

# Safety Update Report

## Electrically Heated Tobacco Product (EHTP) and Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS)

**International Birth Date:** 04-Nov-2014

**Period Covered:** 01-Jan-2023 to 31-Dec-2023

**Product Name:** Electrically Heated Tobacco Product (EHTP) and Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS)

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## EXECUTIVE SUMMARY

This Safety Update Report (SUR) is compiled following some key principles of the International Council for Harmonisation (ICH) guideline E2C (R2) and provides a comprehensive and critical analysis of the safety profile of the Electrically Heated Tobacco Product (EHTP) and the Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS) within the period from 01-Jan-2023 to 31-Dec-2023 (Data Lock Point, DLP).

The Development International Birth Date (DIBD), which corresponds to the date of first approval for conducting a clinical study for the THS, was 30-Apr-2013. The International Birth Date (IBD), which corresponds to the date of the first market launch for the THS (*IQOS*<sup>TM</sup>), was 04-Nov-2014. The new generation of THS was first launched on 18-Aug-2021, under brand name of *IQOS ILUMA*<sup>TM</sup>. The THS uses a heat-not-burn technology that generates an aerosol from heating tobacco rather than burning it. Depending on the device, the heating of the EHTP is obtained through either a heating blade that is placed inside the THD (*IQOS*), or induction technology where a metal strip, referred to as the susceptor, is integrated into the tobacco stick (*IQOS ILUMA*).

Up to the DLP of this SUR the THS had been marketed in 76 markets worldwide: Albania, Andorra, Armenia, Austria, Aruba, Bahrain, Belarus, Bhutan, Bosnia & Herzegovina, Bulgaria, Canada, Canary Islands, Colombia, Costa Rica, Croatia, Curacao, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, Estonia, France, Georgia, Germany, Greece, Greek Cyprus, Guatemala, Hungary, Indonesia, Israel, Italy, Japan, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Latvia, Lebanon, Lithuania, Malaysia, Maldives, Mexico, Moldova, Monaco, Montenegro, Morocco, Netherlands, New Zealand, North Macedonia, Pakistan, Palestine, Philippines, Poland, Portugal, Reunion, Romania, Russia, Salvador, Saudi Arabia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Tonga, Tunisia, Turkish Cyprus, Ukraine, United Arab Emirates, United Kingdom, United States (U.S.), and Uzbekistan.

No actions (e.g., withdrawal or suspension of a marketing approval) were taken due to safety reasons by the competent authorities or by Philip Morris International (PMI) for the THS products during the period covered by this report.

The Reference Safety Information (RSI) used during the SUR reporting period for clinical studies and post-marketing safety surveillance was the Summary of Product Information (SPI) version 8.0 for THS (dated 24-Oct-2023).

The estimated cumulative subject exposure in clinical studies from the DIBD (30-Apr-2013) until the DLP of this SUR was 2,728 subjects. Cumulatively, 6,298 subjects were exposed to EHTP in PMI-sponsored pre-market studies up to the DLP of this SUR. The post-marketing exposure presented in number of units sold showed 19,652,061 for the reporting period and 112,420,820 cumulatively for THD, and 112,943,395,160 for the reporting period and 513,138,451,365 cumulatively for EHTP.

Three PMI-sponsored clinical studies (P1-AAA-02-JP, P1-REXC-10, and P1-PK-12) have been completed during the period covered by this SUR. One clinical study (P1-COPD-04-INT) was ongoing during this reporting period.

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During this reporting period, no signals were open, ongoing or closed.

New information received during the reporting period of this SUR and cumulatively since the IBD up until the DLP was evaluated regarding the important identified risks of: (1) Hypersensitivity; (2) Accidental exposure to product by child; (3) Burning sensation as well as the important potential risk of Thermal burn; and, (4) the missing information concerning the exposure to the THS during pregnancy and lactation. No update was deemed necessary for the important identified risks and missing information. PMI decided to close the potential risk of Thermal burn and exclude it from the future SUR analysis.

Of note, the majority of spontaneous reports received by PMI are not medically confirmed, i.e., they were received directly from consumers and not from HCPs. Additionally, information regarding spontaneous cases is scarce for at least 2 main reasons: i) PMI is not able to contact consumers that do not provide affirmative consent to be contacted back by PMI; and ii) data privacy restrictions in several countries prohibit requesting consumer contact details when an AE is reported to PMI. Nevertheless, the evaluation of new information as well as the cumulative analysis did not show any change in the safety profile of the THS. PMI will continue to evaluate all new safety information related to the product.

Taken together, the data presented in this SUR did not lead to any safety-related actions (e.g., withdrawal or suspension of a marketing approval).

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## LIST OF ABBREVIATIONS

AAA	Abdominal Aortic Aneurysm
AE	Adverse Event
BT	Blend Test
CC	Conventional Cigarette
COPD	Chronic Obstructive Pulmonary Disease
COT	Commercial Offer Test
DIBD	Development International Birth Date
DLP	Data Lock Point
EHTP	Electrically Heated Tobacco Product
HCP	Health Care Professional
HTP	Heated Tobacco Product
IBD	International Birth Date
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Report
LLT	Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities
NR	Not Randomized
NRT	Nicotine Replacement Therapy
PBA	Perception and Behaviour Assessment
PMI	Philip Morris International
PT	Preferred Term
RRP	Reduced-Risk Product
RSI	Reference Safety Information

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SA	Smoking Abstinence
SAE	Serious Adverse Event
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPI	Summary of Product Information
SUR	Safety Update Report
THD	Tobacco Heating Device
THS	Tobacco Heating System
WOT	Whole Offer Test

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# 1 INTRODUCTION

This Safety Update Report (SUR) is compiled following some key principles of the International Council for Harmonisation (ICH) guideline E2C (R2) and provides a comprehensive and critical analysis of the safety profile of the Electrically Heated Tobacco Product (EHTP) and the Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS) within the period of 01-Jan-2023 to 31-Dec-2023 (Data Lock Point, DLP).

The Development International Birth Date (DIBD), which corresponds to the date of first approval for conducting a clinical study for the THS was 30-Apr-2013. The International Birth Date (IBD), which corresponds to the date of the first market launch for the THS (*IQOS*<sup>TM</sup>), was 04-Nov-2014. The new generation of THS was first launched in August 2021, under brand name of *IQOS ILUMA*<sup>TM</sup>.

The THS uses a heat-not-burn technology that generates an aerosol by heating tobacco rather than burning it.<sup>[1]</sup> This technology is part of the Philip Morris International (PMI) Reduced-Risk Products (RRPs) portfolio. The RRP's present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking. The RRP's aim to substantially reduce or eliminate the exposure to harmful and potentially harmful constituents found in cigarette smoke, while providing nicotine delivery, taste, ritual, and a sensory experience similar to cigarettes in order to offer an acceptable substitute to cigarette smokers who would otherwise continue to smoke.

The THS consists of 2 main components: the EHTP, which is a tobacco stick, and the THD, which contains the holder and the charger. Depending on the THS version the holder and the charger can be either 2 separate elements or 1 element. The EHTP is designed to function with the holder and is composed of a tobacco plug, a hollow acetate tube, a polylactic acid polymer-film filter, a mouthpiece filter, and of outer and mouth-end papers. Additionally, it contains non-flammable wrapping paper<sup>1</sup> to prevent the self-sustaining combustion of the tobacco plug should one try to light the EHTP like a cigarette. Depending on the device, the heating of the EHTP is obtained through either a heating blade that is placed inside the THD (*IQOS*), or induction technology where a metal strip, referred to as the susceptor, is integrated into the tobacco stick (*IQOS ILUMA*). Product technical specifications and constituents, as well as product user instructions, are described in the Summary of Product Information (SPI) for THS version 8.0 ([Appendix 1](#)) dated 24-Oct-2023.

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<sup>1</sup> In selected markets alu-wrapper paper is authorized for use instead of non-flammable paper.

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## 2 WORLDWIDE MARKETING STATUS

The first commercial launch of THS was in Japan on 04-Nov-2014 (IBD). Up to the DLP of this SUR (31-Dec-2023), the THS had been marketed in 76 markets worldwide: Albania, Andorra, Armenia, Austria, Aruba, Bahrain, Belarus, Bhutan, Bosnia & Herzegovina, Bulgaria, Canada, Canary Islands, Colombia, Costa Rica, Croatia, Curacao, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, Estonia, France, Georgia, Germany, Greece, Greek Cyprus, Guatemala, Hungary, Indonesia, Israel, Italy, Japan, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Latvia, Lebanon, Lithuania, Malaysia, Maldives, Mexico, Moldova, Monaco, Montenegro, Morocco, Netherlands, New Zealand, North Macedonia, Pakistan, Palestine, Philippines, Poland, Portugal, Reunion, Romania, Russia, Salvador, Saudi Arabia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Tonga, Tunisia, Turkish Cyprus, Ukraine, United Arab Emirates, United Kingdom, United States (U.S.), and Uzbekistan.

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### **3 ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS**

No actions (e.g., withdrawal or suspension of a marketing approval) against the THS products were deemed necessary for safety reasons by competent authorities or by PMI during the period covered by this report.

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## 4 CHANGES TO REFERENCE SAFETY INFORMATION

The SPI for THS version 7.0 was updated during the reporting period to version 8.0 (dated 24-Oct-2023) ([Appendix 1](#)). The update included:

- Addition of newly launched products;
- Addition of a new Sections 3.5.2.2 Summary of Adverse Events from Post-Marketing Experience, where information about the Individual Case Safety Report (ICSRs)/Adverse Events (AEs) and the most represented System Organ Classes (SOCs) for THS from the post-market experience were added; and,
- Minor text changes.

The SPI version 8.0 was used as the Reference Safety Information (RSI) for all the clinical studies, as well as for post-marketing safety surveillance.

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## 5 ESTIMATED EXPOSURE

### 5.1 Cumulative Subject Exposure in Clinical Studies

Cumulatively, up to the DLP of this SUR, a total of 15 PMI-sponsored open-label randomized controlled clinical studies have been completed and 1 study was ongoing.

The estimated cumulative subject exposure in clinical studies from the DIBD (30-Apr-2013) until the DLP is based on the safety population and on the number of subjects randomized to the EHTP, comparators or Smoking Abstinence (SA) in PMI-sponsored completed studies and ongoing studies (enrollment/randomization schemes).

The inventory of all PMI-sponsored clinical studies at DLP is presented in [Table 5-1](#) below and shows the Study Title, Study Status at DLP, Exposure Duration, and estimated Safety Population as well as the number of subjects exposed to EHTP, Conventional Cigarettes (CC), Nicotine Replacement Therapy (NRT), and SA, including the subjects exposed to the THS but Not Randomized (NR).

**Table 5-1 Cumulative Subject Exposure in Clinical Studies**

Study Title	Study Status	Exposure Duration	Safety Population <sup>1</sup>	EHTP	CC	NRT	SA	NR
ZRHR-PK-01-EU	Closed	Single use	62	62	44	18	0	0
ZRHR-PK-02-JP	Closed	Single use	65	62	44	18	0	3
ZRHM-PK-05-JP	Closed	Single use	73	62	44	18	0	11
ZRHM-PK-06-US	Closed	Single use	64	62	44	18	0	2
ZRHR-REXC-03-EU	Closed	5 Days	169	80	41	0	39	9
ZRHR-REXC-04-JP	Closed	5 Days	166	80	40	0	40	6
ZRHM-REXA-07-JP	Closed	3 Months	175	78	42	0	40	15
ZRHM-REXA-08-US	Closed	3 Months	165	80	41	0	39	5
ZRHR-ERS-09-US	Closed	6 Months	1,039	488	496	0	0	55
P1-OHS-01-JP	Closed	6 Months	179	87	85	0	0	7
ZRHR-ERS-09-EXT-US	Closed	Up to 1-year	672 <sup>2</sup>	309	363	0	0	0
P1-EXC-01-EU	Closed	3 Months	94	40	26	0	27	1
P1-AAA-02-JP	Closed	Up to 3-years	48	16	16	0	16	0
P1-COPD-04-INT	Ongoing	Up to 3-years	306	221	40	0	27	18
P1-REXC-10	Closed	5 Days	91	61	19	0	0	11

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Study Title	Study Status	Exposure Duration	Safety Population <sup>1</sup>	EHTP	CC	NRT	SA	NR
P1-PK-12 <sup>3</sup>	Closed	3 Days	32	30	30	0	0	2
<b>Total Exposure</b>	<b>NA</b>	<b>NA</b>	<b>2,728</b>	<b>1,509</b>	<b>1,052</b>	<b>72</b>	<b>228</b>	<b>145</b>

<sup>1</sup>The overall safety population does not sum up the total of subjects in studies arms due to pharmacokinetic/ pharmacodynamic crossover studies.

<sup>2</sup>Study ZRHR-ERS-09-US-EXT is an extension of study ZRHR-ERS-09-US; therefore, subjects in study ZRHR-ERS-09-US-EXT are also included in study ZRHR-ERS-09-US.

<sup>3</sup>The subjects were exposed to all study products; thus, there were 30 subjects in each study arm.

The estimated cumulative exposure in clinical studies broken down by demographic factors is shown in [Table 5-2](#) below.

**Table 5-2 Cumulative Subject Demographics in Clinical Studies**

Demographics		Total
<b>Gender</b>	Male	1,567
	Female	1,161
	<b>Total</b>	<b>2,728</b>
<b>Race</b>	Caucasian (White)	1,677
	Asian (Japanese)	710
	Black or African American	292
	Native Hawaiian or Other Pacific Islander	16
	American Indian or Alaska Native	7
	Other	26
	<b>Total</b>	<b>2,728</b>

No studies have been performed by PMI to date in special populations such as pediatric populations and/or pregnant/breastfeeding women.

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## 5.2 Cumulative Participants Exposure from Passive Surveillance Pre-Market Studies

Since May-2014, PMI has carried out and completed 8 pre-market studies including: (i) 7 pre-market studies (Blend Tests (BT), Whole Offer Tests (WOT), Commercial Offer Test (COT)); and, (ii) 1 Perception and Behaviour Assessment (PBA) study. There were no studies ongoing nor closed during the reporting period of this SUR.

The estimated passive surveillance pre-marketing exposure to the THS in these studies is based on the safety population who was exposed to at least 1 EHTP variant, either Regular, Menthol, or both Regular and Menthol.

The inventory of all PMI-sponsored pre-market studies at DLP of this SUR, including the Study Title, Study Status at DLP, Country, as well as the estimated Safety Population and the number of subjects exposed to EHTP variants (THS Regular, Menthol, both Regular and Menthol) is presented in [Table 5-3](#) below.

**Table 5-3 Cumulative Exposure in Pre-Marketing Studies**

Study Title	Country	Safety Population (N)	EHTP Variant			Study Status
			Regular (N)	Menthol (N)	Regular and Menthol (N)	
P1-BT1-IT	Italy	1,047	836	211	0	Completed
P1-WOT2-IT	Italy	643	292	310	41	Completed
P1-WOT1-CH	Switzerland	580	344	236	0	Completed
P1-WOT1-DE	Germany	593	593	0	0	Completed
P1-WOT1-KO	South Korea	1,316	724	354	238	Completed
P1-BT1-RU	Russia	611	611	0	0	Completed
THS-PBA-07-US	Unites States	1,158	441	512	205	Completed
P1_COT_DK	Denmark	350	350	350	350	Completed
<b>Total Exposure</b>	<b>NA</b>	<b>6,298</b>	<b>4,191</b>	<b>1,973</b>	<b>834</b>	<b>NA</b>

N=Number of subjects

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### 5.3 Cumulative and Interval Consumer Exposure from Post-Marketing Experience

It is difficult to estimate a “Defined Daily Dose” to which consumers are exposed because daily use varies depending on each consumer’s preference. Thus, the consumer exposure to the THS from post-marketing experience is based on worldwide “In Market Sales,” which represents the number of THDs and EHTPs that were sold to retailers.

Both the cumulative exposure and the interval exposure covering the reporting period for THD and EHTP is presented in [Table 5-4](#) below.

**Table 5-4 Period and Cumulative Consumer Exposure**

	Reporting period (n)	Cumulative (n)
<b>THD</b>	19,652,061	112,420,820
<b>EHTP</b>	112,943,395,160	513,138,451,365

n=number of units sold

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## 6 DATA IN SUMMARY TABULATIONS

### 6.1 Reference Information

The summary tabulations presented in [Appendices 2a-2b-2c](#) of this SUR were generated from the PMI global safety database. The analysis of AEs was performed using the Medical Dictionary for Regulatory Activities (MedDRA) versions effective at the time of AE processing (latest version used 26.1).

The seriousness of the AEs corresponds to the seriousness assigned to events included in the ICSRs using the criteria established in ICH-E2A (Clinical safety data management: Definitions and standards for expedited reporting).<sup>[2]</sup> When serious and non-serious events are included in the same ICSR, the individual seriousness per event is reflected in the summary tabulations.

Of note, most of the spontaneous reports received by PMI are not medically confirmed, i.e., they are received from consumers directly and not from health care professionals (HCPs).

### 6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

Cumulative summary tabulations of Serious Adverse Events (SAEs) received from all PMI-sponsored clinical studies, from the DIBD (30-Apr-2013) until the DLP of this SUR are presented in [Appendix 2a](#). The summary tabulations are presented by MedDRA SOC for both the THS and the comparator arm CC.

The cumulative summary tabulations present 79 SAEs reported in 60 ICSRs. A total of 32 SAEs were reported in the THS arms, 31 SAEs in the CC arm, and 16 SAEs in the SA arm.

The most represented SOCs in the THS arms included: *Injury, poisoning and procedural complications* (n=8); and *Infections and infestations* (n=7). All but 3 SAEs were assessed as having no causal relationship to THS use by principal investigators and by PMI. In case of these 3 SAEs, the principal investigator was unable to assess whether they were related to THS use. These SAEs concerned 1 consumer who enrolled in a study P1-AAA-02-JP entitled “A controlled, open-label, 3-arm parallel group, multi-center study to evaluate the Abdominal Aortic Aneurysm (AAA) growth rate in adult smoking patients randomized to either cigarette smoking or IQOS use and to compare with the AAA growth rate in patients who had stopped smoking.” This case is presented in [Section 7.2](#).

