation through the endothelial release of prostaglandin I_2 (prostacyclin), nitric oxide (NO) and adrenomedullin, causing endothelium-dependent vasodilation (and natriuresis). ETB also mediates clearance of circulating endothelin-1 (ET-1) in the pulmonary circulation. Tissue and plasma concentrations of ET-1

are found to be raised in patients with atherosclerosis, myocardial infarction, congestive heart failure and pulmonary hypertension, suggesting a pathogenic role. As an ET antagonist, Bosentan is proposed to block the pathological process and improve symptoms in patients with WHO functional class III and to reduce the number of new digital ulcers in systemic sclerosis (and on-going digital ulcer disease).

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Since Bosentan 62.5 mg and 125 mg tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

With the exception of one bioequivalence study, no new clinical data were provided with these applications. A bioequivalence study was performed, which compared the pharmacokinetics of the applicant's Bosentan 125 mg tablets with those of the reference product, Tracleer® 125mg film-coated tablets, in healthy subjects under fasting conditions. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For a manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

The RMS and CMSs considered that the applications could be approved at the end of procedure (Day 210) on 06 November 2014. After a subsequent national phase, licences were granted in the UK on 08 December 2014.

II Quality aspects

II.1 Introduction

The applications are submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The applicant has specified Tracleer® 62.5 mg and 125mg film-coated tablets as the reference medicinal products (MA Holder: Actelion Registration Limited).

Bosentan 62.5 mg tablets are formulated as light orange, round, approximately 6.20 mm in diameter, biconvex film-coated tablets, debossed with "IB1" on one side and plain on the other side.

Bosentan 125 mg tablets are formulated as light orange, oval, approximately 11.00 mm in length, 5.00 mm in width, biconvex, film-coated tablets debossed with "IB2" on one side and plain on the other side.

The excipients are qualitatively identical in both products. The excipients in the tablet core are: maize starch, pregelatinised starch (maize), sodium starch glycolate (type A), povidone and magnesium stearate. The excipients in the Opadry yellow film coating are: hypromellose, triacetin, talc, titanium dioxide (E171), iron oxide yellow (E172) and iron oxide red (E172).

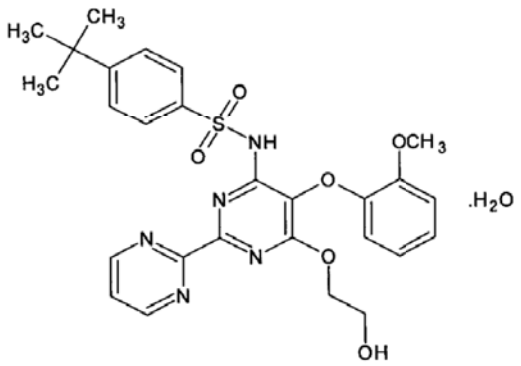
The tablets are presented in polyvinylchloride/polyethylene/polyvinylidene chloride (PVC/PE/PVDC)-aluminium foil blisters or aluminium-aluminium blisters.
Bosentan 62.5 mg tablets are packed into cartons in pack sizes of 14, 56 or 112 tablets.
Bosentan 125 mg tablets are packed into cartons in pack sizes of 56 or 112 tablets.

II.2 Drug Substance

Bosentan monohydrate

INN:	Bosentan monohydrate
Chemical Name:	4-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl) pyrimidin-4-yl] benzene-1-sulfonamide monohydrate 4-(1,1-Dimethylethyl)-N-(6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)(2,2'-bipyrimidin)-4-yl) benzenesulfonamide monohydrate

Structure:



Molecular formula: $C_{27}H_{29}N_5O_6S.H_20$
Molecular weight: 569.64
Appearance: white to yellowish colour powder

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance bosentan monohydrate.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used to contain the active substance. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical development

The aim of the pharmaceutical development was to formulate generic products of both Bosentan 62.5 mg and 125 mg tablets that were essentially similar, stable, and bioequivalent to the reference products Tracleer® 62.5 mg and 125 mg film-coated tablets, authorised to Actelion Registration Limited.

