1 ABSTRACT

Title:
A Non-interventional Post-authorisation Safety Study (PASS) as an Effectiveness Check of the Prescriber Checklist for Mycamine® (micafungin)

Keywords:

Mycamine® (micafungin), antifungal treatment, PASS, additional risk minimization measures (aRMM), prescriber checklist, healthcare provider survey

Rationale and Background:

Mycamine® (micafungin) was first authorized in Japan on 08 Oct 2002 and authorized in Europe on 25 Apr 2008. In Europe, due to the potential risk for development of liver tumours, based on pre-clinical data, use of Mycamine® (micafungin) is restricted to use only if other antifungals are not appropriate. The Prescriber Checklist and an Administration and Monitoring Guide were aRMM implemented in Europe to minimize the potential risks associated with Mycamine® (micafungin). The effectiveness of these aRMM was assessed in 2 previous studies, both of which were survey studies focused on process indicators as described in the GVP Module XVI (i.e., receipt and use of the aRMM, and knowledge of the information included in the aRMM).

Based on results from the second effectiveness survey study, the Administration and Monitoring Guide was retired and the Prescriber Checklist was updated to emphasize the potential risk for development of liver tumours and the restricted indication. Due to high knowledge levels of information regarding other risks previously included in the aRMM (specifically, information regarding hypersensitivity as a contraindication, interaction with other drugs, and use during pregnancy), this information was removed from the updated Prescriber Checklist. The updated Prescriber Checklist was disseminated in 26 European countries upon approval of each national competent authority (NCA). This study was conducted to address the requirements of GVP Module XVI to assess the effectiveness of the aRMM, specifically, the updated Prescriber Checklist distributed to HCPs based in European countries. This non-interventional study was designated as a PASS.

Research Question and Objectives:
The overall goal of this study was to perform an effectiveness evaluation of the updated Prescriber Checklist for Mycamine® among prescribers of Mycamine® (micafungin). Specific objectives were:

- Primary objective: Assess prescribers' knowledge levels of:
  - Potential risk of liver tumours associated with Mycamine®, and
  - The restricted indication for Mycamine® (because of the potential risk of liver tumours, Mycamine® should only be used if other antifungals are not appropriate).
- Secondary objectives:
  - Assess prescribers' reported levels of receipt of the updated Prescriber Checklist.

- Assess prescribers' knowledge levels of other information included in the updated Prescriber Checklist, specifically:
  - Assess the knowledge of the hepatic precautions for use.
  - Assess the knowledge of the precaution for use related to haemolytic anaemia/haemolysis in patients with a history of these conditions.
  - Assess the knowledge of the precaution for use in patients with a history of renal impairment.

Study Design:

This was a multi-national, non-interventional, cross-sectional survey study to evaluate the effectiveness of the updated Mycamine® Prescriber Checklist. The survey was a single wave and was planned to launch in each country a minimum of 3 months after the updated Prescriber Checklist had been disseminated in each country.

Setting

This survey was conducted in France, Germany, Greece, Netherlands, Poland, Spain and Sweden.

Inclusion Criteria:

1. Healthcare professionals (HCPs) must have prescribed Mycamine® (micafungin) within 12 months prior to taking the survey.
2. HCPs must have provided permission to share their anonymized responses with the EMA or NCAs.

Exclusion Criteria:

1. HCPs who participated in the cognitive pre-testing of the survey questionnaire for the study.
2. HCPs who have been direct employees of Astellas, ICON, Syneos, Parexel, GfK, EMA, or an NCA in the participating countries within the past 5 years.

Patients and Study Size, including Dropouts

The study endeavored to collect a minimum of 420 completed HCP surveys with an approximate 75:25 sample split of 308 completed surveys from countries where local guidelines were "more aligned" with the Mycamine® (micafungin) label (France, Germany, Poland, Sweden) and 112 completed surveys from "less aligned" countries (Greece, Netherlands, Spain).