### 6.3 Cumulative Summary Tabulations of Serious Adverse Events from Pre-Market Studies

Cumulative summary tabulations of SAEs received from all PMI-sponsored pre-market studies up until the DLP of this SUR are presented in [Appendix 2b](#). The summary tabulations are presented by MedDRA SOC for the THS.

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The cumulative summary tabulations present 25 SAEs reported in a total of 11 ICSRs. None of the SAEs were assessed as causally related to THS by the principal investigators and by PMI, and in the case of 1 SAE, an assessment was not provided by the principal investigator. The most represented SOC included: *Injury, poisoning and procedural complications* (n=12); and *Infections and infestations* (n=7).

## 6.4 Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Events from Post-Marketing Experience

Cumulative and interval summary tabulations of AEs generated from the PMI global safety database are presented in [Appendix 2c](#). The latest MedDRA version used for AE analysis was 26.1. All SAEs and non-serious AEs received from unsolicited sources (spontaneous post-marketing safety reports and literature review) within the interval covered by this SUR and cumulatively from the IBD (04-Nov-2014) are presented in the summary tabulations organized by MedDRA SOC.

The definition of “spontaneous report” is derived from ICH E2C (R2) Guidance, and refers to an unsolicited communication by an HCP or consumer to a competent authority, marketing authorization holder or other organization (e.g. Regional Pharmacovigilance Centre, Poison Control Centre) that describes 1 or more suspected AEs in an individual (e.g. consumer) who was using or exposed to the THS. A spontaneous report is not derived from a study or any organized data collection systems where AE reporting is actively sought. Most of the spontaneous reports received by PMI are not medically confirmed, i.e., they were received directly from consumers and not via HCPs.

- Interval summary tabulations of non-serious AEs and SAEs from post-marketing experience showed 53,944 AEs (834 serious and 53,110 non-serious) from 34,736 ICSRs. The most represented SOC (>5%) were: *Respiratory, thoracic and mediastinal disorders* (42.33%, n=22,836; 110 serious and 22,726 non-serious); *Gastrointestinal disorders* (18.15%, n=9,791; 73 serious and 9,718 non-serious); *Nervous system disorders* (11.35%, n=6,125; 75 serious and 6,050 non-serious); *General disorders and administration site conditions* (9.37%, n=5,056; 44 serious and 5,012 non-serious); and *Injury, poisoning and procedural complications* (6.77%, n=3,653; 65 serious and 3,588 non-serious).

The most frequently reported events (>5%) were *Cough* (14.77%, n=7,967; 19 serious and 7,948 non-serious); *Throat irritation* (7.38%, n=3,981; 2 serious and 3,979 non-serious); *Headache* (5.75%, n=3,104; 8 serious and 3,096 non-serious); and *Oropharyngeal pain* (5.46%, n=2,945; 2 serious and 2,943 non-serious).

Out of the total 834 SAEs, the most frequently reported (>5%) were: *Angina pectoris* (24.70%, n=206); *Accidental exposure to product by child* (5.88%, n=49); and *Pneumonia* (5.52%, n=46).

Concerning the 206 serious events of *Angina pectoris*, the most frequently reported verbatim (>5%) was “heart pain”, “acute pain in the heart”, and “pain in the heart”,

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all of which correspond to the MedDRA coding *Angina pectoris*. In most of these cases, the consumers' medical history was not provided. The mean age of the consumers was 33.52 years. Out of these 206 events, 1 event of *Angina pectoris* led to hospitalization and 205 were assessed as medically important conditions. The limited information about these events does not allow one to conclude whether the consumer indeed experienced *Angina pectoris*. However, considering the verbatim reported, the mean age of the consumers, and the fact that most of the cases did not lead to hospitalization, it is likely that these cases refer to chest pain or chest discomfort. *Chest pain* and *Chest discomfort* are expected AEs with the use of NRT (e.g. Summary of Product Characteristics for Nicorette 15mg Inhalator, McNeil Products)[3] with a frequency categorized as uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ). *Angina pectoris* is considered as an unlisted event according to the SPI version 8.0.

*Accidental exposure to product by child* is an important risk known for THS products and is presented in Sections 15.3.1.2 and 15.4.1.2.

Concerning the 46 serious events of *Pneumonia*, the most frequently reported verbatim ( $>5\%$ ) was "pneumonia" and "lung infection". In most of these cases, the consumers' medical history was not provided. The mean age of the consumers was 38.64 years. Out of these 46 events, 7 events of *Pneumonia* led to hospitalization. One case of hospitalization was reported as a fatal outcome. This case concerned a 78-year-old male patient who experienced *Pneumonia* 19 days after he started using THS. The medical history included unspecified lung disease and covid-19. Given the limited amount of information received, the causality is difficult to assess in this non-medically confirmed case. In the remaining 39 cases, the event of *Pneumonia* was recognized as medically important condition. *Pneumonia* is considered as an unlisted event according to the SPI version 8.0.

- Cumulative summary tabulations of non-serious AEs and SAEs from post-marketing experience showed 341,611 AEs (5,776 serious and 335,835 non-serious) from 199,791 ICSRs. The most represented SOC ( $>5\%$ ) were: *Respiratory, thoracic and mediastinal disorders* (31.44%, n=107,414; 779 serious and 106,635 non-serious); *Gastrointestinal disorders* (17.56%, n=59,980; 347 serious and 59,633 non-serious); *Nervous system disorders* (11.38%, n=38,879; 498 serious and 38,381 non-serious); *General disorders and administration site conditions* (11.01%, n=37,613; 235 serious and 37,378 non-serious); *Injury, poisoning and procedural complications* (11.01%, n=37,609; 263 serious and 37,346 non-serious); and *Product issues* (7.41%, n=25,313; 5 serious and 25,308 non-serious).

The most frequently reported events ( $>5\%$ ) were *Cough* (10.02%, n=34,236; 78 serious and 34,158 non-serious); *Headache* (5.98%, n=20,442; 50 serious and 20,392 non-serious); *Thermal burn* (5.60%, n=19,128; 22 serious and 19,106 non-serious); and *Oropharyngeal pain* (5.05%, n=17,265; 31 serious and 17,234 non-serious).

Of the total 5,776 SAEs reported, the most frequently reported ( $>5\%$ ) were: *Angina pectoris* (20.74%, n=1,198) and *Hypersensitivity* (15.15%, n=875).

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Concerning the 1,198 serious events of *Angina pectoris*, the most frequently reported verbatim (>5%) was “heart pain” and “heartache”, both corresponding to the MedDRA coding *Angina pectoris*. In most of these cases, the consumers’ medical history was not provided. The mean age of the consumers was 33.74 years. Of these 1,198 events, 12 events of *Angina pectoris* led to hospitalization and 1 was life-threatening. The only life-threatening case did not lead to consumer’s hospitalization. The consumer mentioned “it was too painful as the heart would stop.” The remaining 1,185 events were upgraded to serious as they were assessed as medically important conditions. Given the limited information about the events does not allow one to conclude whether the consumer indeed experienced *Angina pectoris*. However, considering the verbatim reported, the mean age of the consumers, the short median latency (the time between the start of the product use and the event onset), and the fact that most of the cases did not lead to hospitalization, it is likely that these cases refer to chest pain or chest discomfort. *Chest pain* and *Chest discomfort* are expected AEs with the use of NRT (e.g. Summary of Product Characteristics for Nicorette 15mg Inhalator, McNeil Products)[3] with a frequency categorized as uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ). *Angina pectoris* is considered as an unlisted event according to the SPI version 8.0.

As discussed in Sections 15.3.1.1 and 15.4.1.1, *Hypersensitivity* is a known important identified risk for THS products.

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## 7 SUMMARY OF SIGNIFICANT SAFETY FINDINGS FROM CLINICAL STUDIES DURING THE REPORTING PERIOD

A listing of interventional studies with a primary objective of post-authorization safety monitoring that were ongoing or closed during the review period of this SUR is presented in [Appendix 4](#).

### 7.1 Completed Clinical Studies

Three PMI-sponsored clinical studies (P1-AAA-02-JP, P1-REXC-10, and P1-PK-12) have been completed for THS products during the period covered by this SUR.

- **Study P1-AAA-02-JP** is a controlled, open-label, 3-arm parallel group, multi-center study to evaluate the AAA growth rate in adult smoking patients randomized to either cigarette smoking or THS use and to compare the AAA growth rate in patients who had stopped smoking.

**Safety results:** The study started on 03-Oct-2018 and was closed on 06-Apr-2023. The safety population included female and male Japanese patients diagnosed with AAA, who were aged  $\geq 50$  years, and have smoked CC daily for at least 5 years prior to AAA diagnosis. In total, 48 subjects were enrolled and exposed to the study product. Among the exposed subjects, 15 reported 26 SAEs.

Six SAEs in 3 subjects have been reported in THS arm (2 SAEs of *Atrial fibrillation* and 1 SAE of each event of *Death*, *Lumbar spinal stenosis*, *Patella fracture*, and *Femoral neck fracture*). The fatal case concerns a 71-year-old male Japanese subject with relevant ongoing diseases of AAA (as per inclusion criteria in the study protocol), arterial hypertension and a smoking history of 20 cigarettes/day. An image autopsy was performed with the finding of a dominant edema in the back of the lungs. It was confirmed that the AAA did not rupture. The cause of the study subject's death remains unknown. As reported in the previous SUR, the death was assessed as not reasonably related to THS by the study sponsor, and it was not possible for principal investigator to assess the case.

Six SAEs in 5 subjects have been reported in CC arm (*Cerebral haemorrhage*, *Angina unstable*, *Cataract*, *Inflammatory pseudotumour*, *Large intestinal polyp*, and *Tarsal tunnel syndrome*). As reported during the previous reporting period, the first case concerns a 79-year-old male subject with a medical history of hypertension and chronic renal failure, ongoing diseases of AAA (as per inclusion criteria in the study protocol) and smoking 25 cigarettes/day, who died in the hospital due to intracerebral hemorrhage. The event of *Cerebral haemorrhage* was assessed as related to cigarettes by both the principal investigator and the sponsor. In other 2 cases, the events of *Inflammatory pseudotumour* and *Tarsal tunnel syndrome*, were assessed as not related to cigarettes by both the principal investigator and the sponsor. In 1 case, the event of *Cataract* was reported in a 74-year-old male subject in which the causality can be explained as being related to old age of the subject. The remaining case reported 2 events of *Angina unstable* and *Large intestinal polyp* that were assessed as related to cigarettes.

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Fourteen SAEs in 7 subjects were reported in SA arm (4 SAEs of *Large intestine polyp*, and 1 SAE of each event *Acute myocardial infarction*, *Angina pectoris*, *Appendicitis*, *Cardiac failure acute*, *Gastroenteritis*, *Ileus*, *Inguinal hernia*, *Myocardial ischaemia*, *Peripheral arterial occlusive disease*, and *Pneumonia*) where the assessment of causal relationship to the products is not applicable.

**Safety conclusions:** The proportion of subjects experiencing AEs was comparable across the study arms. The majority of AEs during the study were assessed as mild or moderate in severity and the majority of these AEs were reported as resolved at the end of the study. No SAEs related to THS use or to study procedures were reported. One death case occurred in the THS arm in a 70-year-old male subject with no reasonable causal relationship to the use of THS, and another death case occurred in the CC arm, which was assessed as related to CC smoking. No new safety issues were identified concerning the THS products.

- **Study P1-REXC-10** is a randomized, controlled, open-label, 4 parallel arms study to demonstrate reductions in exposure to selected harmful and potentially harmful constituents of CC smoke in healthy smokers switching to different versions of THS compared to continuing CC smoking, for 5 days in confinement.

**Safety results:** Study started on 04-Nov-2022 and was closed on 04-Feb-2023. The safety population included healthy male and female subjects between 21 and 65 years old, who have been smoking for  $\geq 3$  years, and did not plan to quit smoking within the next 3 months. In total, 91 subjects were enrolled and exposed to the study products. No SAEs were reported in the study.

**Safety conclusions:** No AEs led to discontinuation or were considered as SAEs. All AEs were assessed as either mild or moderate in severity and were reported as recovered/resolved by the end of the study. Overall, the results of this study demonstrate that there are no additional safety concerns associated with any of the THS products when compared to CC.

- **Study P1-PK-12** is a single-center, randomized, controlled, open-label study in smoking healthy subjects to investigate the nicotine pharmacokinetic profiles following single use of THS with a regular or a menthol stick, compared to smoking of a single CC.

**Safety results:** Study started on 16-Feb-2023 and was closed on 02-Apr-2023. The safety population included healthy male and female subjects between 21 and 65 years old, who have been smoking for  $\geq 3$  years and who did not plan to quit smoking within the next 3 months. In total, 32 subjects were enrolled and exposed to the study products. No SAEs were reported in the study.

**Safety conclusions:** There were no SAEs reported during the study and no subjects discontinued from the study due to an AE. All events in this study were assessed as mild in severity and no AEs were considered as related to study product. In summary, no safety signals were observed in this study.

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## 7.2 Ongoing Clinical Studies

One PMI-sponsored clinical study (P1-COPD-04-INT) for the THS was ongoing during the period covered by this SUR.

- **Study P1-COPD-04-INT** is a 3-year, 3-group, preference, multi-center study to demonstrate the slowing of disease progression when switching from CC smoking to the THS in mild to moderate Chronic Obstructive Pulmonary Disease (COPD) subjects with a history of chronic bronchitis symptoms.

First subject in this study was screened in December 2022. The safety population included male and female subjects between 40 and 65 years old, who were diagnosed with COPD and had a history of chronic bronchitis symptoms, and who had a smoking history of at least 10 years. Until 31-Dec-2023, 306 subjects were enrolled to the study. Among them, 4 subjects reported 4 SAEs during the review period of this SUR.

Three SAEs in 3 subjects have been reported in THS arm (*Atrial flutter*, *Incisional hernia*, and *Chronic obstructive pulmonary disease*). All SAEs caused hospitalization of the study subjects and were reported as resolved. All 3 SAEs were assessed as not related to THS use by both the principal investigator and the sponsor.

One SAE in 1 subject was reported in SA arm (Preferred Term (PT): *COVID-19*) where the assessment of causal relationship to the products is not applicable.

No new safety concerns were identified for THS in the ongoing study until the DLP of this SUR.

## 7.3 Long-term Follow-up in Clinical Studies

No long-term follow-up information was received by PMI during the period covered by this SUR.

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## 8 SUMMARY OF SIGNIFICANT SAFETY FINDINGS FROM PASSIVE SURVEILLANCE PRE-MARKET STUDIES DURING THE REPORTING PERIOD

A listing of non-interventional studies with a primary objective of post-authorization safety monitoring that were ongoing or closed during the review period of this SUR is presented in [Appendix 4](#).

### 8.1 Completed Passive Surveillance Pre-Market Studies

No PMI-sponsored pre-market studies were completed for the THS during the period covered by this SUR.

### 8.2 Ongoing Passive Surveillance Pre-Market Studies

No PMI-sponsored pre-market studies were ongoing for the THS during the period covered by this SUR.

### 8.3 Other Non-Interventional Studies

There was 1 PMI-sponsored non-interventional study conducted during the reporting period of this SUR.

- **Actual Use Study of THS 3.0 – P1-PMTA I4-07-US** is a multi-site, 2-arm, mid-term, prospective observational study.

This study was conducted in the U.S. The first subject was enrolled to the study on 19-Jan-2023 and the last subject completed the study on 10-Apr-2023.

This THS 3.0 Actual Use Study involved an assessment of subject-reported consumption of the EHTP used with the THD, and of CC and other tobacco product use behaviors. Subjects were able to consume CC, EHTP, and other tobacco products *ad libitum*. The study consisted of 2 THS study arms (3.0 Mono Device and 3.0 Mid Device) into which subjects were randomized. The study also included a human factors component – the Usability and Comprehension Assessment. A subset of subjects completed an interview to understand whether they can demonstrate and comprehend the correct use of the product based on product instructions for use and safety warnings and instructions.

The number of enrolled subjects was 987, the safety population was equal to 884 subjects. Overall, a total of 29 ICSRs with 42 AEs were reported. All reported AEs were assessed as non-serious. The most frequently reported events were *Cough* and *Headache*, followed by *Nausea*, *Oropharyngeal pain*, and *Oropharyngeal discomfort*.

In summary, this study revealed no new safety concerns related to the THS.

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## 9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

Four non-PMI sponsored clinical trials (APM-PMI IIS, HW-001-DE, IIS.PMI.2022.1, and IIS.PMI.2022.2) were ongoing for the THS during the period covered by this SUR.

- **Study APM-PMI IIS** is a 5-year cohort observational clinical study to assess possible harm-reduction effects of the THS in comparison with combustible cigarettes.

The goal of this study was to evaluate whether the presence of respiratory symptoms, functional exercise incapacity, and exacerbation rate across time are the same between the exposure and the control groups through hypothesis testing. This study was initiated in 2018 and closed in 2023 at the Academy of Preventive Medicine of Kazakhstan.

A total of 1,200 participants were recruited including 807 in the CC arm and 393 in THS arm at the DLP of this SUR. No new participants were enrolled during the review period (01-Jan-2023 to 31-Dec-2023). A total of 79 SAEs in 42 subjects were reported in THS arm up to 31-Dec-2023. Among these 79 SAEs, the seriousness criteria were fatal in 4 SAEs (*Cardiac failure acute*, *Myocardial ischemia*, *Completed suicide*, and *COVID-19*), life-threatening in 1 SAE (*Acute myocardial infarction*), and hospitalization in 74 SAEs.

As reported during the previous reporting period, all fatal SAEs were assessed as not related to THS.

- **Study HW-001-DE** is an open-label, 6-arm parallel group, single-center preference clinical study on the effects of smoking cessation or switching from cigarette smoking to the THS in adult smokers who have been diagnosed with inflammatory bowel disease and are under treatment.

The main goal of this study is to evaluate the effects of SA or switching from cigarette smoking to THS on the clinical course of ulcerative colitis and Crohn's disease in current adult smokers (19 to 75 years) who were diagnosed with inflammatory bowel disease and are under treatment. This study was initiated in 2022 and closed in 2023 in Germany.