The development of the products has been adequately described. Comparative dissolution and impurity profiles have been demonstrated between Bosentan 62.5 mg and 125 mg tablets and the UK reference medicinal products, Tracleer® 62.5 mg and 125 mg film-coated tablets.

In order to show Bosentan 62.5 mg and 125 mg tablets are equivalent to the UK reference medicinal product, Tracleer® 62.5 mg and 125 mg film-coated tablets, with regard to bioavailability, a bioequivalence study was performed. This is discussed in Section IV – Clinical aspects.

All the excipients used in the manufacture of the proposed formulation, other than the film-coating excipient, Opadry yellow, comply with their respective European Pharmacopoeia monographs. Opadry yellow complies with a satisfactory in-house specification.

Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients are sourced from animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the finished products, together with an appropriate account of the manufacturing process. The manufacturing process has been validated for the smallest scale batches and a commitment has been provided that process validation will be performed on the largest scale batches for each strength of product.

Product Specifications
The finished product specifications are satisfactory. Satisfactory batch analysis was performed on three batches, for each strength of product. Certificates of analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished products, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with special storage conditions of "Do not store above 30 °C" for the PVC/PE/PVDC-aluminium blisters. The aluminium-aluminium blisters do not require any special storage conditions.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III Non-clinical aspects

No new non-clinical data have been submitted and none are required for these types of applications. The applicant's non-clinical overview has been written by an appropriately qualified person. The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is adequate.

Since the formulations of Bosentan 62.5 mg and 125 mg tablets are intended for generic substitution, they will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

IV Clinical aspects

IV.1 Introduction
With the exception of bioequivalence data, no new clinical data have been submitted and none are required for applications of this type. The applicant's clinical overview has been

written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, balanced, randomized, two-treatment, four-period, two sequence, single oral dose, fully replicated crossover, to compare the pharmacokinetics of the test product Bosentan 125 mg tablets versus the reference product Tracleer® 125 mg film-coated tablets in healthy, adult, human, male subjects under fasting conditions.

Volunteers received the test or reference treatment after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. The two treatment periods were separated by a 10-day washout period.

The main pharmacokinetic results are presented below:

Bioequivalence results for ln-transformed test/reference ratios with 90% Confidence Intervals

Treatment	Test	Reference	90% CI	Ratio %
C_{max} (ng/ml)	2699.643	2558.549	95.58 - 116.48	105.5
AUC_{0-t} (ng/ml/h)	14162.760	13828.624	95.19 - 110.19	102.4
$AUC_{0-\infty}$ (ng/ml/h)	14328.638	13955.177	95.56 - 110.32	102.7

The 90% confidence intervals were within the acceptance criteria of 80.00%-125.00%. Based on these results, the proposed product, Bosentan 125 mg tablets, can be considered to be bioequivalent with the reference product Tracleer® 125 mg film-coated tablets.

Bosentan 125 mg tablets meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98). It is, therefore, justified that the results and conclusions from the bioequivalence study on the 125 mg strength product are extrapolated to the 62.5 mg strength product.

IV.3 Pharmacodynamics

No new pharmacodynamics data are required for these applications and none have been submitted.

IV.4 Clinical efficacy

No new clinical efficacy data are required for these applications and none have been submitted.

