22 September 2011
EMA/891763/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Onduarp

International non-proprietary name: **telmisartan / amlodipine**

Procedure No. **EMEA/H/C/002118**

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

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan

1. Background information on the procedure

1.1 Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 6 July 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Onduarp, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 December 2010.

The applicant applied for the following indication:

Treatment of essential hypertension in adults:

Add on therapy

Onduarp is indicated in adults whose blood pressure is not adequately controlled on amlodipine.

Replacement therapy

Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of Onduarp containing the same component doses.

The legal basis for this application refers to Article 10(c) Informed consent application.

The application submitted is composed of administrative information together with a letter from Boehringer Ingelheim International GmbH allowing use to be made of relevant quality, non-clinical and/or clinical data of the original marketing authorisation for Twynsta.

This application is submitted as a multiple of Twynsta authorised on 07 October 2010 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application. The original medicinal product Twynsta was approved in the EU on 07 October 2010.

1.2 Steps taken for the assessment of the product

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

Rapporteur: Harald Enzmann Co-Rapporteur: Alar Irs

- The application was received by the EMA on 6 July 2011.
- The procedure started on 29 July 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 25 August 2011 .
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 29 August 2011.
- The Final joint assessment report was circulated on 12 September 2011.
- During the meeting on 19 – 22 September 2011, 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 Onduarp on 22 September 2011.

2. Scientific discussion

2.1 Introduction

This marketing authorisation application for Onduarp (telmisartan / amlodipine) has been submitted by Boehringer Ingelheim International GmbH as an informed consent application in accordance with Article 10c of Directive 2001/83/EC, as amended.

The MAH (Boehringer Ingelheim International GmbH) for Twynsta, which was authorised on 07 October 2010, 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 the Onduarp medicinal product are identical to the up-to-date quality, non-clinical and clinical profile of Twynsta. The application for Onduarp concerns the identical strengths to those approved for Twynsta and consists of only Module 1. Information on the scientific discussion can be found in the Twynsta CHMP assessment reports and in the European Public Assessment Report (EPAR) published on the EMA website.

The approved indication is:

"Treatment of essential hypertension in adults:

Add on therapy

ONDUARP is indicated in adults whose blood pressure is not adequately controlled on amlodipine.

Replacement therapy

Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of ONDUARP containing the same component doses"

2.2 Quality aspects

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

2.3 Non-clinical aspects

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

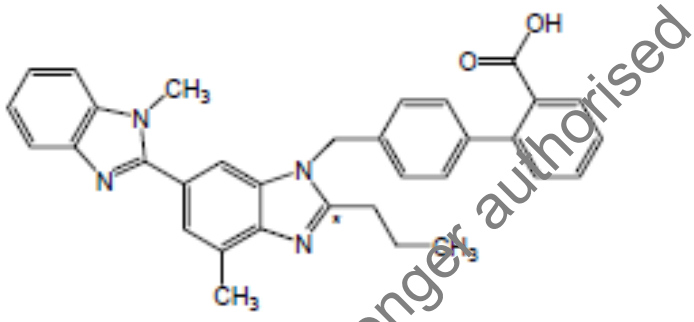
Currently ongoing experimental studies are aimed to investigate the potential additive or synergistic effects due to compound specific properties that have been described for telmisartan and amlodipine in the pre-clinical/clinical literature on top of their blood pressure lowering effect.

Results of these ongoing studies on the beneficial effects of Telmisartan/Amlodipine treatment beyond blood pressure lowering should be provided.

An Environmental Risk Assessment (ERA) has been provided, which is identical to the version submitted for the Twynsta initial Marketing Authorisation. The medicinal product subject to this application is intended to be administered at comparable dose levels and for indications that are already approved in the European Community for Twynsta. Based on the assumption that the product

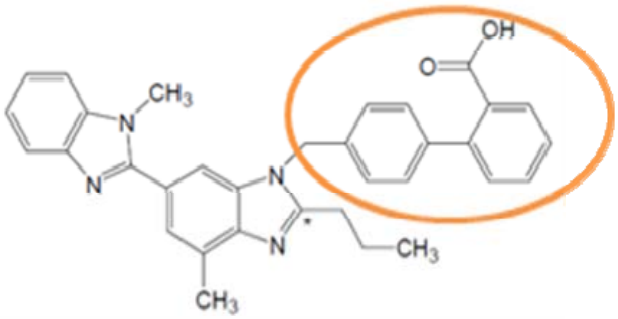
is intended to substitute for identical products on the market, the approval of the referred product should not result in an increase of the total quantity of the active ingredients released in to the environment. Therefore, it should not result in an increase of risk to the environment during storage, distribution, use and disposal.