Until the DLP of this report, 100 subjects were screened with 93 enrolled and distributed on THS, CC and SA arms. The total number of subjects enrolled under the SA arm were 26 (13 with Chron's disease and 13 with ulcerative colitis), 37 under CC arm (24 with Chron's disease and 13 with ulcerative colitis) and 30 under THS arm (18 with Chron disease and 12 with ulcerative colitis). No SAEs were reported in subjects from this study up to 31-Dec-2023.

- **Study IIS.PMI.2022.1** is a prospective, single-center, open-label, randomized study on effects of switching from cigarettes to tobacco heating system on coronary atherosclerosis progression in patients with stable coronary artery disease.

The main goal of this study is to evaluate the impact of heated versus combusted tobacco products on progression of atherosclerosis in patients with coronary artery disease, without indications for invasive treatment, who are unable or unwilling to quit smoking. This study was initiated in 2023 in Poland.

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Study is aiming to recruit 180 subjects further randomized 1:1 to either THS arm or CC arm and follow them for 18 months. Until the DLP of this SUR, 43 subjects were enrolled in the study. No SAEs were reported in subjects from this study up to 31-Dec-2023.

- **Study IIS.PMI.2022.2** is an open-label, not-randomized study on evaluation of THS compared to CC smoking during the closed tibia fracture healing in orthopedic smokers' patients.

The goal of this study is to investigate the role of switching from CC smoking to THS on the clinical outcome of closed tibia fractures from smokers' orthopedic adult (30 years and older) patients. Validated and standardized assays, medical state and self-reported outcomes will be evaluated in orthopedic patients' smokers or switch from CC to using THS throughout 6 months compare to ex-smokers (control). This study was initiated in 2023 in Germany.

The study is aiming to recruit 150 subjects that will be further distributed on THS, CC and SA arms. Until the DLP of this report, 33 subjects were enrolled and randomized to THS arm (15), CC arm (8), and SA arm (10). No SAEs were reported in subjects from this study up to 31-Dec-2023.

In summary, no new safety concerns were identified for THS in non-PMI sponsored clinical trials until the DLP of this SUR.

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## 10 NON-CLINICAL DATA

No safety findings concerning the non-clinical use of the THS became available during the reporting period of this SUR from PMI-sponsored studies.

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## 11 LITERATURE

PMI performs a systematic review of published articles to generate and maintain a comprehensive library of all articles that discuss the THS or associated category products. The library includes articles published by PMI or by independent third parties sponsored or not sponsored by PMI. To ensure rapid and timely identification, the main sources for the literature search are PubMed, Scopus, Embase, SciFinder, Google Scholar, and RightFind. Email alerts are received on a daily basis by using the search queries described below:

- PubMed:** (((eclipse OR accord OR "Heatstick" OR "revo") AND cigarette AND heat\* NOT (resin OR column)) OR "tobacco heating"[Title/Abstract] OR "heated cigarette\*"[Title/Abstract] OR "electrically heated cigarette\*"[Title/Abstract] OR "EHCSS"[Title/Abstract] OR "Electrically Heated Cigarette Smoking System\*"[Title/Abstract] OR "primarily heat\* tobacco"[Title/Abstract] OR "tobacco heating cigarette\*"[Title/Abstract] OR "EHCSS-K3"[Title/Abstract] OR "EHCSS-K6"[Title/Abstract] OR "heated tobacco"[Title/Abstract] OR "tobacco heating system"[Title/Abstract] OR ("heat-not-burn"[Title/Abstract] AND "tobacco"[Title/Abstract]) OR "IQOS"[Title/Abstract] OR "HEETS"[Title/Abstract] OR "heatsticks\*"[Title/Abstract] OR ("heat-not-burn"[Title/Abstract] AND "tobacco"[Title/Abstract]) OR ("HNB"[Title/Abstract] AND "tobacco"[Title/Abstract]) OR ("THS"[Title/Abstract] AND "tobacco"[Title/Abstract]) OR ("Lil"[Title/Abstract] AND "tobacco"[Title/Abstract]) OR ("TEEPS"[Title/Abstract] AND "tobacco"[Title/Abstract])) OR ("Modified risk tobacco product\*"[Title/Abstract] OR ("non-cigarette combustible\*"[Title/Abstract]) OR ("noncombustible cigarette\*"[Title/Abstract]) OR ("Risk continuum "[Title/Abstract] AND "tobacco"[Title/Abstract]))
- Scopus:** ALL(tobacco W/2 heat\*)OR ALL("heated tobacco product") OR ALL("heated tobacco product\*") OR ALL("heated tobacco") OR ALL("tobacco heating system") OR ALL("tobacco heating system\*") OR ALL("heat not burn") OR ALL(iqos) OR ALL(heets) OR ALL(heatstick\*) OR ALL("electrically heated cigarette smoking system") OR ALL("electrically heated cigarette") OR ALL(ehcss) OR ALL(heat\* W/2 cigarette)OR ALL("modified risk tobacco product") OR ALL("modified risk tobacco product\*") OR ALL(lil W/2 tobacco) OR ALL(tees W/2 tobacco) OR ALL(hnb AND tobacco) OR ALL("noncombustible cigarette") OR ALL("non-cigarette combustible") OR ALL("Risk continuum" AND tobacco) OR ALL(thh AND tobacco) AND NOT ALL("third hand smok\*" OR "thirdhand smok\*")
- Embase:** ths:ab AND tobacco:ab NOT ('third hand smok\*' OR 'thirdhand smok\*') OR (tobacco NEAR/2 heat\*) OR 'heated tobacco product'/exp OR 'heated tobacco product\*' OR 'heated tobacco' OR 'tobacco heating system'/exp OR 'tobacco heating system\*' OR 'heat not burn' OR iqos OR heets OR heatstick\* OR 'electrically heated cigarette smoking system'/exp OR 'electrically heated cigarette' OR ehcss OR (heat\* NEAR/2 cigarette) OR 'modified risk tobacco product'/exp OR 'modified risk tobacco

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product\*' OR (lil NEAR/2 tobacco) OR (teeps NEAR/2 tobacco) OR (hnb:ti,ab,kw AND tobacco:ti,ab,kw) OR 'noncombustible cigarette' OR 'non-cigarette combustible' OR ('risk continuum' AND tobacco)

- **Google Scholar:** ("heated cigarette\*") OR ("tobacco heating") OR ("heated tobacco") OR ("tobacco heating system") OR ("heat-not-burn" "tobacco") OR ("IQOS") OR ("HEETS") OR ("heatsticks ") OR ("heat not burn" "tobacco") OR ("THS" "tobacco") OR ("HNB" "tobacco"); Articles excluding patents ("noncombustible cigarette") OR ("non-cigarette combustible") OR ("risk continuum" "tobacco")
- **SciFinder:** "heat not burn" OR "tobacco heating system" OR "modified risk tobacco" OR "electrically heated cigarette" OR "heated tobacco"
- **RightFind:** "heated cigarette" or "tobacco heating" or "heated tobacco" or "tobacco heating system" or ( "heat-not-burn" and Tobacco ) or IQOS or HEETS or heatsticks or ( HNB and Tobacco ) or ( Lil and Tobacco ) or "Modified risk tobacco product" or "primarily heat tobacco" "noncombustible cigarette" or "non-cigarette combustible" or ( "risk continuum" and Tobacco )

This comprehensive library was screened for publications containing new safety information associated with the THS products published during the reporting period from 01-Jan-2023 to 31-Dec-2023 inclusive.

Two articles were identified to include new safety related information and are presented below.

**The first article** by Giosuè Giordano Incognito et al.<sup>[4]</sup> compared the effects of using HTPs or CC on maternal and neonatal outcomes in a retrospective, monocentric study conducted at San Marco Hospital, Italy, from July 2021 to July 2022. The authors compared a cohort of pregnant patients who used HTPs, with pregnant women smoking CC, ex-smokers (SA) and non-smokers. In total, 642 women were enrolled, of which 270 were non-smokers, 114 were SA, 120 were CC, and 138 were HTP. The CC group had the greatest weight gain and had more difficulty getting pregnant. The CC and SA groups experienced more frequently threats of preterm labor, miscarriages, temporary hypertensive spikes, and higher rates of cesarean sections. Preterm delivery was more associated with CC and HTP groups. The CC and HTP groups had lower awareness of the risks to which the mother and the fetus are exposed. The CC group was more likely to be depressed and anxious. Biochemical parameters did not show significant differences between the groups. The CC group had the greatest difference in days between the gestational age calculated based on the last menstrual period and the one based on the actual ultrasound age. The average percentile newborn weight range of CC was lower, as well as the mean 1st minute and the 5th minute Apgar scores. The comparison of the data obtained between CC and HTP underlines the greater danger of CC. Nevertheless, the authors did not recommend HTPs because the maternal–fetal outcomes are not superimposable to the non-smokers' outcomes.

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**PMI comment:** In above study, authors evaluated effects of HTP use on maternal and neonatal outcomes. Maternal HTP use was associated with 4 times greater threat of preterm birth and 2 times greater preterm birth than non-smokers. The study had the following limitations: retrospective study design and total number of patients evaluated. Moreover, a large confounder is the fact that women who smoked CC appear to be older and from lower socio-economic levels than those who used HTPs. Women who used HTPs also appeared to be using it for fewer years than smokers, although the authors did not provide any smoking history. This potential bias may have influenced the results on the risk of preterm birth, infertility, and fetal growth restriction. The effect of THS use during pregnancy and lactation was recognized as missing information and is closely monitored by PMI. According to the THS SPI, women who are pregnant, breastfeeding, or think they may be pregnant, should quit tobacco and nicotine use altogether.

**The second article** by Gustaf Lyytinen et al.[5] evaluated the impact of HTP use on vascular function by investigating the effects of a brief HTP usage on arterial stiffness and platelet thrombus formation in healthy volunteers. In this randomized crossover study, 24 healthy young adults with occasional tobacco use were assigned to the HTP *IQOS* 3 Multi and “no-exposure” was used as a control, with a wash-out period of at least 1 week in-between. Arterial stiffness was assessed through pulse wave velocity and pulse wave analysis. Blood samples, collected at baseline and 5 min following exposure, were analyzed with the Total-Thrombus-formation analysis system evaluating platelet and fibrin-rich thrombus formation tendency. The exposure to HTPs caused immediate heightened pulse wave velocity (+0.365 m/s, 95% CI: +0.188 to 0.543;  $p = 0.004$ ) and enhanced augmentation index corrected to heart rate (+6.22%, 95% CI: +2.33 to 10.11;  $p = 0.003$ ) compared to the no-exposure occasion. Similarly, blood pressure and heart rate transiently increased immediately following HTP inhalation. Platelet thrombus formation significantly increased following HTP exposure (area under the curve +59.5, 95% CI: +25.6 to 93.4;  $p < 0.001$ ) compared to no-exposure. No effect was seen on fibrin-rich thrombus formation following HTP-exposure. Brief HTP use in healthy young adults had immediate AEs on vascular function resulting in increased arterial stiffness and platelet thrombus formation, known risk factors for the development of atherosclerosis.

**PMI comment:** In above study, authors evaluated the impact of HTP use on vascular function in healthy young adults that were current occasional tobacco users. The study determined that HTP exposure causes a transient increase in arterial stiffness as well as heightened platelet thrombogenicity, both of which are strongly associated with the development of atherosclerotic disease in humans. A limitation of this study is its small size. Furthermore, this study included volunteers with lower nicotine tolerances that in certain cases caused nausea and/or coughing, potentially reducing the exposure dose in the affected subjects. Though, this detail was not explicitly stated in the publication, it appears that the participants used 2 EHTPs consecutively and were exposed to 28 puffs as each EHTP lasts up to 14 puffs, which may cause a higher intake of the nicotine during 1 use of the product. As the study included only young and healthy individuals, it may be difficult to extrapolate results to older individuals with, in some cases, already established cardiovascular disease. The used method is relatively novel, with most studies to date being relatively small.

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Therefore, the method currently has no identified definite threshold value that correlate to increased thrombotic risk. The study did not evaluate the duration of the acute increase in platelet thrombogenicity in humans following HTP exposure with additional measurements past 5 min post exposure. Long term health impacts should be studied in further research.

Despite the new safety related information presented above, the review of these recently published articles concerning THS products did not identify any new safety concerns.

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## 12 OTHER PERIODIC REPORTS

No other periodic reports have been prepared for the THS by PMI during the period covered by this SUR.

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### 13 LATE-BREAKING INFORMATION

No potentially important safety findings concerning THS products were identified after the DLP and until the date of release of this SUR.

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## 14 OVERVIEW OF SIGNALS: NEW, ONGOING OR CLOSED

PMI conducts periodic and ad-hoc safety signal detection activities of current safety data within its global safety database. The sources of safety data within the global safety database include spontaneous reports, published literature, and clinical and other studies with medical oversight (safety data from clinical and other studies captured in the global safety database include only SAEs).

The 3 key steps in PMI's signal detection process are:

1. Initial signal detection: the identification of a new potential signal during the assessment of studies sponsored by PMI (i.e. PMI-sponsored clinical, post-market research studies, and passive surveillance pre-market studies) and during the assessment of information obtained from unsolicited sources such as: literature monitoring, call centers, poison centers, PMI-sponsored social media platforms/local, global websites, non-sponsored social media, and AEs reported by PMI employees involved in the internal panel testing.
2. Signal validation: verification of the existence of a new potential causal association or a new aspect of a known association, with justification for further analysis.
3. Signal assessment: thorough investigation of the validated signal, including the preparation of a Signal Evaluation Report.

During the reporting period, no signals were open or closed.

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## 15 SIGNAL AND RISK EVALUATION

### 15.1 Summary of Safety Concerns

A summary of the safety concerns at the beginning of the reporting period of this SUR is presented in [Table 15-1](#) below. New information received during the period covered by this SUR (01-Jan-2023 to 31-Dec-2023) has been evaluated regarding: a) 3 important identified risks of *Hypersensitivity*, *Accidental exposure to product by child*, and *Burning sensation*; b) 1 important potential risk of *Thermal burn*; c) as well as about missing information regarding exposure to the THS during pregnancy and lactation.

**Table 15-1 Summary of Safety Concerns at the Beginning of the Reporting period**

	Risk	Search criteria for Risk Assessment	Interval Retrieved AEs within Safety Database
Important Identified Risks	Hypersensitivity	Standardised MedDRA Query (SMQ) Hypersensitivity (Narrow)	<u>1,158 AEs of hypersensitivity retrieved:</u>  Most reported AEs (>1%): <ul style="list-style-type: none"> <li>- Hypersensitivity, n=440</li> <li>- Rash, n=180</li> <li>- Pharyngeal swelling, n=129</li> <li>- Urticaria, n=77</li> <li>- Gingival swelling, n=53</li> <li>- Lip swelling, n=45</li> <li>- Rash macular, n=42</li> <li>- Swollen tongue, n=36</li> <li>- Eczema, n=17</li> <li>- Swelling face, n=16</li> <li>- Dermatitis allergic, n=15</li> <li>- Mouth swelling, n=13</li> </ul>
	Accidental exposure to product by child	<u>Selected PTs:</u> <ul style="list-style-type: none"> <li>- Accidental exposure to product by child</li> <li>- Accidental exposure to product packaging by child</li> </ul> <u>Selected age groups:</u> <ul style="list-style-type: none"> <li>- Adolescent</li> <li>- Child</li> <li>- Infant</li> <li>- Neonate</li> </ul> <u>Selected age units:</u> <ul style="list-style-type: none"> <li>- Months</li> <li>- Years</li> </ul>	<u>897 AEs retrieved:</u> <ul style="list-style-type: none"> <li>- Accidental exposure to product by child, n=897</li> </ul> <u>Co-reported AEs (&gt;1%):</u> <ul style="list-style-type: none"> <li>- Vomiting, n=149</li> <li>- Mood altered, n=28</li> <li>- Cough, n=20</li> <li>- Nausea, n=18</li> <li>- Pallor, n=16</li> <li>- Adverse event, n=14</li> <li>- Respiratory tract irritation, n=12</li> <li>- Crying, n=10</li> <li>- Mouth haemorrhage, n=9</li> <li>- Asthenia, n=8</li> <li>- Diarrhoea, n=7</li> <li>- Malaise, n=6</li> </ul>

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	Risk	Search criteria for Risk Assessment	Interval Retrieved AEs within Safety Database
			<ul style="list-style-type: none"> <li>- Drooling, n=6</li> <li>- Somnolence, n=6</li> <li>- Saliva discolouration, n=5</li> </ul>
	Burning sensation	<u>Customized search of MedDRA PTs and Lowest Level Terms (LLTs):</u> <ul style="list-style-type: none"> <li>- Burning sensation</li> <li>- Burning sensation mucosal</li> <li>- Skin burning sensation</li> <li>- Oral discomfort (only the following LLTs are included in the risk assessment): <ul style="list-style-type: none"> <li>- Burning corner of mouth</li> <li>- Burning lips</li> <li>- Burning mouth</li> <li>- Burning oral sensation</li> <li>- Lip burning sensation of</li> <li>- Oral hot feeling</li> <li>- Oral mucosal burning sensation)</li> </ul> </li> </ul>	<u>2,715 AEs retrieved:</u> <ul style="list-style-type: none"> <li>- Burning sensation, n=844</li> <li>- Burning sensation mucosal, n=2</li> <li>- Skin burning sensation, n=5</li> <li>- Oral discomfort*, n=1,864</li> </ul> <p>(only the following selected LLTs under the PT Oral discomfort are included in the risk assessment:</p> <ul style="list-style-type: none"> <li>- Lip burning sensation of, n=1427</li> <li>- Burning lips, n=243</li> <li>- Burning mouth, n=92</li> <li>- Oral mucosal burning sensation, n=78</li> <li>- Burning oral sensation, n=13</li> <li>- Oral hot feeling, n=11)</li> </ul> <p>* note that the total number of AEs under the PT Oral discomfort is 1,945 out of which 1,864 were included in the risk assessment. The following LLTs have been excluded from the risk assessment:</p> <ul style="list-style-type: none"> <li>- Oral discomfort, n=37</li> <li>- Lip discomfort, n=23</li> <li>- Discomfort in mouth, n=18</li> <li>- Oral cavity discomfort, n=3</li> </ul>
Important Potential Risks	Thermal burn	<u>Customized search of MedDRA PTs:</u> <ul style="list-style-type: none"> <li>- Airway burns</li> <li>- Burn oral cavity</li> <li>- Burns first degree</li> <li>- Burns second degree</li> <li>- Burns third degree</li> <li>- Burns fourth degree</li> <li>- Thermal burn</li> <li>- Thermal burns of eye</li> </ul>	<u>1,501 AEs retrieved:</u> <ul style="list-style-type: none"> <li>- Thermal burn, n=884</li> <li>- Burn oral cavity, n=609</li> <li>- Airway burns, n=5</li> <li>- Thermal burns of eye, n=1</li> <li>- Burns third degree, n=1</li> <li>- Burns first degree , n=1</li> </ul>
Missing Information	Pregnancy and lactation	MedDRA SOC: - "Pregnancy, puerperium and perinatal conditions"  MedDRA SMQs (Narrow): - "Neonatal exposures via breast milk"	<u>346 AEs retrieved:</u> <ul style="list-style-type: none"> <li>- Exposure during pregnancy, n=293</li> <li>- Pregnancy, n=12</li> <li>- Exposure via breast milk, n=11</li> <li>- Maternal exposure during breast feeding, n=8</li> <li>- Maternal exposure during pregnancy, n=7</li> <li>- Abortion spontaneous, n=3</li> <li>- Morning sickness, n=3</li> </ul>