IV.5 Clinical safety

With the exception of the data collected during the bioequivalence study, no new data have been provided and none are required. The bioequivalence study appears to have been conducted safely with no serious adverse events, deaths or intra/post-study laboratory tests

showing clinically significant abnormalities. This supports the claim that bosentan is well-tolerated.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bosentan 62.5 mg and 125 mg tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns

Important identified risk (s)	• Hepatotoxicity • Teratogenicity • Thrombocytopenia with decrease in haemoglobin concentration • Fluid retention • 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)
Important potential risk (s)	• Seminiferous tubule atrophy • Vasculitis
Missing information	• Long term safety and outcomes in paediatric population • Use in pregnancy and lactation

Planned risk minimisation activities

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified risk: Hepatotoxicity	Accord product information for Bosentan has the following information on this safety concern: Section 4.3: Bosentan Accord is contraindicated in patients with baseline values of liver	MAH will provide an educational kit for prescribers and an information booklet for

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	aminotransferases, i.e., aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT), greater than 3 times the upper limit of normal. Section 4.4: Elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases (AST and/or ALT), associated with bosentan are dose dependent. The accumulation of bosentan in hepatocytes leading to cytolysis with potentially severe damage of the liver, or an immunological mechanism, are not excluded. Liver dysfunction risk may also be increased when medicinal products that are inhibitors of the bile salt export pump, e.g., rifampicin, glibenclamide and cyclosporine A, are co-administered with bosentan, but limited data are available. Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Bosentan Accord. In addition, liver aminotransferase levels must be measured 2 weeks after any dose increase. **Recommendations in case of ALT/AST elevations** **ALT/AST levels Treatment and**	patients in each Member State, explaining the safety of bosentan (especially its effects on the liver). 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.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	monitoring recommendations **> 3 and ≤ 5 × ULN** The result should be confirmed by a second liver test; if confirmed, a decision should be made on an individual basis to continue Bosentan tablets, possibly at a reduced dose, or to stop Bosentan Accord administration. Monitoring of aminotransferase levels should be continued at least every 2 weeks. If the aminotransferase levels return to pre-treatment values continuing or re-introducing Bosentan Accord according to the conditions described below should be considered. **> 5 and ≤ 8 × ULN** The result should be confirmed by a second liver test; if confirmed, treatment should be stopped and aminotransferase levels monitored at least every 2 weeks. If the aminotransferase levels return to pre-treatment values re-introducing Bosentan Accord according to the conditions described below should be considered. **> 8 × ULN** Treatment must be stopped and re-introduction of Bosentan tablets is not to be considered. In the case of associated clinical symptoms of liver injury, i.e., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	fatigue, flu-like syndrome (arthralgia, myalgia, fever), treatment must be stopped and re-introduction of Bosentan Accord is not to be considered. <u>Re-introduction of treatment</u> Re-introduction of treatment with Bosentan tablets should only be considered if the potential benefits of treatment with Bosentan tablets outweigh the potential risks and when liver aminotransferase levels are within pre-treatment values. The advice of a hepatologist is recommended. Re-introduction must follow the guidelines detailed in section 4.2. Aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks, and thereafter according to the recommendations above. Pulmonary arterial hypertension associated with HIV infection: An increased long-term risk of hepatic toxicity and haematological adverse events cannot be excluded when bosentan is used in combination with antiretroviral medicinal products. Concomitant use with other medicinal products: Concomitant use of Bosentan with glibenclamide	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	is not recommended. Section 4.5: *Glibenclamide:* An increased incidence of elevated aminotransferases was observed in patients receiving concomitant therapy. Both glibenclamide and bosentan inhibit the bile salt export pump, which could explain the elevated aminotransferases. This combination should not be used. Due to the marked hepatotoxicity of nevirapine, which could add to bosentan liver toxicity, this combination is not recommended. Section 4.8: Hepatobiliary disorders:-Commonly Abnormal liver function test, Uncommonly: Aminotransferase elevations associated with hepatitis and/or jaundice and rarely Liver cirrhosis, liver failure. In the post-marketing period rare cases of unexplained hepatic cirrhosis were reported after prolonged therapy with Bosentan in patients with multiple co-morbidities and therapies with medicinal products. There have also been rare reports of liver failure. These cases reinforce the importance of strict adherence to the monthly schedule for monitoring of liver function for the duration of treatment with	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Bosentan <u>Uncontrolled studies in paediatric patients with PAH (AC-052-356 [BREATHE-3]; AC-052-365 [FUTURE 1])</u> The safety profile in this population (BREATHE-3: n = 19, bosentan 2 mg/kg twice daily; treatment duration 12 weeks; FUTURE 1: n = 36, bosentan 2 mg/kg twice daily for 4 weeks followed by 4 mg/kg twice daily; treatment duration 12 weeks) was similar to that observed in the pivotal trials in adult patients with PAH. In BREATHE-3, the most frequent adverse reactions were flushing (21%), headache, and abnormal liver function test (each 16%). In FUTURE 1, the most frequent adverse reactions were infections (33%) and abdominal pain/discomfort (19%). There were no cases of liver enzyme elevations in the FUTURE 1 study. *Laboratory abnormalities* <u>Liver test abnormalities</u> In the clinical programme, dose-dependent elevations in liver aminotransferases generally occurred within the first 26 weeks of treatment, usually developed gradually, and were mainly asymptomatic. In the post-marketing period rare	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	cases of liver cirrhosis and liver failure have been reported. The mechanism of this adverse effect is unclear. These elevations in aminotransferases may reverse spontaneously while continuing treatment with the maintenance dose of Bosentan or after dose reduction, but interruption or cessation may be necessary. In the 20 integrated placebo-controlled studies, elevations in liver aminotransferases ≥ 3 times the upper limit of normal (ULN) were observed in 11.2% of the bosentan-treated patients as compared to 2.4% of the placebo-treated patients. Elevations to ≥ 8 × ULN were seen in 3.6% of the bosentan- treated patients and 0.4% of the placebo-treated patients. Elevations in aminotransferases were associated with elevated bilirubin (≥ 2 × ULN) without evidence of biliary obstruction in 0.2% (5 patients) on bosentan and 0.3% (6 patients) on placebo.	
Important Identified risk: Teratogenicity	Accord product information for Bosentan has the following information on this safety concern: Section 4.3: Bosentan is contraindicated in Women of child-bearing potential who are not using reliable methods of contraception.	MAH will provide an educational kit for prescribers and an information booklet for patients in each Member State, explaining the

