Committee for Medicinal Products for Human Use
EMA/CHMP/556801/2013
EMEA/H/C/001043/PSUV/0027

MULTAQ

International non-proprietary name: dronedarone

Procedure No. EMEA/H/C/001043/PSUV/0027

Period covered by the PSUR: 01 August 2012 to 31 January 2013

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

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Scientific conclusions

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

The benefit-risk balance for dronedarone remains positive.

The totality of the cases of renal failure in previous PSUR assessment and the presented de-challenge cases in this PSUR did not show a clear evidence for a direct nephrotoxicity of dronedarone. Nevertheless, this cannot be considered as an evidence of lack of association with dronedarone. For this reason, it is not accepted to remove the safety concern "Renal Failure" from the list of important potential risks in the RMP.

Among the 10 reported cases of renal failure where there is no specified alternative explanation, most of the recovered cases (n=6) were compatible with a pre-renal etiology or a possible role of concomitant drugs, with no clear evidence for direct nephrotoxicity of dronedarone. The authors of the published article in British Journal of Clinical Pharmacology also mentioned that the reported patients were old with several concomitant illnesses, and it is possible that these conditions may have precipitated their renal failure. Nonetheless, this obviously cannot be considered as an evidence of lack of association with dronedarone, and the amended warning in 4.4 is proposed.

Therefore, in view of available data regarding dronadarone, the PRAC considered that changes to the product information were warranted.

SmPC

The SmPC is amended as follows:

*Larger increases in creatinine after dronedarone initiation have been reported in the postmarketing setting. Some cases also reported increases in blood urea nitrogen**, possibly due to hypoperfusion secondary to developing CHF (pre-renal azotaemia). In such cases dronedarone should be stopped (see sections 4.3 and 4.4).*** ~~*In most cases, these effects appear to be reversible upon drug discontinuation.*~~ *It is recommended to monitor renal function periodically and to consider further investigations as needed.*

In addition, the package leaflet is revised accordingly as follows.

Package leaflet

- Section 2

A warning should be revised as follows:

Heart and blood tests

While you are taking MULTAQ, your doctor may perform tests to check your medical condition and how the medicine is working for you.

- *Your doctor may look at your heart's electrical activity using an ECG (electrocardiogram) machine.*
- *Your doctor will order blood tests to check your liver function before you start taking MULTAQ and during treatment.* ~~*In some cases MULTAQ treatment may need to be stopped.*~~
- *Your doctor may also do other blood tests. The results of one of the blood tests (blood creatinine levels) may be changed by MULTAQ. Your doctor will take this into account when*

checking your blood levels and will use another reference of the "normal" value of blood creatinine.

In some cases MULTAQ treatment may need to be stopped

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

Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD template version 9 and update the list of local representatives in the Package Leaflet.

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

On the basis of the scientific conclusions for Multaq, the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing the active substance dronadarone 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.