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	Risk	Search criteria for Risk Assessment	Interval Retrieved AEs within Safety Database
		<ul style="list-style-type: none"> <li>- "Pregnancy, labour and delivery complications and risk factors (excl. abortions and stillbirth)"</li> <li>- "Foetal disorders"</li> <li>- "Functional lactation disorders"</li> <li>- "Neonatal disorders"</li> <li>- "Normal pregnancy conditions and outcomes"</li> <li>- "Termination of pregnancy and risk of abortion"</li> </ul>	<ul style="list-style-type: none"> <li>- Paternal exposure during pregnancy, n=2</li> <li>- Increased foetal movements, n=1</li> <li>- Caesarean section, n=1</li> <li>- Pre-eclampsia, n=1</li> <li>- Foetal growth restriction, n=1</li> <li>- Stillbirth, n=1</li> <li>- Gestational diabetes, n=1</li> <li>- Placenta praevia, n=1</li> </ul> <p><u>Co-reported AEs (&gt;1%):</u></p> <ul style="list-style-type: none"> <li>- No adverse event, n=236</li> <li>- Passive smoking, n=23</li> <li>- Nausea, n=11</li> <li>- Malaise, n=6</li> <li>- Anxiety, n=5</li> <li>- Nicotine dependence, n=5</li> <li>- Vomiting, n=5</li> </ul>

PMI decided to close the potential risk of *Thermal burn* and exclude it from future SUR analysis. The data supporting this decision were included in the following Sections 15.3.2.1 and 15.4.2.1.

## 15.2 Signal Evaluation

No signal was closed during the reporting period.

## 15.3 Evaluation of Risks and New Information

### 15.3.1 New information on Important Identified Risks

#### 15.3.1.1 Hypersensitivity

A search covering the period from 01-Jan-2023 up to the DLP of this SUR was performed in the global safety database to retrieve all the hypersensitivity-related events with THS use. The electronic search included non-serious AEs and SAEs from solicited and unsolicited sources and was conducted using the MedDRA SMQ Hypersensitivity (narrow scope).

A total of 1,158 AEs of hypersensitivity-related events with THS use (14 serious and 1,144 non-serious) were received in 1,040 ICSRs. Among the 1,040 ICSRs, 529 cases reported use of *IQOS*<sup>TM</sup>, 348 cases reported *IQOS ILUMA*<sup>TM</sup>, and 227 cases reported unspecified *IQOS* device. It is worth noting, that 1 case can report multiple EHTPs and THDs.

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Among 1,158 AEs of hypersensitivity-related events, the most reported AEs (>1%) were: *Hypersensitivity* (38.00%, n=440; 1 serious and 439 non-serious); *Rash* (15.54%, n=180; 2 serious and 178 non-serious); *Pharyngeal swelling* (11.14%; n=129; all non-serious); *Urticaria* (6.65%, n=77; all non-serious); *Gingival swelling* (4.58%, n=53; all non-serious); *Lip swelling* (3.89%, n=45; all non-serious); *Rash macular* (3.63%, n=42; all non-serious); *Swollen tongue* (3.11%, n=36; all non-serious); *Eczema* (1.47%, n=17; all non-serious); *Swelling face* (1.38%, n=16; 1 serious and 15 non-serious); *Dermatitis allergic* (1.30%, n=15; all non-serious); and *Mouth swelling* (1.12%, n=13; all non-serious).

The SAEs that were reported more than once were: *Angioedema* (n=5, 2 recovered/resolved and 3 with unknown outcome); *Rash* (n=2, 2 recovering/resolving); and *Circulatory collapse* (n=2, 2 recovered/resolved). The remaining SAEs that were reported once included *Swelling face* (recovering/resolving); *Shock* (recovered/resolved); *Hypersensitivity* (unknown); *Tracheal oedema* (recovering/resolving), and *Oropharyngeal blistering* (not recovered/resolved). As per the current RSI *Circulatory collapse*, *Swelling face*, *Shock*, *Tracheal oedema*, and *Oropharyngeal blistering* are unlisted for THS, whereas *Angioedema*, *Rash* and *Hypersensitivity* are listed PTs. None of the serious hypersensitivity-related events was assessed as life-threatening or resulted in death.

The AEs belonging to the MedDRA SMQ Hypersensitivity represented 2.15% (1,158/53,944) of the total AEs originating from post-marketing experience that were received during the period covered by this SUR. The number of cases under the MedDRA SMQ Hypersensitivity was estimated to be 50.41 per 1 million users. This calculation is based on the number of cases falling under the MedDRA SMQ Hypersensitivity and reported during the reporting period of this SUR (n=1,040). The calculation also includes the number of users during this period, which is estimated to be 20.63 million (based on EHTP PMI's sales data and the assumption that a consumer uses 15 *HeatSticks*<sup>TM</sup> per day (based on experience from studies/surveys that PMI conducted) during the reporting period of this SUR). Taking into consideration an under-reporting of 90% specific to a spontaneous AE reporting system,[6] the reporting frequency rate for cases falling into the MedDRA SMQ Hypersensitivity was estimated to be 0.05 per 100 users (after correction for under-reporting). Based on the RSI for nicotine replacement therapies (such as Summary of Product Characteristics for Nicorette 15mg Inhalator, McNeil Products),[3] Hypersensitivity is a common ( $\geq 1/100$ ,  $< 1/10$ ) AE. The estimated reporting frequency rate (after correction for under-reporting) for cases falling under the MedDRA SMQ Hypersensitivity for the THS is therefore considered not to be higher than what is already known for nicotine replacement therapies.

At this point, the evaluation of new information received during the SUR reporting period does not support a revision of the risk characterization of *Hypersensitivity*. PMI will continue to perform regular review of hypersensitivity-related events in the context of its ongoing evaluation of new safety information for the THS.

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### 15.3.1.2 Accidental exposure to product by Child

A search covering the reporting period of this SUR (01-Jan-2023 to 31-Dec-2023) was performed in the global safety database to retrieve AEs related to accidental exposure to the EHTP by children. The electronic search included non-serious AEs and SAEs of accidental exposure to the THS product by children from solicited and unsolicited sources (PTs: *Accidental exposure to product by child* and *Accidental exposure to product packaging by child*). The selected age groups were adolescent, child, infant, and neonate. The selected age units were months and years.

A total of 897 events of *Accidental exposure to product by child* (49 serious and 848 non-serious) were received in 897 ICSRs. Among the 897 ICSRs, 60 cases reported use of IQOS™, 831 cases reported IQOS ILUMA™, and 74 cases reported unspecified IQOS device. As mentioned before, 1 case can report multiple EHTPs and THDs.

Among 49 serious cases of *Accidental exposure to product by child*, 43 reported hospitalization of the child and the remaining 6 cases included events that were assessed as medically important conditions. None of these serious cases were reported as life-threatening, resulted in death, required surgical intervention, or lead to other medical complications related to accidental ingestion of the product.

A total of 402 AEs were co-reported. In 71.57% of ICSRs concerning accidental exposure by children, no health-related events were co-reported (*No adverse event*, n=642). In the remaining cases, the most frequent (>1%) co-reported events were: *Vomiting* (37.06%, n=149; 20 serious and 129 non-serious), *Mood altered* (6.97%, n=28; 1 serious and 27 non-serious), *Cough* (4.98%, n=20; all non-serious), *Nausea* (4.48%, n=18; 1 serious and 17 non-serious), *Pallor* (3.98%, n=16; 7 serious and 9 non-serious), *Adverse event* (3.48%, n=14, all serious), *Respiratory tract irritation* (2.99%, n=12; all non-serious), *Crying* (2.49%, n=10; 1 serious and 9 non-serious), *Mouth haemorrhage* (2.24%, n=9; all non-serious), *Asthenia* (1.99%, n=8; all non-serious), *Diarrhoea* (1.74%, n=7, all non-serious), *Malaise* (1.49%, n=6, all non-serious), *Droping* (1.49%, n=6, 1 serious and 5 non-serious), *Somnolence* (1.49%, n=6, all non-serious), and *Saliva discolouration* (1.24%, n=5; all non-serious).

The evaluation of the new information received during the SUR reporting period does not support a revision of the risk characterization of *Accidental exposure to product by child*. PMI will continue to perform regular review of accidental exposure by children related events in the context of its ongoing evaluation of new safety information for the THS.

### 15.3.1.3 Burning sensation

A search covering the period from 01-Jan-2023 up to the DLP of this SUR was performed in the global safety database to retrieve data related to this risk. The electronic search included all SAEs and non-serious events from solicited and unsolicited sources. The following selected MedDRA PTs were part of the search criteria: *Burning sensation*, *Burning sensation mucosal*, *Skin burning sensation*, and *Oral discomfort*. Only a selected list of LLTs under the PT *Oral discomfort* were included in the analysis, namely: *Burning corner of mouth*, *Burning lips*, *Burning mouth*, *Burning oral sensation*, *Lip burning sensation of*, *Oral hot feeling*, and

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*Oral mucosal burning sensation*. The other LLTs (*Discomfort in mouth*, *Lip discomfort*, *Oral cavity discomfort*, *Oral discomfort*) were excluded being considered out of scope for this risk assessment. The electronic search included all non-serious AEs and SAEs events from all sources for the THS.

A total of 2,715 non-serious AEs were received in 2,637 ICSRs. Among the 2,637 ICSRs, 1,324 cases reported use of *IQOS*<sup>TM</sup>, 1,166 cases reported *IQOS ILUMA*<sup>TM</sup>, and 231 cases reported unspecified *IQOS* device. As mentioned before, 1 case can report multiple EHTPs and THDs.

The retrieved AEs among the selected PT list were: *Burning sensation* (n=844), *Burning sensation mucosal* (n=2), *Oral discomfort* (n=1,864), and *Skin burning sensation* (n=5). The AEs retrieved among the selected LLTs under the PT *Oral discomfort* were: *Lip burning sensation of* (n=1,427), *Burning lips* (n=243), *Burning mouth* (n=92), *Oral mucosal burning sensation* (n=78), *Burning oral sensation* (n=13), and *Oral hot feeling* (n=11). Of note, the total number of AEs under the PT *Oral discomfort* was 1,945; out of which 1,864 were included in the risk assessment. The LLTs excluded from the risk assessment were: *Oral discomfort* (n=37), *Lip discomfort* (n=23), *Discomfort in mouth* (n=18), and *Oral cavity discomfort* (n=3).

There was an increase in the number of burning sensation cases when compared with the previous reporting period. This increase was caused by an update in the coding convention applied in April 2023. In order to better distinguish between an actual 1st degree burns vs burning sensation, the event verbatim mentioning a skin burn (e.g. lip, finger, hand), without any additional details that reasonably indicate a 1st degree burn (e.g. local pain, redness, local treatment applied), were to be coded to *Burning sensation* instead of *Thermal burn*.

The evaluation of the new information received during the SUR reporting period does not support a revision of this risk characterization at this point. PMI will continue to perform regular review of related events in the context of its ongoing evaluation of new safety information for the THS.

### 15.3.2 New information on Important Potential Risks

#### 15.3.2.1 Thermal burn

A search covering the period from 01-Jan-2023 up to the DLP of this SUR was performed in the global safety database to retrieve data related to thermal burns while using the THS. The electronic search included all non-serious AEs and SAEs from solicited and unsolicited sources for the THS. The search criteria included a list of selected MedDRA PTs as follows: *Airway burns*, *Burn oral cavity*, *Burns first degree*, *Burns second degree*, *Burns third degree*, *Burns fourth degree*, *Thermal burns of eye*, and *Thermal burn*.

A total of 1,501 AEs (4 serious and 1,497 non-serious) were received in 1,482 ICSRs. Among the 1,482 ICSRs, 815 cases reported use of *IQOS*<sup>TM</sup>, 590 cases reported *IQOS ILUMA*<sup>TM</sup>, and 141 cases reported unspecified *IQOS* device. As mentioned before, 1 case can report multiple EHTPs and THDs.

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The reported events of thermal burn included: *Thermal burn* (n=884; 1 serious and 883 non-serious); *Burn oral cavity* (n=609; all non-serious); *Airway burns* (n=5; 1 serious and 4 non-serious); *Thermal burns of eye* (n=1; serious); *Burns third degree* (n=1; serious); and *Burns first degree* (n=1; non-serious).

Among the 4 SAEs, 2 serious events of *Thermal burn of eye* and *Burns third degree* were both upgraded to serious as they were assessed as medically important conditions. It was not reported if any treatment was provided, and the outcome is unknown for both events. The remaining 2 serious events were assessed as serious as they resulted in hospitalization. In case of event of *Thermal burn*, it was not reported if any treatment was provided, and the event was reported as not resolved. The consumer that experienced the event of *Airway burns* received an unspecified treatment and recovered from the event.

Concerning the body site affected by the burn, in 70.02% (n=1,051) of cases, the consumer reported the oral cavity (including mouth, lips, and tongue). In 20.05% (n=301) of cases, the affected body site was not specified. In 9.26% (n=139) of the cases, the reported body site were fingers and/or hands, and in 0.67% (n=10), another body site (airway, eye, hair, arm, face) was reported.

There was a decrease in the number of thermal burn cases observed in the current review period. The decrease in numbers supports the decision to close this risk of *Thermal burn*. PMI will continue to perform standard monitoring of all cases originating from spontaneous sources, including the reports of thermal burn, to identify any new safety information that may arise.

### 15.3.3 Update on missing information

#### 15.3.3.1 Pregnancy and Lactation

A search covering the period from 01-Jan-2023 to the DLP of this SUR was performed in the global safety database to retrieve data related to pregnancy and lactation. The electronic search for pregnancy reports included all non-serious AEs and SAEs from solicited and unsolicited sources and was carried out under the MedDRA SOC "Pregnancy, puerperium and perinatal conditions" and the following MedDRA SMQs (Narrow): "Neonatal exposures via breast milk", "Pregnancy, labour and delivery complications and risk factors (excl. abortions and stillbirth)", "Foetal disorders", "Functional lactation disorders", "Neonatal disorders", "Normal pregnancy conditions and outcomes", "Termination of pregnancy and risk of abortion".

A total of 346 (8 serious and 338 non-serious) pregnancy related AEs were received in 329 ICSRs. Among the 329 ICSRs, 93 cases reported use of *IQOS™*, 92 cases reported *IQOS ILUMA™*, and 157 cases reported unspecified *IQOS* device. As mentioned before, 1 case can report multiple EHTPs and THDs.

The 346 pregnancy related AEs included: *Exposure during pregnancy* (n=293; 1 serious and 292 non-serious), *Pregnancy* (n=12; all non-serious), *Exposure via breast milk* (n=11; all non-serious), *Maternal exposure during breast feeding* (n=8; all non-serious), *Maternal*

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*exposure during pregnancy* (n=7; all non-serious), *Abortion spontaneous* (n=3; all serious), *Morning sickness* (n=3; all non-serious), *Paternal exposure during pregnancy* (n=2; all non-serious), *Increased foetal movements* (n=1; non-serious), *Caesarean section* (n=1; non-serious), *Pre-eclampsia* (n=1; non-serious), *Foetal growth restriction* (n=1; serious), *Stillbirth* (n=1; serious), *Gestational diabetes* (n=1; serious), and *Placenta praevia* (n=1; serious).

During the review period, there were 8 SAEs concerning pregnancy reported in 7 ICSRs. Among the serious events, 1 (PT: *Exposure during pregnancy*, n=1) was assessed as serious due to hospitalization and the remaining events (n=7) were assessed as medical important conditions. None of the serious events were life-threatening or had a fatal outcome. The outcomes for all events are unknown.

There were 357 non-serious co-reported AEs reported, with the top ones (>1%) including: *No adverse event* (66.11%, n=236), *Passive smoking* (6.44%, n=23), *Nausea* (3.08%, n=11), *Malaise* (1.68%, n=6), *Anxiety* (1.40%, n=5), *Nicotine dependence* (1.40%, n=5), and *Vomiting* (1.40%, n=5).

There was an increase in the number of pregnancy cases when compared with the previous reporting period. This increase was caused by an implementation of a tool on 04-Jan-2021, which routinely screens certain non-sponsored websites and non-sponsored social media with a defined list of keywords for the identification of AE complaints. The other reason for the increase in the number of cases was marketing campaigns conducted in local markets, which solicit the reporting of AEs. The valid cases from both sources are processed and stored in the global safety database as spontaneous. Among 329 ICSRs identified in this reporting period, 114 ICSRs (34.65%) originated from non-sponsored social media and 43 ICSRs (13.07%) from campaigns, which sums up to almost half of the cases reported during the review period.

The information received on the risk associated to the exposure during Pregnancy and lactation to the THS during the reporting period did not bring new insights on this matter. PMI will continue to perform regular review of these events to assure the ongoing evaluation of new safety information.