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.4: *Women of child-bearing potential* As bosentan tablets may render hormonal contraceptives ineffective, and taking into account the risk that pulmonary hypertension deteriorates with pregnancy as well as the teratogenic effects observed in animals: Bosentan treatment must not be initiated in women of child-bearing potential unless they practise reliable contraception and the result of the pre-treatment pregnancy test is negative. Hormonal contraceptives cannot be the sole method of contraception during treatment with bosentan. Monthly pregnancy tests are recommended during treatment to allow early detection of pregnancy. Section 4.6: 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. Use in women of child-bearing potential: Before the initiation of Bosentan treatment in women of child-bearing potential, the absence of pregnancy	safety of bosentan (especially its effects in pregnancy). 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.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	should be checked, appropriate advice on reliable methods of contraception provided, and reliable contraception initiated. Patients and prescribers must be aware that due to potential pharmacokinetic interactions, Bosentan may render hormonal contraceptives ineffective. Therefore, women of child-bearing potential must not use hormonal contraceptives (including oral, injectable, transdermal or implantable forms) as the sole method of contraception but must use an additional or an alternative reliable method of contraception. If there is any doubt about what contraceptive advice should be given to the individual patient, consultation with a gynaecologist is recommended. Because of possible hormonal contraception failure during Bosentan treatment, and also bearing in mind the risk that pulmonary hypertension severely deteriorates with pregnancy, monthly pregnancy tests during treatment with Bosentan are recommended to allow early detection of pregnancy. Breast-feeding: It is not known whether bosentan is excreted into human breast milk. Breast-feeding is not recommended during treatment with Bosentan.	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Fertility Fertility studies in rats showed no effects on sperm parameters or fertility Section 5.3: Bosentan has been shown to be teratogenic in rats at plasma levels higher than 1.5 times the plasma concentrations achieved at the therapeutic dose in humans. Teratogenic effects, including malformations of the head and face and of the major vessels, were dose dependent. The similarities of the pattern of malformations observed with other ET receptor antagonists and in ET knock-out mice indicate a class effect. Appropriate precautions must be taken for women of child-bearing potential.	
Important Identified risk: Thrombocytopenia with decrease in haemoglobin concentration	Accord product information for Bosentan has the following information on this safety concern: Section 4.4: Treatment with bosentan has been associated with dose-related decreases in haemoglobin concentration. In placebo-controlled studies, bosentan-related decreases in haemoglobin concentration were not progressive, and stabilised after the first 4–12 weeks of treatment. It is recommended that haemoglobin concentrations be checked prior to initiation of treatment, every month during the first 4 months	MAH will provide an educational kit for prescribers and an information booklet for patients in each Member State, explaining the safety of 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

