ABSTRACT

Study GS-EU-337-2030
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Title of Study: Observational, Cross-Sectional Post-Authorisation Safety Study to Assess Healthcare Provider Awareness of Risks Related to Sofosbuvir and Ledipasvir/Sofosbuvir

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Rationale and Background: Postmarketing cases of serious symptomatic cardiac arrhythmia (bradycardia) have been reported in patients taking the antiarrhythmic drug amiodarone with sofosbuvir (SOF, Sovaldi®) in combination with the direct-acting antivirals daclatasvir (DCV, Daklinza™) or simeprevir (SMV, Olysio ™), or with ledipasvir/sofosbuvir (LDV/SOF, Harvoni®). This post-authorisation safety study is intended to assess the awareness of European healthcare providers of this risk following the dissemination of a direct healthcare professional communication (DHPC) in May 2015. The study will examine if healthcare providers are aware of the risk associated with concomitant use of these drugs and patient monitoring recommendations following distribution of the DHPC.

Research Question and Objectives:

The primary objective of this study is as follows:

- Determine the proportion of healthcare providers aware of the risk of clinically significant arrhythmias when SOF (in combination with DCV or SMV) or LDV/SOF is prescribed concurrently with amiodarone.

The secondary objectives of this study are as follows:

- Assess healthcare provider perceptions regarding the current frequency of concomitant use of amiodarone with SOF + DCV, SOF + SMV, or LDV/SOF among patients in their care.
- Characterize and assess the frequency of current reported healthcare provider approaches to assessing and reducing patient risk related to co-medication with amiodarone and SOF + DCV, SOF + SMV, or LDV/SOF.
- Determine the proportion of respondents who report having changed their prescribing behaviour following awareness of the risk and assess the frequency of specific reported prescribing changes.
- Among the subset of respondents who have cared for patients co-prescribed amiodarone with

SOF + DCV, SOF + SMV, or LDV/SOF, determine the proportion of respondents who have implemented increased patient monitoring following awareness of the risk and characterize the approaches to patient monitoring being employed to reduce the occurrence of these events.
Study Design: This study is a cross-sectional survey of European healthcare providers responsible for the treatment of chronic hepatitis C (CHC) patients.
Setting: Bulgaria, Denmark, France, Germany, Hungary, Spain, and the United Kingdom
Subjects and Study Size: The study questionnaire collected data on healthcare providers responsible for the treatment of CHC patients in several European countries. In order to participate in the study, respondents were required to indicate that they were responsible for the care and treatment of CHC patients. Gilead specified that a minimum of 200 completed surveys would be obtained for the final analysis. The final analysis included 301 respondents.
Variables and Data Sources: The sample was selected from a panel of healthcare providers and was representative of the various practice specialties that received the DHPC and care for CHC patients (including gastroenterologists, hepatologists, infectious disease physicians, cardiologists, general practitioners/internists, and pharmacists). The data source is the healthcare provider survey responses. All collected data is in aggregate according to healthcare provider recall; no individual patient data was collected. The study questionnaire was designed to collect information on the following variables: country of practice, provider specialty and practice size (i.e. number of CHC patients seen), awareness and source of knowledge of the risk described in the DHPC, history of prescribing SOF or LDV/SOF, perceptions regarding the frequency of co-medication with the drugs of interest (i.e. the proportion of patients co-prescribed these drugs), reported healthcare provider approaches to assessing and reducing the risk of patients under their care, and the proportion of respondents who report having changed their prescribing behaviour following awareness of the risk and the frequency of specific prescribing changes. Among the subset of respondents who have cared for patients co-prescribed amiodarone with either SOF + DCV, SOF + SMV, or LDV/SOF, the survey determined the proportion of respondents who have implemented increased patient monitoring following awareness of the risk and characterized the frequency of various reported approaches to patient monitoring. Data from the survey questionnaire were summarized descriptively (e.g. counts, proportions, means, ranges) overall, as well as by country and provider specialty.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: The final data for this study included 301 healthcare provider respondents. Physicians comprised 90% of the survey sample (n=272). The sample consisted of similar numbers of hepatologists (n=71; 24%), cardiologists (n=67; 22%), gastroenterologists (n=62; 21%), and infectious disease physicians (n=57; 19%). A smaller number of participants were pharmacists (n=29; 10%) and internal medicine specialists/general practitioners (n=15; 5%).

Results: Among all healthcare provider respondents, 64% of respondents were aware that there is a risk of cardiac disorders associated with co-prescription of amiodarone with SOF+DCV, LDV/SOF, or SOF+SMV; 52% were aware that bradyarrhythmia specifically is associated with co-prescription of amiodarone with SOF+DCV, LDV/SOF, or SOF+SMV. When restricted to healthcare providers who prescribe or dispense the three SOF regimens of interest, awareness of the risk was slightly higher but generally comparable (70% were aware that risk of cardiac disorders is associated with any of these regimens and 55% were aware of the bradyarrhythmia risk specifically). Among respondents aware of the risk of bradyarrhythmia with any of the SOF regimens of interest, 24% report that the DHPC was the source of awareness. Other sources of awareness included conferences (44%), journals (40%), the SmPC (35%), peer discussion (35%), and online alert/discussion (30%).

Only 28% of physician respondents and 24% of pharmacist respondents reported that any of the CHC patients cared for in the three months prior to the survey were co-prescribed amiodarone with one of the SOF regimens of interest. Those physician respondents estimate that 10% of patients treated with any of the three SOF regimens of interest in the three months prior to survey completion are co-prescribed amiodarone; this corresponds to 4% of all CHC patients (treated and untreated) who are co-treated with the SOF regimens of interest and amiodarone.

Respondents who were aware of the bradyarrhythmia risk report that common approaches to assessing and reducing patient risk include assessing concomitant medications before starting a new therapy, educating patients on the risks of treatment, and educating patients on signs and symptoms of concern. The majority of physician respondents who are aware of the bradyarrhythmia risk report that they would avoid amiodarone altogether and seek alternative cardiac drugs.

Among physician respondents who care for patients co-treated with amiodarone and the SOF regimens of interest, half of respondents report that they have decreased co-prescription following awareness of the risk, while approximately one third of physician respondents report that they have made no changes to co-prescription. Among physician respondents who report caring for patients co-medicated with amiodarone and the SOF regimens of interest and who were aware of the bradyarrhythmia risk, almost all report use of electrocardiogram (ECG) testing (88%) and an increased frequency of monitoring/visits (70%) to assess and reduce patient risk of bradyarrhythmia. Most of these respondents also report that they have increased the use of ECG testing (90%), the use of physical examination (75%), and the use of out-patient cardiac monitoring (70%) since becoming aware of the risk.

DISCUSSION: Awareness of the risk of cardiac disorders and of bradyarrhythmia in patients coprescribed SOF+DCV, LDV/SOF or SOF+SMV with amiodarone was 64% and 52%, respectively, among all healthcare providers surveyed, and 70% and 55% when limited to healthcare providers caring for patients treated with these three SOF regimens. The level of awareness was lower than the pre-defined target benchmark of 80% among European healthcare providers. Only 24% of respondents specified the DHPC as the source of awareness; the other primary sources of awareness included conferences (44%), journals (40%), the SmPCs (35%), and peer discussion (35%). Most healthcare providers report that they have not seen co-medicated CHC patients or that they have seen a small proportion of co-medicated patients. Many healthcare providers who are aware of the bradyarrhythmia risk report that they have taken actions to reduce patient risk, including decreasing co-prescription with amiodarone and increasing patient monitoring.

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