## 15.4 Characterization of Risks

### 15.4.1 Important Identified Risks

#### 15.4.1.1 Hypersensitivity

Worldwide, the prevalence of allergic diseases has increased substantially in the last few decades.[7, 8] One possible reason for such an increase may be the changing exposure to known and unknown risk factors[9] such as smoking. An increased risk of allergic diseases among individuals exposed to tobacco smoke is biologically plausible as smoking is known to facilitate sensitization to perennial indoor allergens, such as those caused by furry animals,

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as well as to some outdoor allergens such as pollen.[10] Smoking augments nasal responses to allergen in atopic subjects and increases IgE, immunoglobulin G4, and postallergen histamine levels in nasal lavage fluid.[11, 12] Tobacco smoke has a number of harmful effects on the immune system,[13] e.g. on humoral and cellular immunity. The putative direct effect of tobacco smoke on the skin is unclear,[14] but smoke might directly impair skin-barrier function via the effects of reactive oxygen species on keratinocytes.[15, 16] Several studies have assessed the association between smoking exposure and allergic diseases.[17] Nicotine replacement therapies based on nasal inhalation of nicotine also showed *Hypersensitivity* as a common ( $\geq 1/100$ ,  $< 1/10$ ) undesirable effect (e.g. Nicorette Inhalator). A recently published survey performed on Korean middle and high school students, suggested that both EC and HTP have the potential to cause and aggravate allergic rhinitis through airway inflammation or toxicity.[18]

The SPI version 8.0 dated 24-Oct-2023, mentions that hypersensitivity events may occur in users of the THS, in particular those with a past medical history of an allergic condition, such as food, pet, or dust allergies. In case of signs and symptoms that may indicate a serious allergic event, users should stop using the THS and contact their physician immediately.

To characterize this risk, a cumulative search from the IBD (04-Nov-2014) to the DLP of this SUR was performed in the global safety database to retrieve hypersensitivity-related events with THS product use. The electronic search included all non-serious AEs and SAEs from all sources and was conducted under the MedDRA SMQ Hypersensitivity (narrow).

Cumulatively, 11,269 hypersensitivity-related AEs with THS use (1,082 serious and 10,187 non-serious) were received in 9,790 ICSRs. Among the 9,790 ICSRs, 7,636 cases reported use of *IQOS*<sup>TM</sup>, 437 cases reported *IQOS ILUMA*<sup>TM</sup>, and 2,045 cases reported unspecified *IQOS* device. As mentioned before, 1 case can report multiple EHTPs and THDs.

Among 11,269 hypersensitivity-related AEs, the most reported AEs ( $>1\%$ ) were: *Hypersensitivity* (34.27%, n=3,862; 875 serious and 2,987 non-serious); *Rash* (21.47%, n=2,419; 29 serious and 2,390 non-serious); *Pharyngeal swelling* (8.64%, n=974; 5 serious and 969 non-serious); *Gingival swelling* (5.55%, n=625; 2 serious and 623 non-serious); *Rash macular* (5.21%, n=587; 6 serious and 581 non-serious); *Lip swelling* (4.90%, n=552; 3 serious and 549 non-serious); *Urticaria* (4.84%, n=545; 5 serious and 540 non-serious); *Swollen tongue* (1.78%, n=201; 1 serious and 200 non-serious); *Mouth swelling* (1.35%, n=152; 1 serious and 151 non-serious); *Swelling face* (1.27%, n=143; 1 serious and 142 non-serious); and *Rash pruritic* (1.11%, n=125; 2 serious and 123 non-serious).

The most reported SAEs ( $>1\%$ ) were: *Hypersensitivity* (80.87%, n=875, 510 resolved or resolving, 238 with unknown outcome, and 127 not resolved); *Angioedema* (5.08%, n=55, 34 resolved or resolving, 17 with unknown outcome, and 4 not resolved); *Oropharyngeal blistering* (2.96%, n=32, 13 with unknown outcome, 12 not resolved, and 7 resolved or resolving); *Rash* (2.68%, n=29, 22 resolved or resolving, 6 not resolved, and 1 with unknown outcome); and *Laryngeal oedema* (2.59%, n=28, 11 not resolved, 10 resolved or resolving, and 7 with unknown outcome). None of the SAEs led to the consumer's death.

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As mentioned in Section 15.3.1.1, the reporting frequency rate of cases of *Hypersensitivity* is estimated to be 0.05 per 100 users for the current reporting period, after correction for under-reporting. Based on the RSI for nicotine replacement therapies (such as Summary of Product Characteristics for Nicorette 15mg Inhalator, McNeil Products), *Hypersensitivity* is a common ( $\geq 1/100$ ,  $< 1/10$ ) AE. The estimated reporting frequency rate (after correction for under-reporting) of cases of *Hypersensitivity* for the THS is, therefore, considered not to be higher than what is already known for nicotine replacement therapies.

The newly identified safety information did not change the knowledge on this risk. PMI will continue to perform regular review of the events of *Hypersensitivity* upon the THS use to ensure the ongoing evaluation of new safety information.

#### 15.4.1.2 Accidental exposure to product by child

Unintentional ingestion of tobacco products is a leading reason for infant and child nicotine exposures worldwide. A European retrospective study published the outcomes of e-liquid exposure incidents reported to 10 Poison Centers in 2017. Out of 277 incidents analyzed, unintentional exposure was the most frequently cited type of exposure (71.3%). Among all analyzed poisoning incidents, 42.7% were among the children population. Exposure via ingestion was more frequent among pediatric patients ( $\leq 5$  years) compared with children of 6–18 years and adults (87.0% vs. 59.3% vs. 57.6%  $p < 0.001$ ).[19]

Similar results have been shown by a retrospective analysis conducted in the U.S. of exposures associated with nicotine and tobacco products (including e-liquid, CC) among children younger than 6 years old.[20, 21] Chewing tobacco (67.3%) and snuff (25.0%) accounted for most of the other tobacco product exposures. Most children were exposed through ingestion (95.5%) or multiple routes including ingestion (2.8%), and only 1.7% through non-ingestion routes.[20] A study at the Czech Republic poisons control center was conducted during a 7-year period (2012–2018) to analyze cases of acute exposure to ECs, e-liquids, and EHTPs containing nicotine based on toxicological consultations showed similar results. From 119,229 consultations, 148 cases concerned acute exposure to nicotine-containing e-liquid. Children and adolescents were exposed in 91 (61%) cases, including exposure of neonates and infants in 54 (36%) cases. The main route of exposure was ingestion in 88% of cases, inhalation in 6% of cases, ocular in 4% of cases, and intravenous administration in 2% of cases. The sources of exposure were: the cartridge with e-liquid (107 cases; 72%), refillable tank (29 cases; 20%), and EHTPs (9 cases, 6%).[22]

Infants are susceptible to accidental tobacco ingestion because of a natural curiosity and a tendency for oral exploration.[23, 24] Ingestion of as little as 1mg of nicotine by a small child can produce symptoms such as nausea and vomiting. Severe toxic effects of nicotine ingestion may include weakness, convulsions, unresponsiveness, and impaired respiration, and ultimately, may lead to respiratory arrest and death.[25]

As described in SPI version 8.0 dated 24-Oct-2023, toxic effects of nicotine develop rapidly following acute overdose. The current data indicates that 6 to 7mg/kg of acute oral nicotine is an accurate estimate of the acute lethal oral dose in adults. One EHTP contains, on average, 2.4–5.0mg of nicotine. The accidental ingestion of EHTP may potentially cause signs and

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symptoms of nicotine intoxication such as: nausea, hyper-salivation, abdominal pain, vomiting, diarrhea, cold sweat, headache, dizziness, hearing and visual disturbances, mental confusion, tremor, weakness, weak analgesia, increase of respiratory reflex and coughing, increased bronchial secretions, and increase in heart rate and blood pressure. The THS should always be kept away from children. In case of accidental ingestion by children, medical attention should be sought immediately due to risk of nicotine intoxication. Swallowing of EHTPs of *IQOS ILUMA*<sup>TM</sup> can cause serious injury to internal organs due to a small metal part with sharp edges inside the tobacco plug, referred to as “susceptor.”

To characterize the risk of accidental exposure to product by children, a cumulative search from the IBD (04-Nov-2014) until the DLP of this SUR was performed in the global safety database to retrieve data on accidental exposure to the THS by children. The electronic search included all non-serious AEs and SAEs from solicited and unsolicited sources. The selected PTs were *Accidental exposure to product by child* and *Accidental exposure to product packaging by child*. The selected age groups were adolescent, child, infant, and neonate. The selected age units were months and years.

Cumulatively, 6,675 (127 serious and 6,548 non-serious) events of *Accidental exposure to product by child* were received in 6,675 ICSRs. Among the 6,675 ICSRs, 1,827 cases reported use of *IQOS*<sup>TM</sup>, 1,403 cases reported *IQOS ILUMA*<sup>TM</sup>, and 5,267 cases reported unspecified *IQOS* device. Again, it is worth noting that 1 case can report multiple EHTPs and THDs.

In 75.52% of ICSRs reporting accidental exposure to product by children, no health-related events were co-reported (*No adverse event*, n=5,041). In the remaining cases there were a total of 2,269 co-reported events (148 serious and 2,121 non-serious). The most frequently (>1%) co-reported AEs were: *Vomiting* (42.79%, n=971; 50 serious and 921 non-serious), *Pallor* (5.16%, n=117; 16 serious and 101 non-serious); *Cough* (4.80%, n=109; 1 serious and 108 non-serious); *Nausea* (4.41%, n=100; 3 serious and 97 non-serious); *Mood altered* (3.75%, n=85; 2 serious and 83 non-serious); *Irritability* (2.86%, n=65; all non-serious); *Crying* (2.60%, n=59; 2 serious and 57 non-serious); *Asthenia* (2.16%, n=49; 1 serious and 48 non-serious); *Malaise* (1.67%, n=38; 1 serious and 37 non-serious); *Respiratory tract irritation* (1.63%, n=37; all non-serious); *Hiccups* (1.54%, n=35; all non-serious), *Somnolence* (1.50%, n=34; 1 serious and 33 non-serious); *Retching* (1.19%, n=27; 1 serious and 26 non-serious); *Pyrexia* (1.06%, n=24; 3 serious and 21 non-serious); and *Diarrhoea* (1.01%, n=23; all non-serious). None of the serious cases were reported as life-threatening, resulted in death, required surgical intervention, or lead to other medical complications related to accidental ingestion of the product.

Cumulatively, the information received on the accidental exposure by children to the EHTP did not show either a modified trend in the number of cases or an impact on the individual or public health throughout IBD to the DLP of this SUR. PMI will continue to perform regular review of all the reported events of accidental exposure to the THS by children to assure the ongoing evaluation of new safety information.

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#### 15.4.1.2.1 Accidental exposure to product by child concerning *IQOS ILUMA*

Induction-based THS (*IQOS ILUMA*<sup>TM</sup>) was launch first in Japan on 18-Aug-2021. As described in the current SPI version 8.0, the tobacco plug of the EHTP contains a piece of metal, susceptor.

Prior to the launch of *IQOS ILUMA*, PMP S.A. conducted a risk assessment related to potential ingestion of the EHTP or parts of it with the focus on infants and children. The pre-launch risk assessment included analysis of already reported cases of ingestion of EHTP, published scientific articles, and experiments on bespoke mastication and gastro-intestinal hazard models. The main identified typical injuries related to the possible ingestion of the EHTP or parts of it included: injury of the oral cavity, airway obstruction, gastrointestinal tract injury, nicotine and metals poisoning. This pre-launch assessment showed that the risk of injuries related to the accidental exposure to *IQOS ILUMA* EHTP by child is low.

A global analysis of spontaneous cases concerning *IQOS ILUMA* that reported accidental exposure to product by children was performed. Cumulatively, from the first market launch on 18-Aug-2021 until the DLP of this SUR, a total of 1,367 ICSRs of accidental exposure to product by child have been retrieved that reported the use of *IQOS ILUMA*. From the total of 1,367 cases, 1,297 (94.88%) cases were non-serious, and 70 cases were assessed as serious (5.12%). Out of these 70 cases, in 61 cases the child was hospitalized. Among these 61 cases of hospitalization, the susceptor was spontaneously excreted few days later (n=30), or the susceptor was not detected by an x-ray or the x-ray was not performed (n=15), or the susceptor was removed by preventive endoscopy<sup>2</sup> (n=11), or a preventive endoscopy was performed but failed to remove the susceptor (n=5). The remaining 9 serious cases were weighed as being serious as there were reporting events assessed as important medical conditions. None of these serious cases were reported as life-threatening, resulted in death, required surgical intervention, or lead to other medical complications related to accidental ingestion of the product.

Taking into consideration the pre-launch risk assessment, data currently available in the global safety database for all collected cases of accidental exposure by child, PMP S.A has concluded that risk of injuries related to the ingestion of *IQOS ILUMA* EHTP is low and there is no major safety concern identified so far. As a preventive action, an additional warning has been added to the user guide and the package of EHTP to include information about the presence of the susceptor in the EHTP, specifically:

- User guide safety warnings and instructions address the choking, ingestion and handling hazards:
  - “CHOKING HAZARD — SMARTCORE STICKS<sup>TM</sup> contain small metal parts with sharp edges.”
  - “INGESTION HAZARD Swallowed SMARTCORE STICKS<sup>TM</sup> can cause serious injury to internal organs due to small metal parts with sharp edges.

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<sup>2</sup> The endoscopy is part of the standard medical procedure related to the removal of ingested foreign objects from the gastrointestinal track (Foreign Body Ingestion in Children | AAFP).

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Swallowed SMARTCORE STICKS™ can pose a risk of nicotine intoxication. If SMARTCORE STICKS™ are swallowed, seek medical attention immediately.”

- “HANDLING HAZARD — Do not take apart SMARTCORE STICKS™ as they contain small metal parts with sharp edges. Always dispose of SMARTCORE STICKS™ immediately after use according to local waste disposal regulations.”
- The tobacco sticks’ packaging also warns of the ingestion and handling hazard. “Warning. Do not ingest or disassemble. This product contains a sharp metal part which can cause serious injury if swallowed. Keep out of reach of children”.

Close monitoring of the cases of accidental exposure to IQOS ILUMA™ EHTP by children will continue.

#### 15.4.1.3 Burning sensation

EHTPs exposed to humid conditions may result in higher water absorption by the tobacco plug. Consequently, the use of such EHTPs may lead to the production of a warm aerosol, as reported by some users. To avoid exposure of EHTPs to high humidity, PMI has communicated through various channels and updated the user guide to instruct consumers to store the products in a dry and cool place.

To characterize this risk, a cumulative search from the IBD (04-Nov-2014) until the DLP of this SUR was performed in the global safety database. A list of selected MedDRA PTs has been used in the search strategy: *Burning sensation*, *Burning sensation mucosal*, *Skin burning sensation*, and *Oral discomfort*. Only a selected list of LLTs under the PT *Oral discomfort* coding events of burning sensation at the level of the oral cavity were included in the analysis, such as: *Burning corner of mouth*, *Burning lips*, *Burning mouth*, *Burning oral sensation*, *Lip burning sensation of*, *Oral hot feeling*, and *Oral mucosal burning sensation*. The other LLTs (*Discomfort in mouth*, *Lip discomfort*, *Oral cavity discomfort*, *Oral discomfort*) were considered out of scope for this risk assessment. The electronic search included all non-serious AEs and SAEs from solicited and unsolicited sources for the THS.

Cumulatively, 8,983 AEs (7 serious and 8,976 non-serious) were received in 8,813 ICSRs. Among the 8,813 ICSRs, 6,615 cases reported use of IQOS™, 1,256 cases reported IQOS ILUMA™, and 1,139 cases reported unspecified IQOS device. As mentioned before, 1 case can report multiple EHTPs and THDs.

The retrieved AEs among the selected PT list were: *Burning sensation* (n=2,482; 2 serious and 2,480 non-serious); *Burning sensation mucosal* (n=33; all non-serious); *Oral discomfort* (n=6,421; 4 serious and 6,417 non-serious); and *Skin burning sensation* (n=47; 1 serious and 46 non-serious). The AEs retrieved among the selected LLTs under the PT *Oral discomfort* were: *Lip burning sensation of* (n=3,989; 2 serious and 3,987 non-serious); *Burning lips* (n=1,275; 1 serious and 1,274 non-serious); *Burning mouth* (n=647; 1 serious and 646 non-serious); *Oral mucosal burning sensation* (n=204; all non-serious); *Burning oral sensation* (n=168; all non-serious); and *Oral hot feeling* (n=138; all non-serious). Of note, the total number of AEs under the PT *Oral discomfort* was 7,044, out of which 6,421 AEs were

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included in the risk assessment. The LLTs excluded from the risk assessment were: *Oral discomfort* (n=269); *Lip discomfort* (n=199); *Discomfort in mouth* (n=128); and *Oral cavity discomfort* (n=27).

Among the 7 SAEs, 6 events were assessed as serious as they led to hospitalization. In the remaining case, the consumer felt a burning sensation along with sore throat, coughing fit, chest wheezing, and he sensed a plastic, electrical smell coming from the product. The consumer thought he was having a bad asthma attack and reported the events as life-threatening. None of the serious cases had a fatal outcome.

The newly identified safety information did not change the knowledge on this risk. PMI will continue to perform regular evaluation of this risk to ensure the ongoing evaluation of new safety information.

## 15.4.2 Important Potential Risks

### 15.4.2.1 Thermal burn

PMI performed a literature review on thermal burns to smokers or users of other tobacco/nicotine containing products to better characterize the risk of thermal burn with THS. Furthermore, PMI conducted experiments to evaluate whether it is possible to have a thermal burn while using THS under normal use conditions given skin physiology, burn pathophysiology, and the temperatures produced by THS.

