1 April 2016
EMA/255018/2016
Committee for Medicinal Products for Human Use (CHMP)

# Assessment Report

Neparvis

International non-proprietary name: sacubitril / valsartan

Procedure No. EMEA/H/C/004343/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Novartis Europharm Ltd submitted on 14 January 2016 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Neparvis, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 December 2015. The eligibility to the centralised procedure under Article 3(2) (b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The Applicant applied for the following indication:

- Neparvis is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction (see section 5.1).

**The legal basis for this application refers to:**

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information with a letter from Novartis Pharma AG allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application was submitted as a multiple application of Entresto authorised on 19 November 2015 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

***Information on Paediatric requirements***

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0240/2015 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0106/2014 was not yet completed as some measures were deferred.

***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 not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

***Scientific Advice***

The Applicant Novartis Europharm Ltd received Scientific Advice for the reference product Entresto from the CHMP on 25 June 2009, 24 September 2009, 20 September 2012 and 19 December 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

***Licensing status***

The cross reference product Entresto was given a Community Marketing Authorisation in EU on 19 November 2015.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 14 January 2016.
- The procedure started on 2 February 2016.
- The CHMP and PRAC Rapporteurs' joint Assessment Report was circulated to all CHMP members on 7 March 2016.
- During the meeting on 17 March 2016 the Pharmacovigilance Risk Assessment Committee (PRAC) endorsed the relevant sections of the joint CHMP/PRAC Assessment Report.
- The CHMP and PRAC Rapporteurs' updated joint Assessment Report was circulated to all CHMP members on 22 March 2016.
- During the meeting on 1 April 2016, 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 Neparvis.

# 2. Scientific discussion

## *2.1. Introduction*

This application has been submitted as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended. The MAH of the reference product, Entresto, has provided consent to allow access to Module 2 to Module 5 of the initial dossier and any subsequent post-marketing procedures submitted, assessed and approved. The reference product, Entresto had been submitted as a full application under Art 8(3) of Directive 2001/83/EC. As a consequence, the quality, safety and efficacy of Neparvis are identical to the up to date quality, safety and efficacy profile of Entresto.

Heart failure (HF) is a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection. It is a major public health problem associated with a high mortality rate, frequent hospitalizations and poor quality of life. HF is a progressive disease characterized by increasing symptoms that lead to repeated hospitalizations and a significantly greater risk of premature death. A total of 1.0 million patients are hospitalized due to HF each year in the US (Askoxylakis et al 2010) and in Europe, approximately 5% of all acute hospital admissions are HF-related (Braunschweig et al 2011). Approximately 40% of HF patients admitted to the hospital will either die or be readmitted within 1 year and nearly 50% of HF patients die within 4 years of diagnosis (Dickstein et al 2008). The overall 5 year survival rate for HF is as poor as or worse than that for advanced cancer or stroke (Askoxylakis et al 2010, Stewart et al 2010).

Neurohormonal pathways are of critical importance in the pathogenesis and progression of HF. Current HF therapies mainly focus on blocking the detrimental effects of long-term neurohormonal activation (ACEis, ARBs, β-blockers and MRAs) and largely ignore the physiological compensatory effect of the natriuretic peptide system and other endogenous vasodilator systems. Inhibition of neprilysin results in an increase in the activity of natriuretic peptides (NPs) and other vasoactive peptides that potentially exert favorable long-term compensatory effects. However, neprilysin inhibition also leads to an increase of angiotensin II, which is a major mediator of HF development and progression. Therefore, the full compensatory benefit of NEP inhibition can only be leveraged if both the RAS and NEP systems are inhibited simultaneously. Omapatrilat, a dual ACEi/NEPi, was no more effective than an ACEi alone in reducing the risk of death and HF hospitalization in the OVERTURE study of 5,770 HF patients; it was suspected that once-daily dosing of omapatrilat did not provide 24-hour NEP and ACE-inhibition (Packer et al 2002). In addition, omapatrilat treatment was associated with an increased incidence of serious angioedema with airway compromise requiring mechanical support (Kostis et al 2004).

