25 April 2013
Committee for Medicinal Products for Human Use
EMA/CHMP/256061/2013

Twynsta

International non-proprietary name: telmisartan/amlodipine

Procedure No.: EMEA/H/C/001224/PSU 007

Period covered by the PSUR: 08 April 2012 to 07 October 2012

Scientific conclusions and grounds recommending the variation to the terms of the Marketing Authorisations

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for Twynsta, Onduarp the scientific conclusions of PRAC are as follows:

Overall the benefit risk balance of telmisartan and amlodipine containing Fixed Dose Combinations remains favourable in the approved indication, if safety relevant information will be integrated into the product information.

Based on the outcome of an article 20 procedure of Regulation (EC) No 726/2004 the European Commission issued a new contraindication for the interaction of aliskiren and ARBs /ACEIs. Vice versa co administration of telmisartan containing medicinal products with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) should be contraindicated. The PRAC noted that the worksharing procedure (WS0362) recently submitted for conclusion in April 2013, is addressing this request.

A summary of the main scientific data assessed through the article 20 procedure is presented thereafter.

ALTITUDE was a double-blind placebo-controlled, randomised trial that enrolled patients with Type 2 diabetes and nephropathy of approximately 4 years of duration. Aliskiren was tested against placebo when added to standard therapy including an ACE inhibitor (ACEI) or ARB. The goal was to demonstrate an overall improvement in cardiovascular and/or renal disease progression and outcomes with aliskiren therapy.

Review of un-blinded data by the data monitoring committee resulted in a recommendation to cease study medication and begin to close the ALTITUDE study. The report concluded that the study was very unlikely to meet its primary efficacy endpoint of demonstrating an improvement in cardiovascular (CV death, non-fatal MI, non-fatal stroke, resuscitated sudden death and hospitalization for heart failure) or renal outcomes (doubling of serum creatinine, end stage renal disease / renal death). The data also showed a higher incidence of adverse outcomes in the aliskiren arm (non-fatal stroke, ESRD/renal death, hyperkalaemia and hypotension) based on 69% of the projected total primary outcome events.

In the overall randomized population, the hazard ratio (aliskiren vs. placebo) for the primary CV or renal composite endpoint is 1.09 (95% CI: 0.97, 1.22, 2-sided p=0.17). This indicates a potential increased risk with aliskiren.

The hazard ratio for the secondary cardiovascular outcome, consisting of the CV components, is 1.14 (95% CI: 0.99, 1.30, 2-sided p=0.07), again suggesting a lack of benefit and potential harm. The hazard ratio for the non-fatal stroke component within the primary outcome is 1.34 (95% CI: 1.01, 1.77, 2-sided p=0.044) with absolute rates of 2.6% (112 events) vs. 2.0% (85 events) in aliskiren and placebo groups respectively.

The hazard ratio (aliskiren vs. placebo) for the secondary renal outcome, consisting of the renal components is 0.93 (95% CI: 0.76, 1.15, 2-sided p=0.52). Though this suggests the possibility of an overall benefit for aliskiren, the result is heavily impacted by the contribution of doubling of serum creatinine, HR 0.90 (95% CI: 0.71, 1.12). Importantly, the observed rates of end stage renal disease / renal death demonstrate a numerical trend against aliskiren with a HR of 1.22 (95% CI: 0.87, 1.72)).

Although the study was conducted in patients with diabetes, a large proportion of patients had underlying cardiovascular disease and a sizeable proportion of patients did not have renal disease. The

incidence of serious cardiovascular events was of relevance in patients with previous cardiovascular disease. Although the HR increased similarly in patients with and without CV events, the absolute risk of CV events on aliskiren was increased versus placebo in patients with previous cardiovascular disease (15.0% and 13.4%, HR =1.12) compared to patients without previous cardiovascular disease (7.0% and 6.1%, HR = 1.16). Among patients with previous CV events, the highest HR was observed in aliskiren-associated resuscitated sudden death (HR 1.64), and lowest HR was associated with unplanned hospitalisation for heart failure HR (HR 0.98). Additional sub-analyses were conducted to further understand the above findings.

Review of cases of stroke, sudden death, and renal SAEs, showed a numerical excess of events in the aliskiren group compared to placebo in the ALTITUDE study. The absolute risk of developing a CV event is greater in diabetic patients with previous CV events in the aliskiren group and there are concerns on the long-term safety profile of aliskiren in combination with ACEis or ARBs also in non-diabetic patients with a history of cardiovascular events.

Based on the results of the ALTITUDE study the benefit-risk balance for aliskiren when used in diabetic patients or patients with renal impairment receiving ACEis or ARBs was considered negative.

An *ad hoc* expert group on cardiovascular was consulted and was of the opinion that, the data from ALTITUDE give rise to the concern that the combination with ACE inhibitors or ARBs may increase the risk in subjects with diabetes and renal disease (eGFR < 60 ml/min) and/or proteinuria particularly in terms of cerebrovascular and possibly cardiovascular events, hyperkalaemia, progression to end-stage kidney disease.

The expert group also agreed that the available data suggest that the safety concerns raised for the use of aliskiren in combination with ACE inhibitors or ARBs apply also to non-diabetic subjects with previous cardiovascular disease or with severe renal impairment and these patients should be carefully monitored in clinical practice.

Therefore, the PRAC considered that there is sufficient evidence at present to take a recommendation within the PSUR to amend the SmPC for telmisartan/amlodipine introducing the contraindication of concomitant use with aliskiren and the related other changes in the SmPC. This takes into account the outcome of the article 20 procedure by implementing the recommended changes.

The PRAC considered that the worksharing variation running in parallel should take into account the outcome of the article 20 procedure and the PRAC recommendation for this PSUR in order to adopt the same wording for the other telmisartan-containing products (Micardis, Micardis plus, Pritor, Pritor plus, Kinzalmono, Kinzalkomb).

In addition, an already identified interaction of telmisartan and digoxin (listed in the EU-Risk Management Plan for Micardis) should be introduced in subsection 4.5 "interactions linked to telmisartan" of the SmPC. This is implemented for telmisartan/amlopidine within this PSUR and it is recommended to implement the same changes in the WS procedure for the other telmisartan-containing products (Micardis, Micardis plus, Pritor, Pritor plus, Kinzalmono, Kinzalkomb).

A continued surveillance of all cardiovascular events leading to a fatal outcome and a specification of concomitant diseases is recommended.

The unlisted ADR "joint swelling" should be monitored.

In summary, as highlighted above, based on the review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing the active substance-combination of telmisartan and amlodipine remains favourable but recommends that changes to the product information were warranted:

Update of the sections 4.2, 4.3, 4.4, 4.5 of the SmPC concerning an interaction between telmisartan and aliskiren:

Update of the SmPC according to the European Commission Decision on Rasilez (EMEA/H/C/780/WS/308/G), dated 26/11/2012, that the concomitant use of aliskiren with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2). Thereby, concomitant use of the telmisartan containing medicinal products TWYNSTA / ONDUARP with aliskiren (Rasilez) is contraindicated as well.

The Package leaflet has to be updated accordingly.

Update of section 4.5 of the SmPC according to an identified interaction of telmisartan and digoxin.

The Package leaflet has to be updated accordingly.

The amendments recommended to be introduced to the product information are detailed in Annex 1.

The next PSUR should cover the period from 08 October 2012 to 07 April 2013 as already outlined in the EU reference dates list (DLP) and should be submitted within 70 days of the data lock point.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for Twynsta, Onduarp, the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing the active substance telmisartan/amlodipine is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.