As reported in the literature, a thermal burn from direct contact requires the touched object to be extremely hot or an abnormally long contact. The lowest temperature documented to cause a significant burn in 1 second ranges from 69°C to 98°C.[26] With a longer exposure time up to 10 seconds or less, the lowest reported temperature that could cause a significant burn is 60°C.[27-29] The study by Johnson et al. demonstrated that a temperature of 60°C would need to be applied to human skin for 10–20 seconds to cause a superficial partial thickness burn, and 110 seconds to cause a full thickness burn.[30] For scalding burns (wet heat burns) the minimum temperature is 48°C for 5 minutes, 51°C for 3 minutes, 52°C for 1 minute, 56°C for 15 seconds, 60°C for 5 seconds, 64°C for 2 seconds and 68°C for 1 second.[31] The pain threshold requires lower temperature. At already 30°C, thermal receptors for warmth detection start to fire action potentials and when the temperature is further increased to above about 45°C, the nociceptors become active causing perception of pain.[32]

Several experiments were conducted by PMI to assess if and when a thermal burn could occur under normal conditions of THS usage. These investigations showed that when using THS in hot and humid condition, the temperature of the aerosol may be higher (+ 3°C) than compared with dry conditions. What consumers perceive as hot sensation is not only caused by the temperature increase but the amount of energy reaching the skin, which can come from an increase in aerosol mass and/or from an increase of the delta in temperature between the aerosol and the mouth/lips of the consumer. This increase in mass of the aerosol can be induced by an increase in mass of the EHTP caused by a higher water content, which occurs

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when a stick is stored under humid conditions. Due to the additional + 3°C detected under hot and humid conditions, the temperature of the aerosol can reach up to 50.6 °C, which may cause pain/burning sensation that is perceived by the consumer as thermal burn.

To further characterize this risk, a cumulative search from the IBD (04-Nov-2014) to the DLP of this SUR was performed in the global safety database to retrieve events of thermal burn with THS product use. The electronic search included all non-serious AEs and SAEs from solicited and unsolicited sources. The selected PTs were *Airway burns*, *Burn oral cavity*, *Burns first degree*, *Burns second degree*, *Burns third degree*, *Burns fourth degree*, *Thermal burns of eye*, and *Thermal burn*. Cumulatively, 24,640 AEs (35 serious and 24,605 non-serious) were received in 23,877 ICSRs. Among the 23,877 ICSRs, 20,225 cases reported use of IQOS™, 987 cases reported IQOS ILUMA™, and 2,937 cases reported unspecified IQOS device. As mentioned before, 1 case can report multiple EHTPs and THDs.

The reported events of thermal burn included: *Thermal burn* (n=19,128; 22 serious and 19,106 non-serious); *Burn oral cavity* (n=5,226; 3 serious and 5,223 non-serious); *Burns second degree* (n=184; all non-serious); *Airway burns* (n=75; 2 serious and 73 non-serious); *Burns first degree* (n=18; all non-serious); *Burns third degree* (n=6; all serious); and *Thermal burns of eye* (n=3; 2 serious and 1 non-serious). Among the 35 serious events of thermal burn, 25 led to hospitalization and 9 was assessed as medically important conditions. The remaining case concerned an event of *Burn oral cavity*, where the consumer felt that his tongue was scorched and the taste perceptions was lost, which did not improve after the product was stopped. None of the serious events was assessed as life-threatening or resulted in death.

In 73.05% (n=17,999) of cases, the consumer reported the oral cavity (including mouth, lips, and tongue) as the body site affected by the burn. In 19.14% (n=4,716) of cases, the affected body site was not specified. In 7.19% (n=1,772) of the cases, the reported body site were fingers and/or hands and in the remaining 0.62% (n=153), it was other body site (airway, arm, eye, face, hair, leg, neck, pharynx, torso) reported. Information regarding majority of cases reporting *Thermal burn* or *Burn oral cavity* is scarce and did not provide any information concerning the severity of the burns.

Global proportions by month for thermal burn show a seasonal pattern, with a higher number of cases during the end of spring and summer period (May, June, July and August). More than 50% of the reported cases originated from Italy (12.31%), Portugal (10.35%), Japan (9.52%), Romania (7.78%), Poland (7.60%), and Hungary (6.83%), all countries that follow clear seasonal changes.

The presented findings explain the increased reporting rates of thermal burns during the hot and humid months, as these are more likely a sensation of heat that follows the release of increased energy and a minor increase in the temperature of the aerosol that feels like a burn. The aerosol temperature during hot and humid months can reach up to 50.6 °C, which is not high enough for a thermal burn to occur with a brief contact with the skin. Therefore, it is likely that most of the cases of thermal burn pertain to pain/burning sensation. Because of the nature of the cases received from spontaneous sources, it is difficult to ascertain whether these pertain to actual burns or the sensation of a burn. In addition, the majority of these cases

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were reported as non-serious and only a minor percentage (0.14%) were assessed as serious events.

In order to reduce the incidence of thermal burns, a number of risk mitigation activities have been put in place. The first mitigation measure was aimed at the consumers in a form of recommendations included in the user guide. To avoid exposure of EHTPs to high humidity, the consumer was instructed to store the products in a dry and cool place, as well as to not use EHTPs that have been exposed to excessive heat or moisture. Additionally, PMI has introduced changes to the THS itself. The first one concerned an update of the THDs currently available on the market, which limits the energy provided to heat the EHTP. The second one concerns a new design of the EHTP that increases airflow and results in decrease of the aerosol temperature. This design was introduced in the new *IQOS ILUMA*<sup>TM</sup> EHTP. As a result, PMI started noticing a decrease in number of thermal burn cases, which was already evident in previous SUR.

Taking into consideration presented findings from conducted experiments, literature review and analysis of spontaneous cases, PMI decided to close the potential risk of *Thermal burn* and exclude it from the future SUR analysis. PMI will continue to perform standard monitoring of all cases originating from spontaneous sources, including the reports of thermal burn, to identify any new safety information that may arise. If any changes in the reports of thermal burn will be observed, PMI will perform a new evaluation of this safety topic and undertake any necessary actions including reopening of the risk.

### 15.4.3 Missing Information

#### 15.4.3.1 Pregnancy and Lactation

Public health institutes worldwide recommend that mothers should quit using tobacco and nicotine products whilst pregnant [33] because maternal smoking affects fetal wellbeing and growth.[34] Indeed, nicotine is able to cross the placenta, and therefore, may affect fetal development. As pregnancy and lactation constitute exclusion criteria and reason for immediate withdrawal in all completed and ongoing clinical and pre-marketing studies for the THS, its use has not been tested in pregnant and breastfeeding women. An appropriate characterization of the risks to which pregnant women are exposed while using the THS may only be achieved through a long-term monitoring of spontaneous cases reporting AEs associated with the THS usage within this population. Based on the current knowledge and as described in SPI version 8.0 for THS (dated 24-Oct-2023), PMI instructs pregnant women, women who think they may be pregnant, and breastfeeding women against the use of the THS.

To characterize the risk associated with the use of the THS during Pregnancy and lactation, a cumulative search from the IBD (04-Nov-2014) until the DLP of this SUR was performed in the global safety database. The electronic search for pregnancy reports included all non-serious AEs and SAEs from solicited and unsolicited sources and was carried out under the MedDRA SOC "Pregnancy, puerperium and perinatal conditions" and the following MedDRA SMQs (Narrow): "Neonatal exposures via breast milk" "Pregnancy, labour and

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delivery complications and risk factors (excl. abortions and stillbirth," "Foetal disorders," "Functional lactation disorders," "Neonatal disorders," "Normal pregnancy conditions and outcomes," and "Termination of pregnancy and risk of abortion".

Cumulatively, 748 AEs (16 serious and 732 non-serious) were received in 711 ICSRs. Among the 711 ICSRs, 186 cases reported use of *IQOS™*, 97 cases reported *IQOS ILUMA™*, and 446 cases reported unspecified *IQOS* device. As mentioned before, 1 case can report multiple EHTPs and THDs.

The 748 pregnancy related AEs included: *Exposure during pregnancy* (n=534; 2 serious and 532 non-serious); *Maternal exposure during pregnancy* (n=125; all non-serious); *Pregnancy* (n=15; all non-serious); *Morning sickness* (n=15; all non-serious); *Exposure via breast milk* (n=13; all non-serious); *Maternal exposure during breast feeding* (n=11; all non-serious); *Abortion spontaneous* (n=6; all serious); *Paternal exposure during pregnancy* (n=2; all non-serious); *Pre-eclampsia* (n=2; all non-serious); *Primigravida* (n=2; all non-serious); *Multigravida* (n=2; all non-serious); *Maternal exposure timing unspecified* (n=2; all non-serious); *Somatic symptom disorder of pregnancy* (n=1; non-serious); *Increased foetal movements* (n=1; non-serious); *Mastitis* (n=1; serious); *Maternal exposure before pregnancy* (n=1, non-serious); *Live birth* (n=1; non-serious); *Ectopic pregnancy* (n=1; serious); *Umbilical cord around neck* (n=1; non-serious); *Abortion of ectopic pregnancy* (n=1; serious); *Poor feeding infant* (n=1; non-serious); *Caesarean section* (n=1; non-serious); *Infant irritability* (n=1; non-serious); *Foetal growth restriction* (n=1; serious); *Respiratory disorder neonatal* (n=1; non-serious); *Gestational diabetes* (n=1; serious); *Stillbirth* (n=1; serious); *Normal newborn* (n=1; non-serious); *Unintended pregnancy* (n=1; non-serious); *Imminent abortion* (n=1; serious); and *Placenta praevia* (n=1; serious).

Cumulatively, there were 16 SAEs concerning pregnancy reported in 14 ICSRs. Among the serious events, 2 (PT: *Exposure during pregnancy*, n=2) were assessed as serious due to hospitalization, and the remaining events (n=14) were assessed as medical important conditions. None of the serious events was life-threatening or had a fatal outcome. The outcome is unknown for all events.

There were 681 co-reported AEs reported, with the top ones (>1%) including: *No adverse event* (36.42%; n=248); *Passive smoking* (12.19%, n=83); *Nausea* (4.85%, n=33); *Malaise* (4.41%, n=30); *Nicotine dependence* (3.23%, n=22); *Product complaint* (2.06%, n=14); *Anxiety* (1.76%; n=12); *Vomiting* (1.76%; n=12); *Headache* (1.47%; n=10); *Product odour abnormal* (1.32%, n=9); *Illness* (1.17%; n=8); *Cough* (1.17%; n=8); and *Dizziness* (1.03%; n=7).

Cumulatively, the information received on the risk associated with exposure during Pregnancy and lactation to the THS did not show a modified trend in the number of cases, or an impact on the individual or public health throughout IBD and the DLP of this SUR. PMI will continue to perform regular review of these events to assure the ongoing evaluation of new safety information.

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## 16 CONCLUSIONS AND ACTIONS

This SUR covers all relevant safety data related to THS product use that was received by PMI during the period from 01-Jan-2023 to 31-Dec-2023.

Of note, the majority of the spontaneous reports received by PMI are not medically confirmed, i.e., they were received from consumers directly and not from HCPs. Additionally, the information regarding spontaneous cases is scarce for at least 2 main reasons: i) because PMI is not able to contact consumers that do not provide affirmative consent to be contacted back by PMI; and ii) due to data privacy restrictions in several countries that prohibit requesting consumer contact details when an AE is reported to PMI. Nevertheless, the cumulative and interval analysis of the safety information received on all the important identified and potential risks as well as missing information did not show any change in the safety profile of the THS. Taken together, the data presented in this SUR did not lead to any safety-related actions.

PMI will continue to collect and evaluate all new safety information to guarantee adequate supervision of the safety of THS products and their impact on public health.

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## 18 APPENDICES

### 18.1 Appendix 1: Reference Safety Information

THS SPI version 8.0 dated 24-Oct-2023

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PMI RESEARCH & DEVELOPMENT

# **SUMMARY OF PRODUCT INFORMATION (SPI)**

## **Tobacco Heating System (THS)**

<b>Company:</b>	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
<b>Version:</b>	8.0
<b>Release Date:</b>	24 Oct 2023
<b>Replaces Previous Version:</b>	Version 7.0
<b>Previous Release Date:</b>	10 May 2022

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## ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
BoExp	Biomarker(s) of exposure
CYP1A2	Cytochrome P450 1A2
EHTP	Electrically Heated Tobacco Product
HAT	Hollow acetate tube
HCI	Health Canada Intense Smoking Regime
HPHCs	Harmful and Potentially Harmful Constituents
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
NRT	Nicotine Replacement Therapy
PAHs	Polycyclic Aromatic Hydrocarbons
PLA	Polylactic acid
PMI	Philip Morris International
PT	Preferred Term
SPC	Summary of Product Characteristics
SPI	Summary of Product Information
THD	Tobacco Heating Device
THS	Tobacco Heating System

## 1 INTRODUCTION

The Tobacco Heating System (THS), which includes the Electrically Heated Tobacco Product (EHTP) and the Tobacco Heating Device (THD), is a heat-not-burn tobacco product that heats tobacco without combustion. The THS products generate on average 90% lower levels of HPHCs compared to cigarette smoke. The THS products are currently marketed as *IQOS*<sup>TM</sup> with *HeatSticks*<sup>TM</sup>/*HEETS*<sup>TM</sup>, *IQOS ILUMA*<sup>TM</sup> with *TEREA*<sup>TM</sup>/*TEREA Crafted*<sup>TM</sup>/*SENTIA*<sup>TM</sup>/*DELIA*<sup>TM</sup> sticks, *BONDS by IQOS*<sup>TM</sup> with *BLENDS*<sup>TM</sup>, *lii*<sup>TM</sup> *SOLID* with *Fiiit*<sup>TM</sup>, and *lii*<sup>TM</sup> *HYBRID* with *MIIX*<sup>TM</sup>.

The results of clinical studies conducted with the THS<sup>1</sup> have shown a consistent sustained reduction in the levels of biomarkers of exposure (BoExp) to selected HPHCs in smokers who used predominantly the product ad libitum in comparison with those that continued smoking cigarettes.

Importantly, the magnitude of reductions in the BoExp levels to selected HPHCs when using the THS<sup>1</sup> were comparable to those observed when smokers stopped smoking cigarettes (1-4).

In addition, the results of the Exposure Response Studies, measuring the biological response of smokers who predominantly<sup>2</sup> switch to the THS<sup>1</sup> for six months (5) and for a prolonged period of 26 weeks (6) compared with individuals who continued to smoke cigarettes, demonstrated favorable changes in biomarkers of potential harm (also referred to as clinical risk endpoints), similar to those observed upon smoking cessation in the literature likely pointing in the direction of risk reduction in those who switched to the THS<sup>3</sup>.

The purpose of this Summary of Product Information (SPI) is to provide a reference for professionals (e.g., researchers, health care providers) on how commercialized THS products should be used safely and effectively as well as serve as a reference document for safety and efficacy when conducting clinical studies with commercialized products (e.g., for Investigator-Initiated Studies). The SPI is also the document used to determine the expectedness of adverse events (AEs) associated with the use of commercialized THS products. Of note, this document does not replace the THS User Guide, including the Safety Warnings and Instructions, provided with the product and available on the markets' website.

## 2 PRODUCT DESCRIPTION

The THS consists of two main components: the EHTP<sup>4</sup>, which is a tobacco stick, and the THD, which contains the holder and the charger. Depending on the THS version the holder and the charger can be either two separate elements or one element.

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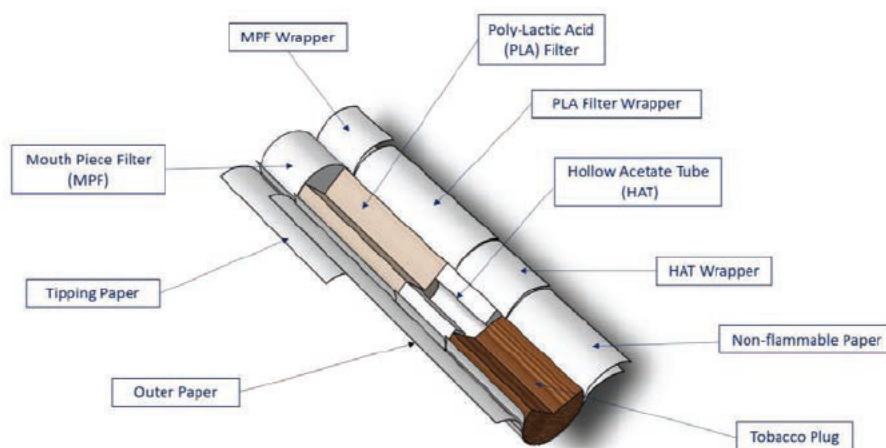
<sup>1</sup> *IQOS*<sup>TM</sup> with *HeatSticks*<sup>TM</sup>/*HEETS*<sup>TM</sup>.

<sup>2</sup> Switching to THS use at  $\geq 70\%$  on average.

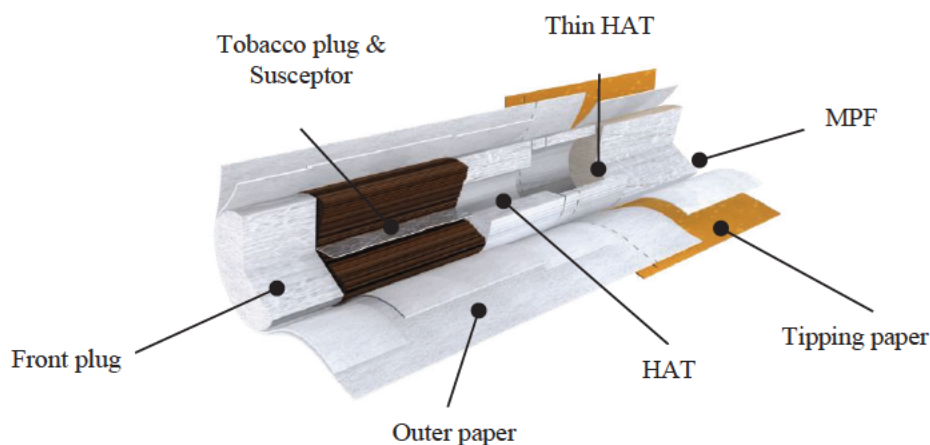
<sup>3</sup> The information in this document pertaining to *IQOS* with *HeatSticks*<sup>TM</sup>/*HEETS*<sup>TM</sup> is considered also applicable to *IQOS ILUMA* with *TEREA*<sup>TM</sup>/*TEREA Crafted*<sup>TM</sup>/*SENTIA*<sup>TM</sup>/*DELIA*<sup>TM</sup>, *BONDS by IQOS*<sup>TM</sup> with *BLENDS*<sup>TM</sup>, *lii*<sup>TM</sup> *SOLID* with *Fiiit*<sup>TM</sup> and *lii*<sup>TM</sup> *HYBRID* with *MIIX*<sup>TM</sup>.