The LCZ696 HF clinical development program was designed to determine whether treatment with LCZ696 could provide a greater benefit in CV mortality and morbidity reduction compared to an ACEi, in HF patients who have been well treated with other HF guideline-recommended therapies. The pivotal phase 3 trial CLCZ696B2314 (also known as PARADIGM-HF) was designed to accomplish this purpose.

LCZ696 (sacubitril/valsartan, Neparvis) is a novel therapy proposed for treatment of heart failure (HF) (New York Heart Association (NYHA) class II-IV) in patients with systolic dysfunction (reduced ejection fraction, HFrEF). Following oral administration, LCZ696 dissociates into valsartan and the pro-drug sacubitril (also known as AHU377, a new molecular entity), which is further metabolized to the neprilysin inhibitor LBQ657. LCZ696 exhibits the mechanism-of-action of an angiotensin receptor neprilysin inhibitor (ARNI) by simultaneously inhibiting neprilysin (neutral endopeptidase 24.11; NEP) via LBQ657 and blocking the angiotensin II type-1 (AT1) receptor via valsartan, resulting in complementary effects on the cardiovascular (CV) system that are beneficial in HF patients.

LCZ696 is formulated as film-coated tablets and each tablet contains sacubitril and valsartan as sacubitril valsartan sodium salt complex in the following strengths: 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg. The 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg strengths are in some publications/studies referred to as 50, 100 or 200 mg.

The following indication was granted by the CHMP to Neparvis (identical to the indication of the reference product Entresto):

Neparvis is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

The recommended posology is:

The recommended starting dose of Neparvis is one tablet of 49 mg/51 mg twice daily, except in the situations described below. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient.

In addition, in patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3-4 weeks) are recommended. Also, a starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥ 100 to 110 mmHg. Also patients with other co-morbidities e.g. moderate renal or hepatic impairment are advised to initiate treatment with the lower dose. The CHMP agreed that LCZ696 should not be co administered with an ACE inhibitor or an ARB. Due to the potential risk of angioedema when used concomitantly with an ACE

inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy. Finally, the valsartan contained within LCZ696 is more bioavailable than the valsartan in other marketed tablet formulations.

## *2.2. Quality aspects*

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

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

Reference has been made to Module 4 data for Entresto, no additional studies have been provided. Since this application is an informed consent of the Entresto application, the non-clinical data in support of the Neparvis application are identical to the up-to-date non-clinical data of the Entresto dossier, which have been assessed and approved, including all post-marketing procedures.

### 2.3.2. Ecotoxicity/environmental risk assessment

The applicant has referred to the Environmental Risk Assessment for Entresto (version dated 28 May 2015). Marketing of Neparvis in the European Union is not expected to increase the environmental risk.

### 2.3.3. Conclusion on the non-clinical aspects

In this informed consent application, there are no new issues related to the non-clinical data. All the non-clinical data have been assessed in the application for reference medicinal product, Entresto and adequately reflected in the Product Information.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

Reference has been made to Module 5 data for Entresto and no additional studies have been provided. Since this application is an informed consent of the Entresto application, the clinical data in support of the Neparvis application are identical to the up-to-date clinical data of the Entresto dossier, which have been assessed and approved, including all post-marketing procedures.

### 2.4.2. Conclusions on the clinical aspects

In this informed consent application, there are no new issues related to the clinical data. All the clinical data have been assessed for Entresto application and adequately reflected in the Product Information.

## 2.5. Risk Management Plan

A risk management plan (RMP) version 1.1 – 14 March 2016 was provided for Neparvis. This RMP corresponds to the Entresto RMP version 1.4, which is the current version (as approved during MAA of Entresto). Only the cover page of the RMP was updated to make it applicable for Neparvis.

## 2.6. Pharmacovigilance

**Pharmacovigilance system**

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

## 2.7. Product information

Product information of Neparvis is identical to the product information for Entresto and was assessed at the time of the IMA application for Entresto. Additionally, the Applicant has aligned the PI annexes with the latest version of the QRD template (v10 - counterfeit legislation), i.e. to implement the standard statements on the Unique Identifier (UI) and its carrier under sections 17 and 18 of Annex IIIA.

