Module 8 : Postmarket Information

8.2 Adverse Experiences Reports

TABLE OF CONTENTS

LIST OF TABLES

1. INTRODUCTION

Since the first *IQOS* Tobacco Heating System (THS) market launch in November 2014, PMP S.A. has implemented a safety surveillance system to collect safety information reported spontaneously and emerging in the context of clinical studies. The aim of the safety surveillance processes is to identify and manage, in a timely manner, all new safety information related to the use of PMI's products (excluding conventional cigarettes).

Since 2015, PMP S.A. also prepares and submits an annual Safety Update Report (SUR) to applicable regulatory agencies, which presents a comprehensive and critical analysis of the safety profile of all *IQOS* device versions and all variants of *HeatSticks* sold worldwide. The data presented in the last SUR submitted in the context of the 2023 PMTA Annual Report did not lead to any safety-related actions.

This module presents a cumulative summary of non-serious AEs and serious (SAEs) spontaneously reported to PMP S.A. from the U.S. market and attributed to *IQOS* products. The period of review is since the first market launch of *IQOS* in November 2014 until the cutoff date of December 31, 2022. The safety analysis presented in this module includes the most reported AE and SAE terms, their distribution in the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs), and percentage of SAEs on the total number of AEs. All AE and SAE data has been extracted from the global safety database as Individual Case Safety Reports (ICSRs).

Of note, PMP S.A. collects safety information reported by either *IQOS* users, or by persons reporting on their behalf. Since the AEs are spontaneously reported, an implied causality to *IQOS* THS products use is assigned unless the role of *IQOS* can be ruled out (*e.g.*, AE onset or medical condition worsening is prior to *IQOS* use). It is worth mentioning that the ICSRs received by PMP S.A. contain scarce information and in most instances are not confirmed by a health care professional. This implies that for most of the reports classified as SAEs, both a reliable medical diagnosis and an accurate description of the experiences and their circumstances are missing, making it difficult to assess the true causal relationship between the use of *IQOS* THS products and the reported events. Moreover in many jurisdictions, either (i) PMP S.A. is legally prohibited from conducting follow-up attempts to retrieve additional information on a specific SAE due to privacy restrictions; or (ii) the reporter did not provide consent to be contacted back by PMI. As a result of this, the PMP S.A. safety team has taken the conservative approach so that any term provided in the reporter's verbatim that falls into the seriousness criteria established in ICH-E2A (ICH, ICH E2A Clinical safety data management: definitions and standards for expedited reporting - Guideline. 1994) and/or into the European Medicines Agency important medical event terms list is upgraded to serious.

2. OVERVIEW OF SAFETY METRICS OF *IQOS* PRODUCTS FROM US MARKET

Cumulatively, from the first launch in November 2014 until the cut-off date of December 31, 2022, a total of (b) (4) ICSRs were spontaneously reported in the U.S. for *IQOS* products. The reported ICSRs included (b) (4) AEs, all of which were assessed as non-serious. Of note, none of these spontaneous reports from the U.S. received by PMI was medically confirmed by healthcare professionals, as they were reported by consumers.

2.1. Most frequently reported MedDRA System Organ Class

The information collected during this review period can be evaluated through the distribution of AEs within the MedDRA SOC terms. The MedDRA SOC terms are the highest level of the MedDRA taxonomy, distinguished by anatomical or physiological system, etiology (disease origin) or purpose. Most of these describe disorders of a specific part of the body. Table 1 shows cumulatively the most frequently reported SOCs (≥ 5%) attributable to *IQOS* products in the U.S., using the MedDRA 25.1 version.

Table 1: Most frequently reported SOCs (≥5%) for *IQOS* products

	Cumulative	
SOCs≥5%	**Number of AEs**	**%**
(b) (4)		

Cumulatively, the most represented MedDRA SOC terms common for *IQOS* products are: (b) (4)

Of note, product issues not associated with AEs are not in scope for safety analysis. Any AEs associated with a product issue that may result in any kind of health-related consequence are

entered into the safety database and analyzed by the PMP S.A. safety team. This is the reason why *Product issues* appear in the list of the most represented SOC terms.

2.2. Most frequently reported MedDRA Preferred Terms

Table 2 shows the most frequent AEs (≥ 5%) cumulatively reported for *IQOS* products in the US, using the MedDRA 25.1 version. Cumulatively, the most reported AEs for *IQOS* products were: (b) (4) All these events were assessed as non-serious.

Table 2: Most frequently reported AEs (≥5%) for *IQOS* products

	Cumulative	
AEs>5%	**Number of AEs**	**%**
(b) (4)		

As listed in the SPI for *IQOS*, (b) (4) are due to nicotine class effects and are known AEs also associated with the use of NRTs (*e.g.*, Nicorette® Inhalator). The remaing PTs of (b) (4) and (b) (4) are product quality related events. (b) (4)
(b) (4)
(b) (4) . An evaluation by PMI showed that *HeatSticks* exposed to humid storage conditions may result in higher water absorption in the tobacco plug. Consequently, the use of such *HeatSticks* may lead to a warm aerosol often perceived as hot by some consumers. To avoid exposure of *HeatSticks* to high humidity, PMI has communicated to users through various channels, including the User Guide, to store the products in a dry and cool place, as well as to not use *HeatSticks* that have been exposed to excessive heat or moisture.

2.3. Most frequently reported Serious Adverse Events

As previously mentioned, there were zero serious AEs cumulatively reported for *IQOS* products in the U.S.

3. CONCLUSION

This module presents a cumulative summary of AEs and SAEs spontaneously reported to PMP S.A. from the U.S. market and attributed to *IQOS* products. The period of review is since *IQOS* first market launch in November 2014 until the cutoff date of December 31, 2022.

The most frequently reported SOCs and AEs identified for *IQOS* products are aligned with the known nicotine class effects and AEs observed during use of other nicotine-containing products such as NRTs. Cumulatively, (b) (4) non-serious AEs were spontaneously reported in the U.S. for *IQOS* products. There were no serious AEs reported for *IQOS* products in the U.S. The safety profile of *IQOS* products from the U.S. market did not show any significant differences when compared to the established global safety profile of all *IQOS* THS products that was presented in the last SUR submitted in the context of the 2023 PMTA Annual Report.

In conclusion, the data presented in this module suggest that the *IQOS* products already available in the U.S. present an unchanged safety profile since the U.S. market authorization. The safety profile of *IQOS* products available in the U.S. is aligned with the global safety profile of all *IQOS* products.