<sup>4</sup> In Hybrid products, such as *MIIX*<sup>TM</sup> the consumable consists of an EHTP and a nicotine-free e-liquid cartridge, which contains the aerosol former and, depending on the variant, may also contain flavors.

Depending on the device, the heating of the EHTP is obtained through either (i) a heating blade<sup>5</sup> or heating pin<sup>6</sup> that is placed inside the THD; (ii) external heating;<sup>7</sup> (iii) or induction technology<sup>8</sup> where a metal strip, referred to as the susceptor, is integrated into the tobacco stick. **Figures 1-4** show the designs and components of the different EHTPs.



**Figure 1** Schematic cross-sectional view of *HeatSticks™/HEETS™/Fiit™* tobacco sticks



**Figure 2** Schematic cross-sectional view of *TEREAT™/TEREA Crafted™/SENTIA™/DELIA™* tobacco sticks

<sup>5</sup> IQOS™

<sup>6</sup> lil™ SOLID

<sup>7</sup> BONDS by IQOS™, lil™ HYBRID

<sup>8</sup> IQOS ILUMA™

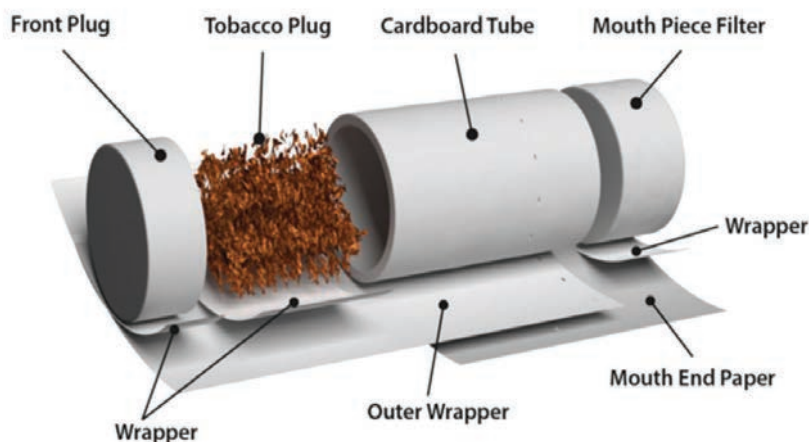


Figure 3 Schematic cross-sectional view of a *BLENDS*™ tobacco stick

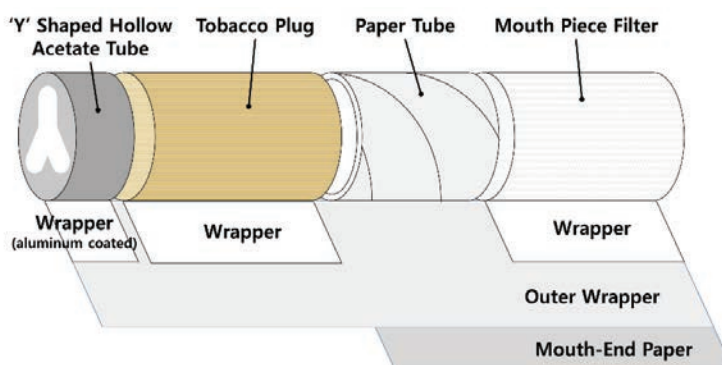


Figure 4 Schematic cross-sectional view of a *MIIX*™ tobacco stick

The composition of the EHTP tobacco substrate is reported in [Table 1](#). Each tobacco stick contains, on average, 2.4 to 5.0 milligrams (mg) of nicotine and, if fully consumed during a single experience, delivers around 0.5 mg nicotine in the aerosol when heated.<sup>9</sup>

<sup>9</sup> In our research publications, we have reported the emission levels in the THS aerosol using a range of puffing regimes, including standard (ISO) or intense (HCI or ISO) regimes. Nicotine yield from *HEETS*™ tobacco sticks using the ISO standard regime is  $0.5 \pm 0.1$  mg nicotine depending on the variant and using the HCI or ISO intense regime the nicotine yield increases to  $1.24 \pm 0.15$  mg nicotine. The nicotine yield as measured using the ISO standard regime is required by regulation in certain countries, and therefore we report 0.5 mg in those circumstances.

**Table 1 Ingredients contained in the EHTP tobacco plug**

Ingredients contained in the EHTP tobacco plug
Tobacco
Glycerin
Water
Cellulose Fibers
Guar Gum
Propylene Glycol
Flavors
Botanicals <sup>10</sup>

## 2.1 Product Name

The THDs are marketed as *IQOS™*, *IQOS ILUMA™*, *BONDS by IQOS™*, *lii™ SOLID*, and *lii™ HYBRID*. The EHTPs are marketed as *HeatSticks™/ HEETS™*, *TEREA™/ TEREACrafted™/ SENTIA™/ DELIA™* sticks, *BLENDS™*, *Fiit™*, and *MIIX™*.<sup>11</sup> Devices must only be used with the tobacco stick specifically designed to be used with that device.

## 2.2 Product Variants

EHTPs are available on the market with different tobacco blends/flavors, including the regular (non-menthol variant) and the menthol variants.

# 3 PRODUCT PARTICULARS

## 3.1 Target Population

The intended population for the THS is legal age adults who would otherwise continue to use tobacco or nicotine-containing products.

Women who are pregnant, breastfeeding, or think they may be pregnant, should not use tobacco or nicotine-containing products.

## 3.2 Product Use

To use the THS, the consumer inserts the EHTP into the holder to heat it. Thereafter, the aerosol is inhaled by placing the lips on the EHTP mouthpiece and drawing air through it.

<sup>10</sup> only in *TEREA Crafted™* (botanicals used: e.g., clove or rosemary or star anise) with expected launch date: Q4, 2023.

<sup>11</sup> The *Miix™* consumable consists of an EHTP and a cartridge filled with propylene glycol and vegetable glycerin; some cartridges contain flavors. There is no nicotine in the cartridge.

The THS should not be used if it appears damaged, tampered with, or broken; has been exposed to excessive cold, heat or moisture; or if its batteries appear to be leaking.

Further details for use are provided in the THS User Guides.

### **3.3 Warnings and Precautions**

#### **3.3.1 Specific Risks that Lead to a Precaution for Use**

##### **3.3.1.1 Hypersensitivity**

Hypersensitivity reactions may occur in users of the THS, in particular in users with a past medical history of allergic condition, such as food, pet, or dust allergies. In case of signs and symptoms that may indicate a serious allergic reaction, users should be instructed to stop using the THS and contact a physician immediately.

##### **3.3.1.2 Risk of Accidental Exposure to Product by Children**

The THS must be always kept away from children, and it must be ensured they do not play with this product. In the event of accidental ingestion of EHTPs by children, medical attention should be immediately sought due to risk of nicotine intoxication (see section 3.7). Swallowing of *TEREA™/TEREA Crafted™/SENTIA™/DELIA™* sticks can cause serious injury to internal organs due to a small metal part with sharp edges inside the tobacco plug.

##### **3.3.1.3 Burning Sensation**

Of note, EHTPs exposed to humid conditions may result in higher water absorption by the tobacco plug. Consequently, the use of such EHTPs may lead to the production of a warm aerosol as reported by some users and in some cases, consumers reported experiencing a thermal burn. To avoid exposure of EHTPs to high humidity, the User Guide instructs users to store the products in a dry and cool place, as well as to not use EHTPs that have been exposed to excessive heat or moisture.

#### **3.3.2 Risks Associated with Starting Using the Product**

The EHTP contains nicotine, which is addictive.

Due to the stimulatory effects of nicotine in the autonomic nervous system, the users of the THS may experience the following transient signs and symptoms: nausea, hyper-salivation, abdominal pain, vomiting, diarrhea, cold sweat, headache, dizziness, hearing and visual disturbances, mental confusion, tremor, weakness, weak analgesia, increase of respiratory reflex and coughing, increased bronchial secretions, increase in heart rate and blood pressure.

#### **3.3.3 Risks Associated with Nicotine Withdrawal**

Users of the THS that stop using the product may experience nicotine withdrawal symptoms. These symptoms usually emerge after nicotine abstinence and reflect an imbalance in brain neurochemistry.

Nicotine withdrawal symptoms can be clustered as affective (irritability, anger, frustration, anxiety, depressed mood, insomnia, dysphoria, hyperalgesia, impatient, restlessness,

nightmares), somatic (tremors, bradycardia, gastrointestinal discomfort, nausea, constipation, increased appetite, hungry, weight gain, coughing, dizziness, sore throat, mouth ulcer) or cognitive (difficulty concentrating, impaired memory).

### **3.4 Interactions**

#### **3.4.1 Smoking-Drug Interactions**

It is well established that exposure to aromatic hydrocarbons from smoking cigarettes accelerates the metabolism of many drugs, particularly those primarily metabolized by Cytochrome P450 1A2 (CYP1A2) (7). The CYP1A2 enzyme-inducing effects of cigarette smoke are thought to be related to exposure to polycyclic aromatic hydrocarbons (PAHs) and other combustion by-products. The levels of these HPHCs are significantly lower in THS compared to cigarette smoking. Consequently, the reduction of PAHs levels may impact CYP1A2 activity. This is not a THS drug interaction per se, but an effect similar to what is observed upon smoking cessation, namely absence of or lesser CYP1A2 induction related to lack of or decreased exposure to PAHs, respectively. Therefore, smokers treated with drugs primarily metabolized by CYP1A2, which have a narrow therapeutic index (e.g., theophylline, olanzapine, clozapine, ropinirole), may need adjustment in the dosage regimen of these drugs when switching from cigarette smoking to THS use.

### **3.5 Undesirable Events**

#### **3.5.1 Summary of Safety Profile**

Hypersensitivity reactions may occur in users of the THS, in particular in users with a past medical history of allergic conditions, such as food, pet, or dust allergies (see specific warnings and precautions in section 3.3.1.1).

The accidental ingestion of EHTPs by children may potentially cause signs and symptoms of nicotine intoxication (see specific warnings and precautions in section 3.3.1.2).

Burning sensation may occur if EHTPs are exposed to humid conditions which may result in higher water absorption by the tobacco plug. Consequently, the use of such EHTPs may lead to the production of a warm aerosol as reported by some users (see specific warnings and precautions in section 3.3.1.3).

As a class effect observed in other nicotine-containing products, the THS may cause some common nicotine-related signs and symptoms when starting use of the product (see specific warnings and precautions in section 3.3.2)

Nicotine withdrawal symptoms may occur when stopping the use of the THS. These symptoms usually emerge after nicotine abstinence (see specific warnings and precautions in section 3.3.3).

### 3.5.2 Risks Associated with the Use of the THS

For the purpose of this document, the list of risks in [Table 2](#) and [Table 3](#) are to be considered expected with THS use.

#### 3.5.2.1 Identified Risks

**Table 2** provides the list of identified risks associated with the use of THS based on clinical studies and post-market surveillance.

**Table 2 List of Identified Risks with THS Use**

System Organ Class	Risk (Preferred term)
Immune System Disorders	- Hypersensitivity
General disorders and administration site conditions	- Burning sensation
Injury, poisoning and procedural complications	- Accidental exposure to product by child

#### 3.5.2.2 Summary of Adverse Events from Post-Marketing Experience

Since 04-Nov-2014 (date of first market launch in Japan) until 30-Jun-2023 (cutoff date for this analysis) there were 281,307 AEs from 161,475 individual case safety reports collected in the PMI global safety database concerning *IQOS™* with *HeatSticks™/HEETS™*, *IQOS ILUMA™* with *TEREA™/SENTIA™* sticks, *BONDS by IQOS™* with *BLENDS™*, *lii™ SOLID* with *Fiit™*, and *lii™ HYBRID* with *MIIX™*. The most represented system organ classes (>5%) were: *Respiratory, thoracic and mediastinal disorders* (n=90694, 32.24%), *Gastrointestinal disorders* (n=49712, 17.67%), *Nervous system disorders* (n=32965, 11.72%), *Injury, poisoning and procedural complications* (n=31308, 11.13%), *General disorders and administration site conditions* (n=27606, 9.81%) and *Product issues* (n=21811, 7.75%). The most frequently reported AEs (>5%) were *Cough* (n=29048, 10.33%), *Headache* (n=17487, 6.22%), *Thermal burn* (n=17200, 6.11%) and *Oropharyngeal pain* (n=14504, 5.16%).

#### 3.5.2.3 Class Effect Risks

**Table 3** provides the list of nicotine class effect risks with THS use, based on safety information included in the Summary of Product Characteristics (SPC) or labels for Nicotine Replacement Therapies (NRTs). Based on Merck Manual online (8) there are five types of NRTs: nicotine gum, nicotine lozenge, nicotine inhalator/inhaler, nicotine nasal spray, and nicotine patch. Based on the route of administration, nicotine gum (9-11), nicotine lozenge (12-14), nicotine inhalator/inhaler (15, 16), and nicotine mouth spray (17) were selected as references for nicotine class effect risks.

AE terms mentioned in the SPCs/labels for nicotine gum (9-11), nicotine lozenge (12-14), nicotine inhalator/inhaler (15, 16), and nicotine mouth spray (17) are not matching Preferred Terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA). Therefore, the AE terms mentioned in [Table 3](#) were coded to match corresponding PTs in MedDRA.

**Table 3 List of Class Effect Risks with Nicotine Use**

System Organ Class	Risk (Preferred Term)
Immune System Disorders	- Anaphylactic reaction

System Organ Class	Risk (Preferred Term)
	- Hypersensitivity
Psychiatric disorders	- Abnormal dreams
	- Agitation
	- Anxiety
	- Disturbance in attention
	- Insomnia
	- Mood altered
	- Irritability
	- Nervousness
	- Depression
Nervous System Disorders	- Headache
	- Dizziness
	- Dysgeusia
	- Burning sensation
	- Paraesthesia
	- Seizure
	- Tremor
Eye Disorders	- Vision blurred
	- Lacrimation increased
Cardiac Disorders	- Palpitations
	- Tachycardia
	- Arrhythmia supraventricular
	- Atrial fibrillation
Vascular Disorders	- Flushing
	- Hypertension
Respiratory, Thoracic and Mediastinal Disorders	- Cough
	- Oropharyngeal pain
	- Throat irritation
	- Laryngeal pain
	- Nasal Congestion
	- Bronchospasm
	- Dysphonia
	- Dyspnoea
	- Sneezing
	- Throat tightness
	- Rhinorrhoea
	- Rhinitis
	- Sinusitis
Gastrointestinal Disorders	- Nausea

System Organ Class	Risk (Preferred Term)
	- Stomatitis
	- Hiccups
	- Abdominal pain
	- Diarrhoea
	- Dry mouth
	- Dyspepsia
	- Gastritis
	- Oesophagitis
	- Flatulence
	- Salivary hypersecretion
	- Vomiting
	- Eructation
	- Glossitis
	- Oral mucosal blistering
	- Oral mucosal exfoliation
	- Paraesthesia oral
	- Dysphagia
	- Hypoaesthesia oral
	- Retching
	- Dry throat
	- Gastrointestinal discomfort
	- Lip pain
	- Oral pain
	- Toothache
	- Gingivitis
	- Tooth disorder
Skin and Subcutaneous Tissue Disorders	- Hyperhidrosis
	- Pruritus
	- Rash
	- Urticaria
	- Angioedema
	- Erythema
	- Dry skin
Musculoskeletal and Connective Tissue Disorders	- Muscle tightness
	- Pain in jaw
	- Musculoskeletal pain
	- Back pain
General Disorders and Administration Site Conditions	- Fatigue
	- Asthenia
	- Chest discomfort

System Organ Class	Risk (Preferred Term)
	- Chest pain
	- Malaise
	- Pyrexia
	- Influenza like illness

### 3.6 Other Effects

The post-market surveillance system has identified reports of gum bleeding reported by consumers using THS.

Quitting smoking has been associated with increased gum bleeding due to an increase in blood flow in gum tissues (18). This effect is transient and seen particularly during the first months after quitting (19).

Because THS heats tobacco instead of burning it, switching to THS reduces the exposure to toxicants/HPHCs found in cigarette smoke by over 90% compared to continued smoking (20). The reduction of these HPHCs may lead to an increase in blood flow in the gum tissues. It is therefore plausible that smokers who switch to THS may experience a transient increase in gingival bleeding. This is likely due to a similar effect observed upon quitting smoking.

### 3.7 Nicotine Overdose

Signs and symptoms suggestive of nicotine intoxication can occur due to the stimulation of the autonomic nervous system by nicotine, if the THS is used in excess, or the EHTP is ingested (e.g., accidentally by children).

Toxic effects of nicotine develop rapidly following acute overdose. The current data indicate that more than 6 to 7mg/kg of oral nicotine is an estimate of the acute lethal oral dose in adults (21). One EHTP contains on average, from 2.4 to 5.0 mg of nicotine.

Signs and symptoms of acute nicotine intoxication include nausea, hyper-salivation, abdominal pain, vomiting, diarrhea, cold sweat, headache, dizziness, hearing and visual disturbances, mental confusion, tremor, weakness, weak analgesia, increase of respiratory reflex and coughing, increased bronchial secretions, increase in heart rate and blood pressure.

Other subsequent conditions may also occur such as faintness, prostration, dyspnea, seizures, hypotension; weak, irregular, rapid pulse rate / transient cardiac standstill or paroxysmal atrial fibrillation. Death may occur within a few minutes following severe nicotine overdose, usually as a result of respiratory failure secondary to paralysis of respiratory muscles.

Acute nicotine intoxication generally requires symptomatic and supportive care. There is no specific antidote for nicotine intoxication. Activated charcoal (22) is recommended if patients are presented shortly after nicotine ingestion, due to the possibility of nicotine-induced seizures, provided the risks do not outweigh the anticipated benefits. If a patient is vomiting, convulsing, or has a decreased level of consciousness, there is a risk of pulmonary aspiration with charcoal administration. Alkaline solutions should be avoided. Treatment is supportive

and includes support of respiration and control of convulsions. Atropine may be used to suppress features of parasympathomimetic stimulation.

