ANNEX IV

SCIENTIFIC CONCLUSIONS

Scientific conclusions

Hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection is not uncommon due to overlapping transmission modes. HCV infection is known to cause suppression of HBV replication in co-infected patients. The virological and immunological aspects of HBV/HCV co-infection are not fully comprehended. Although liver disease activity and progression are generally more severe in the presence of double infection, HBV replication is often suppressed in the presence of HCV coinfection. The European Association for the Study of the Liver (EASL) recommendations on treatment of hepatitis C makes reference to the potential risk of HBV reactivation during or after HCV clearance.

Direct-acting antiviral agents (DAAs) target specific non-structural proteins of the hepatitis C virus and result in disruption of viral replication and infection. Given their increased potency against HCV and lack of anti-HBV activity, the risk of HBV reactivation may be greater with newer HCV treatment regimens than with the previously approved interferon-based HCV treatments. Literature cases (Balagopal et al., 2015; Collins et al., 2015; Ende et al., 2015) described HBV viral load increase after a rapid decline of HCV viral load in patients treated with direct acting antivirals (DAA) in interferon-free regimens, and further cases have been identified in EudraVigilance. Some of the cases identified with DAAs had serious outcomes, with worsening of hepatic status and at least one case where the patient required liver transplantation.

HBV replication after starting treatment with DAAs for HCV infection is not currently described in the product information of currently authorised products and in view of the seriousness of the events described, the need for intervention on HBV replication and the biological plausibility of the replication it was considered that further investigation was warranted. The current referral procedure was triggered by the European Commission (EC) to allow further investigation of the risk of hepatitis B virus replication after starting treatment with DAAs and recommend any appropriate measure to minimise the risk.

Following the initiation of this review, results from a study (Reig et al. 2016) performed between October 2014 and December 2015 in Hepatology Units of four University Spanish hospitals in patients with chronic hepatitis C and a history of hepatocellular carcinoma (HCC) treated with DAAs suggested unexpected early HCC recurrence.

It was considered that in addition to the hepatitis B virus reactivation, the risk of hepatocellular carcinoma should also be further investigated and that consideration should be given for adequate measures to optimise the safe and effective use of these medicinal products. The European Commission therefore extended the scope of the procedure in April 2016 to allow consideration of other data to assess the risk of hepatocellular carcinoma and its impact on the benefit-risk balance for all DAAs in the treatment of chronic hepatitis C.

As both requests for the triggered procedure result from the evaluation of data resulting from pharmacovigilance activities, the EC requested the opinion to be adopted by the Committee for Medicinal Products for Human Use (CHMP) on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC).

Overall summary of the scientific evaluation by the PRAC

In its assessment, the PRAC considered all the data submitted by the MAHs, as well as literature and additional information from a scientific advisory group in relation to the risk of hepatitis B reactivation and to the recurrence and occurrence of hepatocellular carcinoma.

Hepatitis B virus reactivation

With regards to the risk of hepatitis B reactivation, since chronic hepatitis B infection (HbsAg+) was generally considered an exclusion criterion and the collection of data regarding HBV serology and DNA was not mandatory in the development programme of DAAs agents, there is limited information on hepatitis B reactivation obtainable from the completed clinical trials. Therefore data on HBV reactivation with DAAs mostly arose post-marketing.

The available data provide evidence that the reactivation of HBV replication may occur in the context of the treatment of chronic HCV active infection with any form of effective treatment in patients co-infected with HBV and HCV. The reactivation may occur mostly in subjects with detectable HBsAg and active HBV replication of any level, as evaluated by measurable levels of HBV-DNA, but may also occur in subjects without detectable HBsAg though with detectable anti-HBc antibody, of which a small percentage may also present with variable levels of active HBV replication.

Although severe and even fatal cases of HBV reactivation have been described in the literature, the available data indicate that reactivation of HBV replication may mostly be mild and without clinical consequences. The impact of chronic HCV infection characteristics, such as HCV genotype, viral load and histopathologic staging, on the risk of occurrence of HBV reactivation could not be clarified from the available data. It may be assumed however that patients with more advanced liver disease may have a higher risk of severe clinical complications should HBV reactivation occur. Generally, the reactivation occurred shortly after the initiation of treatment in a pattern that implies a correlation with the rapid decrease in HCV viral load which characterises the viral load dynamics with DAAs.

Overall, the PRAC was of the view that evidence exists of a risk of HBV reactivation in HBV/HCV co-infected patients treated with DAAs and therefore HBV reactivation in co-infected patients should be considered as an important identified risk which should be closely monitored through routine risk minimisation activities.

In order to minimise the risk of HBV reactivation, the PRAC recommended that all patients should be screened for HBV infection before initiation of treatment with DAAs and that patients presenting a co-infection HBV/HCV should be monitored and managed according to current clinical guidelines. The product information should reflect these recommendations and inform healthcare professionals about this risk. In addition, patients should be advised to contact their doctor if they have ever been infected with HBV as close monitoring is required.

Hepatocellular carcinoma

With regards to the review of HCC with DAAs, MAHs were requested to perform a comprehensive review of all available data from clinical trials, observational studies, spontaneous reports and published literature on HCC in patients with chronic hepatitis C after treatment with DAAs.