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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. In the post-marketing period, cases of anaemia requiring red blood cell transfusion have been reported. Section 4.8: Treatment with bosentan has been associated with decreases in haemoglobin concentration. Blood and lymphatic system disorders: Common: anaemia, haemoglobin decrease Uncommon: Thrombocytopenia Not known: Anaemia or haemoglobin decreases requiring red blood cell transfusion. A decrease in haemoglobin concentration to below 10 g/dL from baseline was reported in 8.0% of bosentan-treated patients and 3.9% of placebo-treated patients.	the distribution plan.
Important identified risk: Fluid retention	Accord product information for Bosentan has the following information on this safety concern: Section 4.4: No specific study has been performed in patients with pulmonary hypertension and concomitant left ventricular	Currently available data does not support the need for additional risk minimization activities

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	dysfunction. However, 1,611 patients (804 bosentan- and 807 placebo-treated patients) with severe chronic heart failure (CHF) were treated for a mean duration of 1.5 years in a placebo-controlled study (study AC-052-301/302 [ENABLE 1 & 2]). In this study there was an increased incidence of hospitalisation due to CHF during the first 4–8 weeks of treatment with bosentan, which could have been the result of fluid retention. In this study, fluid retention was manifested by early weight gain, decreased haemoglobin concentration and increased incidence of leg oedema. At the end of this study, there was no difference in overall hospitalisations for heart failure nor in mortality between bosentan- and placebo-treated patients. Consequently, it is recommended that patients be monitored for signs of fluid retention (e.g., weight gain), especially if they concomitantly suffer from severe systolic dysfunction. Should this occur, starting treatment with diuretics is recommended, or the dose of existing diuretics should be increased. Treatment with diuretics should be considered in patients with evidence of fluid retention before the start of treatment with Bosentan. Section 4.8: The most commonly reported	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	adverse drug reactions (as occurring in at least 1% of patients on bosentan and at a frequency at least 0.5% more than on placebo) are oedema/fluid retention (13.2%). General disorders and administration site conditions Very common: Oedema, fluid retention Oedema or fluid retention was reported in 13.2% of patients on bosentan and 10.9% of patients on placebo.	
Important identified risk: Pulmonary oedema associated with pulmonary veno-occlusive disease (PVOD)	Accord product information for Bosentan has the following information on this safety concern: Section 4.4: 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 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 Accord who had a suspected diagnosis of pulmonary veno-occlusive disease.	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals)	Accord product information for Bosentan has the following information on this safety concern: Section 4.4: Concomitant use of bosentan with rifampicin is not recommended. Concomitant administration of both a CYP3A4 inhibitors and a CYP2C9 inhibitor with bosentan should be avoided. Section 4.5: 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 dosage of these products may need to be adjusted after initiation, dose change or discontinuation of concomitant Bosentan Accord treatment. Bosentan is metabolised by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan (see ketoconazole). The influence of CYP2C9 inhibitors on bosentan concentration has not been studied. The combination should be used with	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	caution. Concomitant administration with fluconazole, which inhibits mainly CYP2C9, but to some extent also CYP3A4, could lead to large increases in plasma concentrations of bosentan. The combination is not recommended. For the same reason, concomitant administration of both a potent CYP3A4 inhibitor (such as ketoconazole, itraconazole or ritonavir) and a CYP2C9 inhibitor (such as voriconazole) with Bosentan Accord is not recommended. *Hormonal contraceptives*: co-administration of bosentan 125 mg twice daily for 7 days with a single dose of oral contraceptive containing norethisterone 1 mg + ethinyl estradiol 35 mcg decreased the AUC of norethisterone and ethinyl estradiol by 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects. Therefore, hormone- based contraceptives alone, regardless of the route of administration (i.e., oral, injectable, transdermal or implantable forms), are not considered as reliable methods of contraception. *Sildenafil:* co-administration of bosentan 125 mg twice daily (steady state) with sildenafil 80 mg	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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. *Lopinavir+ritonavir (and other ritonavir-boosted protease inhibitors)*: co-administration of bosentan 125 mg twice daily and lopinavir+ritonavir 400+100 mg twice daily for 9.5 days in healthy volunteers resulted in initial trough plasma concentrations of bosentan that were approximately 48-fold higher than those measured after bosentan administered alone. On day 9, plasma concentrations of bosentan were approximately 5-fold higher than with bosentan administered alone. Inhibition