21 March 2013
EMA/CHMP/294640/2013
Committee for Medicinal Products for Human Use (CHMP)

Stayveer

(bosentan)

Procedure No. EMEA/H/C/002644/0000

Marklas Nederland BV

Assessment report for initial marketing authorisation application

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
EC	European Communities
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
PE	Polyethylene
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
RMP	Risk Management Plan

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Marklas Nederlands BV submitted on 30 August 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Stayveer, through the centralised procedure. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 September 2011.

The applicant applied for the following indication:

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 familial) PAH
- PAH secondary to scleroderma without significant interstitial pulmonary disease
- PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology

Some improvements have also been shown in patients with PAH WHO functional class II.

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

The legal basis for this application refers to:

Informed consent application (Article 10c of Directive No 2001/83/EC)

The application submitted is composed of administrative information together with a letter from Actelion Registration Ltd. allowing use to be made of relevant quality, non-clinical and/or clinical data of the original marketing authorisation for Tracleer.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products, Revatio, Volibris and Ventavis.

Derogation of market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a claim addressing the following derogation laid down in Article 8.3 of the Regulation (EC) No. 141/2000: the holder of the marketing authorisation for the orphan medicinal product Tracleer has given his consent to the applicant.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The medicinal product Tracleer to which Stayveer is an informed consent application was granted a marketing authorisation in the EU on 15 May 2002.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Actelion Pharmaceuticals Deutschland GmbH
Basler Strasse 65
D-79100 Freiburg
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pierre Demolis

Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 30 August 2012.
- The procedure started on 14 October 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 November 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 November 2012.
- The PRAC RMP advice and assessment overview was adopted by PRAC on 6 December 2012.
- During the meeting on 13 December 2012 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 December 2012.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 January 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 February 2013.
- The PRAC RMP advice and assessment overview was adopted on 7 March 2013.
- During the meeting on 21 March 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Stayveer.

- The CHMP adopted a report on similarity of Stayveer with Revatio, Volibris and Ventavis on 21 March 2013 .

2. Scientific discussion

2.1. Introduction

This marketing authorisation application for Stayveer has been submitted by Marklas Nederland BV as an informed consent application in accordance with Article 10c of Directive 2001/83/EC, as amended.

The marketing authorisation holder (Actelion Registration Ltd) for Tracleer, which was authorised on 15 May 2002, provided consent to make use of the pharmaceutical, non-clinical and clinical documentation of the initial dossier of this authorised product and any subsequent post-marketing procedures submitted, assessed and approved.

As a consequence, quality, safety and efficacy of Stayveer are identical to the up-to-date quality, non-clinical and clinical profile of Tracleer. The application for Stayveer concerns only the 56 tablet presentations of the 62.5 mg and 125 mg strengths approved for Tracleer and consists only of Module 1. Information on the scientific discussion can be found in the Tracleer CHMP assessment reports and in the European Public Assessment Report (EPAR) published on the EMA website.

The approved indication is:

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 familial) PAH
- PAH secondary to scleroderma without significant interstitial pulmonary disease
- PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology

Some improvements have also been shown in patients with PAH WHO functional class II.

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

2.2. Quality aspects

Since this application is an informed consent of the Tracleer application, the quality data in support of the Stayveer application are identical to the up-to-date quality data of the Tracleer dossier, which have been assessed and approved, including all post-marketing procedures.

2.3. Non-clinical aspects

2.3.1. Introduction

Since this application is an informed consent of the Tracleer application, the non-clinical data in support of the Stayveer application are identical to the up-to-date quality data of the Tracleer dossier, which have been assessed and approved, including all post-marketing procedures.

2.3.2. Ecotoxicity / environmental risk assessment

The data provided related to the environmental risk assessment are considered acceptable.

2.3.3. Conclusion on the non-clinical aspects

In this informed consent application, there are no issues related to the non-clinical data, which have been assessed for Tracleer application and adequately reflected in the Product Information.

2.4. Clinical aspects

Since this application is an informed consent of the Tracleer application, the clinical data in support of the Stayveer application are identical to the up-to-date clinical data of the Tracleer dossier, which have been assessed and approved, including all post-marketing procedures.

Of note, clinical efficacy and safety of bosentan is well documented. In more than 80 clinical studies (43 clinical pharmacology Phase 1 studies, 39 Phases 2 to 4 studies, including pre-IBD studies), 3,400 patients have been exposed to bosentan including: 900 patients in pulmonary arterial hypertension (PAH) studies, 400 patients in idiopathic pulmonary fibrosis, 1,100 patients in congestive heart failure, and 459 patients in digital ulcer (DU) disease associated with systemic sclerosis (SSc).