A study from Reig et al. (2016) showed a signal of HCC recurrence in patients treated with DAAs; similar results were obtained by Conti et al. (2016). Other published data from larger cohorts did not support the findings (Pol et al, 2016). However, these cohorts were either not designed for assessing HCC recurrence, as is the case of the ANRS CO22 HEPATHER cohort, or included a limited number of patients with a previous HCC reaching complete radiological response and subsequently treated with DAAs as in the ANRS CO12 CirVir cohort.

Overall, the PRAC considered that further studies were warranted to further characterise the risk of HCC recurrence associated with DAAs, in order to address remaining uncertainties about this potential risk and conclude on the need for any additional advice on clinical management. Taking all available data into account, the PRAC was of the view that MAHs should conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based

on an agreed protocol setting out criteria for entry and follow-up of patients in terms of timing and method for screening. The protocol of this study shall be submitted to the PRAC by 15 June 2017 and the final study results by Q4 2019.

Based on the findings of Reig et al, concerns on the development of *de novo* HCC in cirrhotic HCV patients treated with DAA were also raised, as these patients may harbour not yet diagnosed HCC. Clinical trial data on incidence of new on-set HCC show higher point estimates for HCC after reaching SVR with IFN-free regimens compared to IFN-containing regimens, also when stratifying by presence of cirrhosis. However, the difficulty of fully controlling confounding in this non-randomised comparison was recognised. Still, it was considered that the impact of DAAs therapies on the incidence and type of de novo HCC should be further investigated by the MAHs through a prospective cohort study to be conducted in HCV infected patients with compensated cirrhosis (CPT-A) without history of HCC and treated with DAAs. The research should capture prospectively the known risk factors for HCC and the periodic image testing for HCC diagnosis, according to current European clinical guidelines (EASL). A feasibility assessment of the use of existing data sources for this purpose should be submitted for PRAC assessment by 15 June 2017. Should the use of existing data sources not show feasible, a proposal for a prospective collection of data should be provided.

The PRAC was also of the view that 'emergence of hepatocellular carcinoma' and 'recurrence of hepatocellular carcinoma' should be considered as important potential risks. In addition, 'patients with previous HCC' should be considered as missing information, since this population was excluded from available clinical trials. The RMP of the relevant medicinal products will be updated accordingly.

In conclusion, the PRAC considered that the benefit-risk balance of DAAs-containing products remained favourable subject to the amendments of the terms of the marketing authorisations.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for direct-acting antiviral agents (DAAs) indicated in the treatment chronic hepatitis C.
- The PRAC reviewed the totality of the data submitted in writing and during the oral explanations by the marketing authorisation holders in relation to the risk of hepatitis B reactivation and to the concerns raised following reports of hepatocellular carcinoma in patients using DAAs, as well as the outcome of the meeting of the scientific advisory group on HIV/Viral diseases.
- Concerning HBV reactivation, the PRAC concluded that available data provide evidence of a risk of HBV reactivation in patients co-infected with HBV/HCV treated for chronic hepatitis C with DAAs. The PRAC was of the view that all patients should be screened for hepatitis B virus infection before initiation of treatment with DAAs. Patients with HBV/HCV co-infection should be monitored during and after treatment according to current clinical guidelines. The product information will include a warning to inform about the risk of hepatitis B reactivation and reflect these recommendations.
- Concerning the risk of recurrence of HCC in patients using DAAs, the PRAC considered that further data are required on the impact of DAAs treatment on the incidence of HCC recurrence. All MAHs of DAAs shall conduct a prospective safety study in a well-defined group of patients based on an agreed protocol setting out criteria for entry and follow-up. A joint study is encouraged.

- The PRAC was also of the opinion that the impact of DAAs treatment on the incidence and type of de novo hepatocellular carcinoma should be further investigated though a prospective cohort study in HCV infected patients with cirrhosis. A joint study is encouraged.

In view of the above, the PRAC considers that the benefit-risk balance of direct-acting antivirals remains favourable subject to the amendments to the terms of the marketing authorisations.

The PRAC, as a consequence, recommends the variation to the terms of the marketing authorisations for Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax.

CHMP opinion and detailed explanation of the scientific grounds for the differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CHMP agreed with the overall scientific conclusions and grounds for recommendation.

In accordance with the PRAC recommendation, in order to evaluate the recurrence of hepatocellular carcinoma associated with direct-acting antivirals, the MAHs shall conduct and submit the results of a prospective safety study using data deriving from a cohort of a well-defined group of patients, based on an agreed protocol setting out criteria for entry and follow-up of patients in terms of timing and method for screening.

After further consideration of the timelines proposed for the submission of the final study report and taking into account that the protocol is due to be submitted by 15 June 2017, the CHMP was of the opinion that the date for the submission of the final study report should be postponed to Q2 2021 in order to allow sufficient time for agreement on a joint protocol and for collection of sufficient data to adequately respond to the scientific question.

The wording of the condition to the marketing authorisation has been amended accordingly.

In addition, interim results should be submitted for PRAC assessment by Q4 2019.

The RMP should be updated accordingly within 3 months of this CHMP opinion.

Overall conclusion

The CHMP, as a consequence, considers that the benefit-risk balance of Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax.