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Committee for Medicinal Products for Human Use (CHMP)

# Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Active substance(s): sofosbuvir / ledipasvir

Procedure No. EMEA/H/C/PSUSA/00010306/201810

Period covered by the PSUR: 10 October 2017 to 09 October 2018

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## Scientific conclusions

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

Decrease in immunosuppressive therapy concentrations requiring dose modification has been observed during the course of hepatitis C treatment in patients taking tacrolimus, as immunosuppressant, and direct-acting antivirals (DAA), such as sofosbuvir/ledipasvir. Based on the absorption, distribution, metabolism and excretion profile of immunosuppressant drugs and sofosbuvir/ledipasvir, a significant pharmacokinetic interaction between these agents is not expected, as reflected in current SmPC of Harvoni. However, the sustained inflammatory response associated with hepatitis C infection may lead to downregulation of certain drug-metabolizing enzymes, including CYP3A. Initiation of DAA-based therapy leads to a rapid viral clearance, normalization of liver function tests and a reduction in inflammation, which thereby leads to enhanced metabolism of CYP3A substrates, such as tacrolimus. Owing to the narrow therapeutic index of tacrolimus, appropriate clinical monitoring and management of immunosuppression with tacrolimus or other drugs with a narrow therapeutic margin that are metabolized by the liver should be carried out.

The Product Information does not make specific recommendations to dose adjustment of immunosuppressive agents at initiation of co-administration, but prescribers should be aware of the potential impact of direct-acting antiviral therapy on immunosuppressive drug levels (and other drugs metabolized by the liver) during therapy, so that they are better alerted on the potential need for dose adjustment.

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

## Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for sofosbuvir / ledipasvir the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing sofosbuvir / ledipasvir is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.