2.5. Pharmacovigilance

Summary of the Pharmacovigilance System

The applicant submitted a signed Summary of the Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the respective GVP module, the CHMP considered the Summary of the Pharmacovigilance System acceptable.

2.6. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

The Applicant has submitted an updated RMP for Stayveer in line with the GVP module V. The RMP is considered as acceptable. The following summary of activities in the risk management plan has been approved.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Important identified risks	Hepatotoxicity Teratogenicity Decrease in haemoglobin concentration
Important potential risks	Pulmonary oedema associated with pulmonary veno-occlusive disease (PVOD) Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals)
Important missing information	Use in children

- **Pharmacovigilance plan**

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Digital Ulcer Outcome (DUO) Registry*	To document adherence to SmPC Requirements for liver function, pregnancy testing	Hepatotoxicity, teratogenicity	Ongoing	Yearly submission cycle with PSUR
Study AC-052-516* : disease characteristics and outcomes of PAH in children and adolescents in	To collect further data on long-term safety and outcomes in Paediatric patients with PAH.	Long-term safety and outcomes in paediatric patients with PAH.	Ongoing	Yearly submission cycle

real world clinical settings: Systematic review of four prospective observational registries"				

* Classified as Category 3

- **Risk minimisation measures**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatotoxicity	• Information in SmPC: - section 4.4 (Special warnings and precautions for use) on liver function: "Elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases (AST and/or ALT), associated with bosentan are dose-dependent. Liver enzyme changes typically occur within the first 26 weeks of treatment, but may also occur late in treatment (see section 4.8)." Information on possible mechanisms for liver aminotransferases provided and warning that the risk may be increased if inhibitors of bile export pumps are coadministered (see sections 4.3 and 4.5 of the SmPC). Warning that: "Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Bosentan" (see further recommendations for dose adjustments in case of ALT/AST elevations and treatment re-introduction under section 4.4 of the SmPC). - Labelled in section 4.8 of the SmPC This information is also reflected in the	• Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. • Educational material supplied to prescribers (as Prescriber Kit) and patients (patient brochure and reminder card). • Patient Reminder Card specifically aimed at facilitating patient's awareness of the need for regular blood tests for liver function.

	PIL. • Restricted medical prescription	
Teratogenicity	• Information in SmPC: Contraindication in section 4.3 of the SmPC: "Pregnancy, Women of childbearing potential who are not using reliable methods of contraception" (see sections 4.4, 4.5, and 4.6). Warning in section 4.4 of the SmPC that: "Bosentan treatment must not be initiated in women of childbearing potential unless they practice reliable contraception (see section 4.5 [Interaction with other medicinal products and other forms of interaction]) and the result of the pretreatment pregnancy test is negative (see section 4.6 [Pregnancy and lactation, Use in women of childbearing potential])." Sections 4.4 and 4.6: "Before the initiation of Bosentan treatment in women of child-bearing potential, the absence of pregnancy should be checked, appropriate advice on reliable methods of contraception provided, and reliable contraception initiated." Sections 4.4 and 4.6: "Patients and prescribers must be aware that, due to potential pharmacokinetic interactions, Bosentan may render hormonal contraceptives ineffective (see section 4.5). Therefore, women of child-bearing potential must not use hormonal contraceptives (including oral, injectable, transdermal, and implantable forms) as the sole method of contraception but should use an additional or an alternative reliable method of contraception. If there is any doubt on what contraceptive advice should be given to the individual patient, consultation with a gynaecologist	• Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. • Educational material supplied to prescribers (as Prescriber Kit) and patients (patient brochure and reminder card), as detailed in Pregnancy Action Plan. • Patient Reminder Card specifically aimed at informing patients of the need to avoid pregnancy and to ensure effective contraceptive measures are used.

	is recommended." Section 4.5 (interaction with other medicinal products and other forms of interaction): "…hormone-based contraceptives alone, regardless of the route of administration (i.e., oral, injectable, transdermal, and implantable forms), are not considered as reliable methods of contraception." This information is also reflected in the PIL. • Restricted medical prescription	
Decrease in haemoglobin concentration	Warning in section 4.4 that treatment with bosentan is associated with a dose-related decrease in haemoglobin concentration and proposals for monitoring. This information is also reflected in the PIL.	• Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. • Educational material supplied to prescribers (as Prescriber Kit) and patients (patient brochure).
Pulmonary oedema associated with veno-occlusive disease	Warning in section 4.4 that pulmonary oedema has been reported with vasodilators (mainly prostacyclins) when used in patients with PVOD disease and to consider PVOD if pulmonary oedema occurs. This information is also reflected in the PIL.	• Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. • Educational material supplied to prescribers (as Prescriber Kit).
Interaction with hormonal contraceptives	Information in sections 4.5 and 4.6 of the SmPC	• Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of