The applicant provided the user testing as previously submitted for Entresto. It was confirmed that the package leaflet meets the criteria for readability. Consultation with target patient groups has not been undertaken for Neparvis. The content of the package leaflet is identical to the approved leaflet of Entresto and therefore no further testing was warranted.

### 2.7.1. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Neparvis (SACUBITRIL / VALSARTAN) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

This Marketing Authorisation application for Neparvis has been submitted by Novartis Europharm Ltd as an informed consent application in accordance with Article 10c of Directive 2011/83/EC, as amended.

As a consequence, quality, safety and efficacy of the Neparvis medicinal product are identical to the up-to-date quality, non-clinical and clinical profile of Entresto. The application for Neparvis concerns the identical strengths to those approved for Entresto and consists of only Module 1. Information on the scientific discussion can be found in the Entresto CHMP assessment reports and in the European Public Assessment Report (EPAR) published on the EMA website.

Consequentially, and in line with the assessment of data undertaken in the framework of the Entresto initial marketing authorisation application as well as within all post-autorisation procedures, the CHMP considers that the benefit/risk balance for Neparvis is positive.

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority of 27 out of 28 votes that the risk-benefit balance of Neparvis indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction 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 medical prescription.

***Conditions and requirements of the Marketing Authorisation***

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

***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.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.***

Not applicable.

The divergent position on the granting of the marketing authorisation is appended to this opinion.

***Paediatric Data***

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0106/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

APPENDIX 1

DIVERGENT POSITION DATED 1 April 2016

The undersigned member of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Neparvis, indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

A positive benefit/risk ratio of Neparvis in the general patient population with symptomatic patients with heart failure and reduced ejection fraction is not considered sufficiently demonstrated.

The study population of the single pivotal trial is not fully representative of the overall population of patients with heart failure.

-The PARADIGM study included chronic symptomatic heart failure patients, mostly in NYHA class II, with a LVEF <35% who had been treated for at least 4 week before screening with stable dose of an ACE inhibitor or an ARB equivalent to enalapril 10 mg/day, a stable dose of a beta-blocker unless intolerant and an MRA as indicated and had evidence of plasma BNP ≥150 pg/mL (or NT-proBNP ≥600 pg/mL).

-The two sequential run-in periods of the pivotal study could have selected the population and hence magnified the benefit of Neparvis and significantly attenuated the risk of adverse events such as angioedema.

-Moreover, the run-in periods led to the exclusion of a relevant number of patients who were not eligible due to ACEi tolerability issues. The sensitivity analyses requested by the CHMP and performed by the Applicant to evaluate the impact of the run-in periods on efficacy results showed effect dilution, had intrinsic methodological limitations, and did not take into account whether the discontinuation was due to enalapril or Neparvis. Hence, the concerns on the potential selection introduced by the run-in periods remain.

Because of the potential effect of the vasopeptidase component of Neparvis on the bradikinin axis there are serious concerns that ACEi-naïve patients treated with Neparvis could be exposed to an increased risk of angioedema. Indeed, the trial design selected patients with an extremely low risk of angioedema by excluding all those patients with potential increased upper respiratory tract reactivity after ACEi challenge.

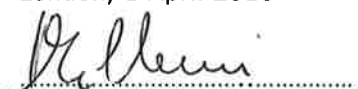
Moreover, Neparvis cannot be considered as first-line therapy because the benefit on the reduction of mortality observed with the treatment with beta-blockers (CIBIS II, COPERNICUS, MERIT-HF studies) and MRA antagonists (RALES and EPHESUS studies) is greater (RRR approximately 34% for beta-blockers in each trial and 30% for MRAs in the RALES trial) compared with the benefit observed with Neparvis; indeed the latter is similar to that observed with ivabradine, as for the EMA approved indication.

The above mentioned concerns support the restriction of Neparvis to indication to the second line therapy of patients with symptomatic chronic heart failure, in a patient population which reflects the one enrolled in the pivotal trial for which a clear benefit-risk ratio has been demonstrated.

Overall, for these reasons, I consider that the benefit/risk ratio is negative for Neparvis in the claimed indication:

Neparvis is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction (see section 5.1).

London, 1 April 2016



Prof. Daniela Melchiorri