For the active ingredient telmisartan, all required studies for the Phase II assessment of telmisartan were provided. Based on the study results no environmental risk for the aquatic compartment and the sediment could be expected. Additionally a potential of telmisartan to bioaccumulate could be excluded. Concerning the active ingredient telmisartan no further risk assessment was required and no special precautions had to be considered (the general disposal advice is included in the Package Leaflet). However, because of new scientific findings, new comments concerning the water-sediment study were raised by the CHMP. The study report on the OECD 308 study on transformation of telmisartan in water/sediment systems indicates that the following ^{14}C- labelled test item (labelled atom indicated by an asterisk) was used:



In the part of the study report on transformation product the following statement is made: “The amount of parent substance in the total river and pond systems slowly declined with time from an initial level of about 97-98% of the applied radioactivity to 90% and 82% after 103 days of incubation in the river and pond total systems, respectively. Besides the parent compound, three very minor degradation products were detected, none individually exceeding 2% of applied in either total systems.” The conclusion of the study report is that there are no relevant transformation products produced. Recently, information has been published on transformation products of a parent active ingredient from the substance class of the “sartans” to which telmisartan also belongs to. Kern et al. (2010) and Helbling et al. (2010) described the formation of a transformation product from valsartan (valsartan acid, 2'-(1H-tetrazol-5-yl)biphenyl-4-carboxylic acid) that is considerably more stable than the parent compound (DT_{50} valsartan acid = 410 x DT_{50} parent). Additionally this persistent transformation product has been detected in the effluent from a sewage treatment plant in the low µg/L range. The molecule under study in Kern et al. (2010) and Helbling et al. (2010) is not telmisartan, but another member of the sartan family. Despite differences in the two molecules, the moiety forming the persistent transformation product is also present in telmisartan (substituted biphenyl moiety, orange circle in the figure below). In telmisartan the substituent is a carboxyl group, whereas in valsartan a tetrazole group is found in the same position. As carboxyl and tetrazole groups are considered to be bioisosteric, this difference is not considered to be substantial. Therefore the formation of a similar transformation product from telmisartan that has been observed from valsartan is considered possible.

The presented OECD 308 study however cannot answer the question whether such a transformation product is formed because the labelled C-atom is not located in the biphenyl moiety in question (see figure below) and consequently the potential transformation product cannot be detected when only screening for radiolabelled transformation products.



In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP therefore recommends the following points for further investigation:

The applicant should examine the possibility of formation of a comparable transformation product as described for valsartan in the case of telmisartan. This issue could be addressed by conducting a study with a radiolabel in a suitable position, or by conducting an unlabelled study and employing analytical methods capable of detecting, identifying and quantifying the potential transformation product, or finally by providing a scientific argumentation that the data as already presented in the water-sediment study for Twynsta are conclusive enough for excluding the formation of a comparable transformation product for telmisartan as described for valsartan.

For the active ingredient amlodipine, a detailed environmental risk assessment was provided. Based on the studies results no environmental risk for the aquatic environment can be expected. However, a study on sediment dwelling organisms is missing and should be provided.

Therefore, in the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation::

- The applicant is requested to submit a test on toxicity to sediment dwelling organisms according to OECD.
- The applicant is requested to identify the metabolite Met1 since according to OECD 308 metabolites with an amount > 10 % should be identified.
- The applicant is requested to provide an experimental determined n-octanol/water partition coefficient for amlodipine since the estimated and calculated log K_{ow} value exceeds a value of 2.

2.4 Clinical aspects

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

2.5 Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The CHMP considered the safety profile of fixed dose combination of telmisartan and amlodipine well established and no safety concerns requiring risk minimisation activities have been identified. A Risk Management Plan (RMP) is therefore not considered necessary. Since for the reference product Twynsta no RMP has been established, the CHMP was of the opinion that none is required for Onduarp.

In line with the reference product Twynsta, the applicant should however closely monitor and discuss in future PSURs all cardiovascular events leading to fatal outcome.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

PSUR

The MAH should follow the PSUR submission cycle as agreed for Twynsta, which is on a 6-monthly cycle, having 07 October —2011 as its data lock point.

The applicant should closely monitor and discuss in the PSURs all cardiovascular events leading to fatal outcome.

2.6 User consultation

A justification for not performing a full user consultation with target patient groups on the Package Leaflet has been submitted by the applicant and has been found acceptable for the following reasons: The Package Leaflet of Twynsta has been successfully user tested in the framework of its evaluation for which the CHMP opinion was adopted on 22 April 2010. Since the proposed Package Leaflet for the current application is identical to the Package Leaflet for Twynsta except for the product-specific information, no further testing is warranted.

3. Benefit-Risk Balance

This Marketing Authorisation application for Onduarp (telmisartan/amlodipine) has been submitted by Boehringer Ingelheim International GmbH 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 Onduarp medicinal product are identical to the up-to-date quality, non-clinical and clinical profile of Twynsta. The application for Onduarp concerns the identical strengths to those approved for Twynsta and consists of only Module 1. Information on the scientific discussion can be found on the Twynsta 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 Twynsta initial marketing authorisation application as well as within all post-autorisation procedures, the CHMP considers that the benefit/risk balance for Onduarp is postive.

4. Recommendations

Outcome

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

treatment of essential hypertension in adults:

Add on therapy

ONDUARP is indicated in adults whose blood pressure is not adequately controlled on amlodipine.

Replacement therapy

Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of

ONDUARP containing the same component doses

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

Risk management system and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The PSUR cycle for the product will follow the cycle of the original medicinal product Twynsta.

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

Not applicable

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

Not applicable.