Variables and Data Sources

Data for the survey were collected by a web-based data capture system, Confirmit. A non-probability sample of HCPs from France, Germany, Greece, Netherlands, Poland, Spain and Sweden were recruited from the target population of HCPs who prescribed Mycamine® (micafungin) at least once within 12 months of completing the survey.

The survey questionnaire included the following:

- Screening questions to determine eligibility for survey participation
- Primary endpoint questions
    - Potential risk of liver tumours associated with Mycamine®
    - The restricted indication for Mycamine®
- Secondary endpoint questions
    - Receipt of the updated Prescriber Checklist
    - Hepatic precautions for use
    - Precaution for use related to haemolytic anaemia/haemolysis in patients with a history of these conditions
    - Precaution for use in patients with a history of renal impairment
- Other questions on the appropriate use and risks associated with Mycamine®
- Brief questions on participant characteristics such as medical specialty, country, years in practice, and number of patients treated with Mycamine®/echinocandins

Results

Overall, 104 HCPs participated in this study (81 HCPs from countries "more aligned" with the Mycamine® (micafungin) aRMM and 23 HCPs from countries "less aligned" with the Mycamine® (micafungin) aRMM for a 78:22 sample split).

Survey results indicate that the knowledge level for the overall sample was slightly below the predefined success criteria for the knowledge levels regarding primary endpoints (≥80%):

- 71.2% of HCPs were knowledgeable about the precaution that the decision to use Mycamine® should take into account the potential risk for the development of liver tumors.
    - Stratification of the responses by country type showed that 76.5% vs. 52.2% of the HCPs in the more vs. less aligned countries, respectively, were knowledgeable about the potential risk of liver tumors associated with Mycamine®.
- 73.1% of HCPs were knowledgeable about the restricted indication for Mycamine® (because of the potential risk of liver tumours, Mycamine® should only be used if other antifungals are not appropriate).
    - Stratification of the responses by country type showed that 80.3% vs. 47.8% of the HCPs in the more vs. less aligned countries, respectively, were knowledgeable about the restricted indication for Mycamine®.

Of 104 survey respondents, 40% were aware of the Prescriber Checklist and 36.5% indicated they or their institution received the Prescriber Checklist.

Over 80% of respondents were aware of the hepatic precautions for use of Mycamine®. Secondary endpoints for knowledge levels of the haemolytic precautions for use of Mycamine® ranged from 70% to 84%, and knowledge of the precautions for use of Mycamine® in patients with a history of renal impairment ranged from 64% to 73%.

Discussion and Conclusions

Results from the survey indicate that overall HCPs' knowledge level of the potential risk of development of liver tumors and restricted indication of Mycamine® were relatively high (≥70%). These results suggest an improvement from knowledge levels reported in the second effectiveness survey study in which ~50% of HCPs were aware of the potential risk of development of liver tumors and of the restricted indication.

Overall, HCPs in countries where local guidelines were more aligned with the Mycamine® risk minimization measures demonstrated a knowledge level at or above 76% for primary and secondary endpoints.

A limitation of this survey was selection bias due to use of a non-probability sample. Low response rates are an inherent problem which has been documented for survey studies that assess HCPs' knowledge levels of risk minimisation measures[1]. In an effort to minimize the impact of selection bias, countries were selected based on a diverse European sample with a good geographic representation (i.e., across Southern, Eastern, Northern, and Western Europe) and local guidelines/ standard of care that were considered more aligned, or less aligned, with the Mycamine® restricted indication. Although response rates were lower than expected and the estimates relatively imprecise, our results found relatively high levels of knowledge among HCPs of the potential risk of liver tumours and the restricted indication from Mycamine®. These results also suggest that HCPs practicing in countries where guidelines are more aligned with Mycamine® risk minimization measures have a greater knowledge of the appropriate use of Mycamine® and risks associated with use of Mycamine®.

Marketing Authorization Holder(s)

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Not applicable.