		bosentan. • Educational material supplied to prescribers (as Prescriber Kit) and patients (patient brochure and reminder card), as detailed in Pregnancy Action Plan. • Patient Reminder Card specifically aimed at informing patients of the need to avoid pregnancy and to ensure effective contraceptive measures are used.
Interaction with sildenafil	Information in section 4.5 of the SmPC	• Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. • Educational material supplied to prescribers (as Prescriber Kit).
Drug Interaction with antiretrovirals	Warnings in section 4.4 regarding the use of bosentan in patients with PAH associated with HIV infection, treated with antiretrovirals, and in section 4.5 regarding interactions with lopinavir + ritonavir (and other ritonavir boosted protease inhibitors) and other antiretroviral agents. Recommendation in the PIL: It is especially important to tell your doctor if you are taking medicines for the treatment of HIV infection.	• Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. • Strengthening of prescriber and patient information through Prescriber Kit, Patient brochure. • Educational material supplied to prescribers (as Prescriber Kit) and patients.

The CHMP endorsed this advice without changes.

2.7. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Tracleer. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Since this application is an informed consent to Tracleer, and in view of the fact that the Stayveer application is identical to the up-to-date quality, efficacy and safety data of the Tracleer dossier, the CHMP considered that the benefit/risk balance for Stayveer is positive in the following indication :

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 familial) PAH*
- *PAH secondary to scleroderma without significant interstitial pulmonary disease*
- *PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology*

Some improvements have also been shown in patients with PAH WHO functional class II.

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

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Stayveer is not similar to Revatio, Volibris, and Ventavis within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Derogation of market exclusivity

The CHMP by consensus is of the opinion that pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the following derogation laid down in Article 8.3 of the same Regulation applies:

the holder of the marketing authorisation for Tracleer has given his consent to the applicant.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Stayveer in the treatment of pulmonary arterial

hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III (some improvements have also been seen in patients with WHO class II) and reduction of the number of new digital ulcers in patients with systemic sclerosis and on-going digital ulcer disease, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that prior to prescribing all health care professionals who intend to prescribe and/or dispense Stayveer are provided with a Prescriber Kit containing the following:

• Information about Stayveer

• Patient Information Booklet/Patient Reminder Card

The information provided about Stayveer shall contain the following key elements:

- That Stayveer is teratogenic in animals
- Use in pregnant women is contraindicated
- The need for effective contraception
- That there is an interaction with hormonal contraceptives
- Monthly pregnancy tests in women of child bearing potential are recommended.
- That Stayveer is hepatotoxic
- Stayveer should not be used in Child Pugh Class B or C, i.e. moderate to severe hepatic impairment.
- Need for liver function tests to be measured:
  - Prior to initiation of treatment
  - At monthly intervals during complete course of the treatment
  - Two weeks after any dose increase.
- Need for close monitoring of liver function and dosage adjustment if levels rise above 3 x upper limit normal (ULN):
  - >3 and $\leqslant$ 5 x ULN: Confirm levels and if confirmed, reduce the daily dose or stop treatment and monitor liver function at least every 2 weeks.
  - >5 and $\leqslant$ 8 x ULN: Confirm levels and if confirmed stop treatment and monitor liver function at least every 2 weeks.
  - In the above circumstances, if the levels return to pre-treatment values, continuing or re-introducing Stayveer may be considered.
  - > 8 x ULN or any of the above with associated clinical symptoms of liver injury: Treatment must be stopped and re-introduction of Stayveer is not to be considered.
- That treatment with Stayveer is associated with a decrease in haemoglobin.
- Need for blood monitoring:
  - Prior to initiation of treatment
  - Monthly during the first 4 months
  - Quarterly thereafter.
- That co-administration of Stayveer with cyclosporine is contraindicated.

The patient information shall contain the following information:

• That Stayveer is teratogenic in animals

• That pregnant women must not take Stayveer

• That women of child bearing potential must use effective contraception

• That hormonal contraceptives on their own are not effective

• The need for regular pregnancy tests

• That Stayveer causes a decrease in haemoglobin and the need for regular blood tests

• That Stayveer is hepatotoxic and the need for regular monitoring of liver function

The MAH shall agree with each National Competent Authority the content of a "Reminder Letter" to all known prescribers of Stayveer, reminding them of the safety concerns with Stayveer in relation to pregnancy.