by ritonavir of transport protein-mediated uptake into hepatocytes and of CYP3A4, thereby reducing the clearance of bosentan, most likely causes this interaction. When administered concomitantly with lopinavir+ritonavir, or other ritonavir-boosted protease inhibitors, the patient's tolerability of Bosentan Accord should be monitored. After co-administration of bosentan for 9.5 days,	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	the plasma exposures of lopinavir and ritonavir decreased to a clinically non significant extent (by approximately 14% and 17%, respectively). However, full induction by bosentan might not have been reached and a further decrease of protease inhibitors cannot be excluded. Appropriate monitoring of the HIV therapy is recommended. Similar effects would be expected with other ritonavir-boosted protease inhibitors. *Other antiretroviral agents*: no specific recommendation can be made with regard to other available antiretroviral agents due to the lack of data. Due to the marked hepatotoxicity of nevirapine, which could add to bosentan liver toxicity, this combination is not recommended. *Cyclosporine A:* co-administration of Bosentan and cyclosporine A (a calcineurin inhibitor) is contraindicated. Indeed, when co-administered, initial trough concentrations of bosentan were approximately 30-fold higher than those measured after bosentan alone. At steady state, bosentan plasma concentrations were 3- to 4-fold higher than with bosentan alone. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. The blood	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	concentrations of cyclosporine A (a CYP3A4 substrate) decreased by approximately 50%. This is most likely due to induction of CYP3A4 by bosentan. *Glibenclamide:* co-administration of bosentan 125 mg twice daily for 5 days decreased the plasma concentrations of glibenclamide (a CYP3A4 substrate) by 40%, with potential significant decrease of the hypoglycaemic effect. The plasma concentrations of bosentan were also decreased by 29%. In addition, an increased incidence of elevated aminotransferases was observed in patients receiving concomitant therapy. Both glibenclamide and bosentan inhibit the bile salt export pump, which could explain the elevated aminotransferases. This combination should not be used. No drug-drug interaction data are available with the other sulfonylureas. *Warfarin:* co-administration of bosentan 500 mg twice daily for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 29% and 38%, respectively. Clinical experience with concomitant administration of bosentan with warfarin in patients with pulmonary arterial hypertension did not result in	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	clinically relevant changes in International Normalized Ratio (INR) or warfarin dose (baseline versus end of the clinical studies). In addition, the frequency of changes in warfarin dose during the studies due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. No dose adjustment is needed for warfarin and similar oral anticoagulant agents when bosentan is initiated, but intensified monitoring of INR is recommended, especially during bosentan initiation and the up-titration period. *Simvastatin:* co-administration of bosentan 125 mg twice daily for 5 days decreased the plasma concentrations of simvastatin (a CYP3A4 substrate) and its active β-hydroxy acid metabolite by 34% and 46%, respectively. The plasma concentrations of bosentan were not affected by concomitant simvastatin. Monitoring of cholesterol levels and subsequent dosage adjustment should be considered. *Rifampicin:* co-administration in 9 healthy subjects for 7 days of bosentan 125 mg twice daily with rifampicin, a potent inducer of CYP2C9 and CYP3A4, decreased the plasma concentrations of bosentan by 58%, and this	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	decrease could achieve almost 90% in an individual case. As a result, a significantly reduced effect of bosentan is expected when it is co-administered with rifampicin. Concomitant use of rifampicin and Tracleer is not recommended. Data on other CYP3A4 inducers, e.g., carbamazepine, phenobarbital, phenytoin and St. John's wort are lacking, but their concomitant administration is expected to lead to reduced systemic exposure to bosentan. A clinically significant reduction of efficacy cannot be excluded.	
Important potential risk: Seminiferous tubule atrophy	None proposed.	None
Important potential risk: Vasculitis	None proposed.	None
Missing information: Long term safety and outcomes in paediatric	Accord product information for Bosentan has the following information on this safety concern: Section 4.2: There is only limited clinical experience in paediatric patients less than 2 years of age indicated for PAH. There are no data on the safety and efficacy in patients under the age	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
population	of 18 years indicated for systemic sclerosis.	
Missing information: **Use in pregnancy and lactation**	Accord product information for Bosentan has the following information on this safety concern: Section 4.3: Contraindicated in pregnancy Section 4.6: Studies in animals have shown reproductive toxicity. There are no reliable data on the use of Bosentan Accord in pregnant women. The potential risk for humans is still unknown. Bosentan Accord is contraindicated in pregnancy. It is not known whether bosentan is excreted into human breast milk. Breast-feeding is not recommended during treatment with Bosentan Accord.	None

V.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the PIL meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applications include an adequate review of published non-clinical and clinical data concerning the efficacy and safety of bosentan. The test product Bosentan 125 mg tablets can be considered bioequivalent with the reference product Tracleer® 125mg film-coated tablets. As the biowaiver criteria are satisfied, these results can also be extrapolated to conclude that Bosentan 62.5 mg tablets are also bioequivalent to Tracleer® 62.5mg film-coated tablets. The benefit/risk assessment is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

The currently approved labelling texts are listed below:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON WITH 14, 56 AND 112 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Bosentan 62.5 mg film-coated tablets
Bosentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 62.5 mg bosentan (as monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablets
14 film-coated tablets
56 film-coated tablets
112 film-coated tablets

5. METHOD AND ROUTE (S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Aluminum-aluminium blisters
This medicinal product does not require any special storage conditions.

PVC/PE/PVDC-aluminium blisters
Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited,
Sage House,
319 Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

12. MARKETING AUTHORISATION NUMBER (S)

PL 20075/0382

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bosentan #62.5 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (FOR PACK OF 14, 56 AND 112 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

Bosentan 62.5 mg film-coated tablets
Bosentan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON WITH 56 AND 112 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Bosentan 125 mg film-coated tablets
Bosentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 125 mg bosentan (as monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablets
56 film-coated tablets
112 film-coated tablets

5. METHOD AND ROUTE (S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Aluminum-aluminium blisters
This medicinal product does not require any special storage conditions.

PVC/PE/PVDC-aluminium blisters
Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited,
Sage House,
319 Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

12. MARKETING AUTHORISATION NUMBER (S)

PL 20075/0383

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bosentan #125 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (FOR PACK OF 56 AND 112 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

Bosentan 125 mg film-coated tablets
Bosentan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

(Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)