Vomiting, which is seen in acute nicotine intoxication cases (23, 24), can help reduce absorption of nicotine and is usually self-limited; therefore, treatment with anti-emetics is not recommended in case of product ingestion.

## **4 PRODUCT PERFORMANCE**

### **4.1 Pharmacokinetic and Pharmacodynamic properties**

Following single use of the THS, clinical studies showed that the average nicotine plasma concentrations peaked around 10 to 14 ng/mL in around six minutes and that the terminal half-life of nicotine was around two to four hours (25).

The results of clinical studies with the THS to date have also shown that users of the product were able to reach nicotine levels similar to those achieved by cigarette smoking, suggesting that nicotine exposure in THS users is similar to cigarette smoking, after a period of adaptation to product use, which can take up to few months.

Product acceptability as measured by nicotine uptake and reduction of urge-to-repeat the experience was comparable to cigarette smoking; thus, the THS offers an experience close to what smokers expect when smoking cigarettes (2, 4).

### **4.2 Summary of Safety Aspects from Non-Clinical Studies**

No new or increased toxicological hazard in the THS aerosol was detected compared with cigarette smoke.

Chemical analysis confirmed that the THS aerosol has significantly lower levels of HPHCs than cigarette smoke (see section 3.6).

The biological activity of the THS aerosol was tested in vitro and in vivo. In vitro studies demonstrated a decreased biological activity of the aerosol generated by THS compared with cigarette smoke. The cytotoxicity (neutral red uptake assay) was reduced by more than 80% in the THS aerosol when compared to cigarette smoke. The genotoxic activity in bacterial cells (Ames assay) and in mammalian cells was decreased for the THS compared to cigarette smoke (26). In vivo 90-day inhalation study performed with the THS demonstrated a lower toxicity compared to the exposure to cigarette smoke (27-29).

The non-clinical assessment performed with the THS supports the conclusion that users of the THS will not be exposed to increased or new hazards when using the THS compared with continued smoking.

## **5 DATE OF FIRST MARKET LAUNCH**

November 2014 (Japan) for *IQOS*<sup>TM</sup> with *HeatSticks*<sup>TM</sup>/*HEETS*<sup>TM</sup>

August 2020 (Russia) for *lii*<sup>TM</sup> *SOLID* with *Fii*<sup>TM</sup>

October 2020 (Japan) for *lii*<sup>TM</sup> *HYBRID* with *Miix*<sup>TM</sup>

September 2021 (Japan) for *IQOS ILUMA*<sup>TM</sup> with *TEREA*<sup>TM</sup> sticks

November 2022 (Philippines) for *BONDS* by *IQOS*<sup>TM</sup> with *BLENDS*<sup>TM</sup> sticks

## **6 DATE OF REVISION OF THE TEXT**

24 Oct 2023

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## 18.2 Appendix 2: Cumulative and Interval Summary Tabulations

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(b) (4)

### 18.2.1 Appendix 2a: Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

MedDRA SOC MedDRA PT	CC	THS unspecified	THS Menthol	THS Regular	SA	Total
<b>Blood and lymphatic system disorders</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>1</b>
Anaemia	0	0	0	1	0	1
<b>Cardiac disorders</b>	<b>2</b>	<b>3</b>	<b>0</b>	<b>0</b>	<b>4</b>	<b>9</b>
Acute myocardial infarction	1	0	0	0	1	2
Angina pectoris	0	0	0	0	1	1
Angina unstable	1	0	0	0	0	1
Atrial fibrillation	0	2	0	0	0	2
Atrial flutter	0	1	0	0	0	1
Cardiac failure acute	0	0	0	0	1	1
Myocardial ischaemia	0	0	0	0	1	1
<b>Congenital, familial and genetic disorders</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>
Nasopalatine duct cyst	1	0	0	0	0	1
<b>Eye Disorders</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>
Cataract	1	0	0	0	0	1
<b>Gastrointestinal disorders</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>6</b>	<b>8</b>
Ileus	0	0	0	0	1	1
Inguinal hernia	0	0	0	0	1	1
Large intestine polyp	1	0	0	0	4	5
Pancreatitis chronic	1	0	0	0	0	1
<b>General disorders and administration site conditions</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>2</b>
Death	1	1	0	0	0	2
<b>Infections and infestations</b>	<b>5</b>	<b>0</b>	<b>1</b>	<b>6</b>	<b>4</b>	<b>16</b>
Appendicitis	0	0	0	1	1	2
Cellulitis	1	0	0	0	0	1
Cellulitis staphylococcal	1	0	0	0	0	1
COVID-19	0	0	0	0	1	1
Epiglottitis	0	0	0	1	0	1
Gastroenteritis	0	0	0	0	1	1
Influenza	0	0	0	1	0	1
Peritonitis	0	0	0	1	0	1
Pneumonia	0	0	0	0	1	1
Pneumonia mycoplasmal	0	0	0	1	0	1
Pyelonephritis acute	1	0	0	1	0	2
Sinusitis	0	0	1	0	0	1
Tooth infection	1	0	0	0	0	1
Urosepsis	1	0	0	0	0	1
<b>Injury, poisoning and procedural complications</b>	<b>4</b>	<b>3</b>	<b>0</b>	<b>5</b>	<b>0</b>	<b>12</b>
Clavicle fracture	1	0	0	0	0	1

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(b) (4)

MedDRA SOC MedDRA PT	CC	THS unspecified	THS Menthol	THS Regular	SA	Total
Femoral neck fracture	0	1	0	0	0	1
Foot fracture	0	0	0	1	0	1
Head injury	0	0	0	1	0	1
Hip fracture	0	0	0	1	0	1
Incisional hernia	0	1	0	0	0	1
Multiple fractures	0	0	0	1	0	1
Patella fracture	0	1	0	0	0	1
Pulmonary contusion	1	0	0	0	0	1
Rib fracture	1	0	0	0	0	1
Skin laceration	0	0	0	1	0	1
Traumatic haemothorax	1	0	0	0	0	1
<b>Metabolism and nutrition disorders</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>1</b>
Diabetic ketoacidosis	0	0	1	0	0	1
<b>Musculoskeletal and connective tissue disorders</b>	<b>2</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>4</b>
Back pain	1	0	0	0	0	1
Costochondritis	0	0	0	1	0	1
Lumbar spine stenosis	0	1	0	0	0	1
Vertebral osteophyte	1	0	0	0	0	1
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	<b>3</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>1</b>	<b>6</b>
Adenocarcinoma of colon	0	0	0	0	1	1
Breast cancer	1	0	0	0	0	1
Inflammatory pseudotumour	1	0	0	0	0	1
Intestinal metastasis	0	0	0	1	0	1
Papillary thyroid cancer	1	0	0	0	0	1
Uterine leiomyoma	0	1	0	0	0	1
<b>Nervous system disorders</b>	<b>4</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>5</b>
Cerebral haemorrhage	1	0	0	0	0	1
Myelopathy	1	0	0	0	0	1
Seizure	0	0	0	1	0	1
Tarsal tunnel syndrome	1	0	0	0	0	1
Transient ischaemic attack	1	0	0	0	0	1
<b>Psychiatric disorders</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>4</b>
Adjustment disorder with depressed mood	1	0	0	0	0	1
Alcohol abuse	0	0	0	1	0	1
Completed suicide	0	0	0	1	0	1
Suicidal ideation	1	0	0	0	0	1
<b>Renal and urinary disorders</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>
Nephrolithiasis	1	0	0	0	0	1
<b>Reproductive system and breast disorders</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>2</b>
Heavy menstrual bleeding	0	0	0	1	0	1
Ovarian cyst	0	1	0	0	0	1

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MedDRA SOC MedDRA PT	CC	THS unspecified	THS Menthol	THS Regular	SA	Total
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>3</b>
Chronic obstructive pulmonary disease	0	1	0	0	0	<b>1</b>
Pleural effusion	1	0	0	0	0	<b>1</b>
Pneumonia aspiration	0	0	0	1	0	<b>1</b>
<b>Social circumstances</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>
Bereavement	1	0	0	0	0	<b>1</b>
<b>Vascular disorders</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>2</b>
Peripheral arterial occlusive disease	0	0	0	0	1	<b>1</b>
Peripheral ischaemia	1	0	0	0	0	<b>1</b>
<b>Total</b>	<b>31</b>	<b>11</b>	<b>2</b>	<b>19</b>	<b>16</b>	<b>79</b>

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### 18.2.2 Appendix 2b: Cumulative Summary Tabulations of Serious Adverse Events from Pre-Market Studies

MedDRA SOC	MedDRA PT	THS	Total
General disorders and administration site conditions	Adverse event	1	2
	Injury associated with device	1	
Infections and infestations	Bronchitis	1	7
	Cholecystitis infective	1	
	Ear infection	1	
	Osteomyelitis	1	
	Pneumonia	2	
	Sepsis	1	
Injury, poisoning and procedural complications	Accident	1	12
	Concussion	1	
	Fall	1	
	Head injury	1	
	Joint injury	1	
	Limb injury	1	
	Muscle strain	1	
	Nerve injury	1	
	Road traffic accident	1	
	Skeletal injury	1	
	Skin abrasion	1	
	Thermal burn	1	
Musculoskeletal and connective tissue disorders	Spinal disorder	1	2
	Spinal pain	1	
Respiratory, thoracic and mediastinal disorders	Tonsillar cyst	1	2
Surgical and medical procedures	Hospitalization	1	
<b>Total</b>		<b>25</b>	<b>25</b>

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### 18.2.3 Appendix 2c: Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Events from Post-Marketing Experience

MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
<b>Blood and lymphatic system disorders</b>	<b>44</b>	<b>235</b>	<b>1</b>	<b>3</b>	<b>45</b>	<b>238</b>
Anaemia	4	17	0	1	4	18
Blood disorder	1	4	0	0	1	4
Coagulopathy	1	3	0	0	1	3
Hypochromic anaemia	1	1	0	0	1	1
Lymph node pain	0	21	0	0	0	21
Lymphadenitis	4	22	0	0	4	22
Lymphadenopathy	33	167	1	2	34	169
<b>Cardiac disorders</b>	<b>780</b>	<b>3023</b>	<b>279</b>	<b>1643</b>	<b>1059</b>	<b>4666</b>
Acute myocardial infarction	0	0	1	4	1	4
Angina pectoris	0	1	206	1198	206	1199
Angina unstable	0	0	2	8	2	8
Arrhythmia	0	0	41	261	41	261
Arteriospasm coronary	0	0	1	4	1	4
Atrial fibrillation	0	0	0	1	0	1
Atrioventricular block	0	2	0	0	0	2
Bradycardia	0	0	2	5	2	5
Cardiac arrest	0	0	2	4	2	4
Cardiac discomfort	14	118	0	1	14	119
Cardiac disorder	71	343	2	11	73	354
Cardiac dysfunction	0	0	0	1	0	1
Cardiac failure	0	0	1	6	1	6
Cardiac failure acute	0	0	1	2	1	2
Cardiac failure chronic	0	0	0	1	0	1
Cardiac fibrillation	0	0	1	3	1	3
Cardiac flutter	0	0	1	4	1	4
Cardiomegaly	0	2	0	0	0	2
Cardiomyopathy	0	0	1	1	1	1
Cardiopulmonary failure	0	0	0	1	0	1
Cardiovascular disorder	8	52	0	1	8	53
Carditis	0	0	0	1	0	1
Coronary artery disease	1	1	0	2	1	3
Coronary artery occlusion	0	0	0	1	0	1
Dressler's syndrome	0	1	0	0	0	1
Extrasystoles	1	21	0	0	1	21
Gastrocardiac syndrome	0	1	0	0	0	1
Left ventricular hypertrophy	0	1	0	0	0	1
Myocardial infarction	0	1	10	80	10	81
Myocardial ischaemia	0	0	1	8	1	8
Palpitations	270	1366	1	13	271	1379
Pericardial effusion	0	0	0	1	0	1
Pericarditis	0	0	1	3	1	3

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Sinus arrhythmia	1	3	0	1	1	4
Sinus tachycardia	0	3	0	1	0	4
Supraventricular extrasystoles	0	1	0	0	0	1
Supraventricular tachycardia	1	1	1	1	2	2
Tachyarrhythmia	0	1	0	1	0	2
Tachycardia	412	1102	3	13	415	1115
Tachycardia paroxysmal	0	1	0	0	0	1
Ventricular extrasystoles	1	1	0	0	1	1
<b>Congenital, familial and genetic disorders</b>	<b>2</b>	<b>8</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>8</b>
Albinism	0	1	0	0	0	1
Congenital anomaly	1	1	0	0	1	1
Cystic fibrosis	0	1	0	0	0	1
Frenulum breve	0	1	0	0	0	1
Gastrointestinal disorder congenital	0	1	0	0	0	1
Kenny-Caffey syndrome	0	1	0	0	0	1
Mucopolysaccharidosis IV	1	1	0	0	1	1
Protuberant ear	0	1	0	0	0	1
<b>Ear and labyrinth disorders</b>	<b>122</b>	<b>786</b>	<b>0</b>	<b>10</b>	<b>122</b>	<b>796</b>
Deafness	0	0	0	5	0	5
Deafness transitory	0	1	0	1	0	2
Ear congestion	5	32	0	0	5	32
Ear discomfort	9	61	0	0	9	61
Ear disorder	0	10	0	0	0	10
Ear dryness	1	1	0	0	1	1
Ear haemorrhage	0	2	0	0	0	2
Ear inflammation	2	4	0	0	2	4
Ear pain	22	75	0	0	22	75
Ear pruritus	1	8	0	0	1	8
Ear swelling	1	6	0	0	1	6
Eustachian tube obstruction	1	1	0	0	1	1
Excessive cerumen production	0	2	0	0	0	2
External ear inflammation	0	1	0	0	0	1
Hypoacusis	2	18	0	1	2	19
Inner ear disorder	0	2	0	0	0	2
Inner ear inflammation	0	2	0	0	0	2
Meniere's disease	0	0	0	1	0	1
Middle ear inflammation	0	1	0	0	0	1
Motion sickness	1	27	0	0	1	27
Otolithiasis	1	1	0	0	1	1
Otorrhoea	0	1	0	0	0	1
Sudden hearing loss	0	0	0	1	0	1
Tinnitus	25	121	0	0	25	121
Vertigo	51	407	0	1	51	408

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Vertigo positional	0	2	0	0	0	2
<b>Endocrine disorders</b>	<b>6</b>	<b>67</b>	<b>3</b>	<b>7</b>	<b>9</b>	<b>74</b>
Autoimmune thyroid disorder	0	0	0	1	0	1
Goitre	0	10	0	0	0	10
Graves' disease	0	0	2	2	2	2
Hyperthyroidism	0	0	1	4	1	4
Hypothyroidism	0	1	0	0	0	1
Thyroid cyst	0	1	0	0	0	1
Thyroid disorder	4	34	0	0	4	34
Thyroid mass	1	6	0	0	1	6
Thyroid pain	1	10	0	0	1	10
Thyroiditis	0	5	0	0	0	5
<b>Eye disorders</b>	<b>153</b>	<b>1126</b>	<b>4</b>	<b>29</b>	<b>157</b>	<b>1155</b>
Abnormal sensation in eye	1	2	0	0	1	2
Accommodation disorder	1	2	0	0	1	2
Asthenopia	4	14	0	0	4	14
Binocular eye movement disorder	0	1	0	0	0	1
Blepharospasm	0	6	0	0	0	6
Blindness	0	0	3	8	3	8
Blindness transient	0	0	0	2	0	2
Blindness unilateral	0	0	0	1	0	1
Chromatopsia	0	1	0	0	0	1
Conjunctival haemorrhage	0	0	0	1	0	1
Conjunctival irritation	0	1	0	0	0	1
Conjunctivitis allergic	0	3	0	0	0	3
Dark circles under eyes	0	6	0	0	0	6
Delayed light adaptation	0	1	0	0	0	1
Dermatochalasis	0	1	0	0	0	1
Diplopia	1	5	0	0	1	5
Dry eye	4	95	0	0	4	95
Eczema eyelids	0	2	0	0	0	2
Erythema of eyelid	0	2	0	0	0	2
Excessive eye blinking	0	3	0	0	0	3
Exophthalmos	0	0	0	1	0	1
Eye allergy	4	9	0	0	4	9
Eye colour change	1	2	0	0	1	2
Eye discharge	4	11	0	0	4	11
Eye disorder	6	27	0	0	6	27
Eye haemorrhage	0	1	0	2	0	3
Eye inflammation	1	6	0	1	1	7
Eye irritation	13	64	0	1	13	65
Eye movement disorder	0	4	0	0	0	4
Eye oedema	0	1	0	0	0	1
Eye pain	21	131	0	0	21	131
Eye paraesthesia	0	1	0	0	0	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Eye pruritus	10	75	0	1	10	76
Eye swelling	8	73	0	3	8	76
Eyelid disorder	0	1	0	0	0	1
Eyelid function disorder	0	1	0	0	0	1
Eyelid irritation	0	3	0	0	0	3
Eyelid oedema	0	3	0	0	0	3
Eyelid ptosis	1	2	0	0	1	2
Eyelid rash	0	2	0	0	0	2
Eyelids pruritus	1	5	0	0	1	5
Foreign body sensation in eyes	0	2	0	0	0	2
Lacrimation increased	21	176	0	2	21	178
Maculopathy	0	1	0	0	0	1
Metamorphopsia	0	2	0	0	0	2
Miosis	0	0	1	1	1	1
Mydriasis	1	5	0	0	1	5
Ocular discomfort	8	31	0	0	8	31
Ocular hyperaemia	10	85	0	0	10	85
Ocular hypertension	0	0	0	1	0	1
Periorbital pain	0	1	0	0	0	1
Periorbital swelling	0	7	0	0	0	7
Photophobia	1	5	0	0	1	5
Photopsia	0	1	0	0	0	1
Swelling of eyelid	3	13	0	0	3	13
Vision blurred	17	131	0	2	17	133
Visual acuity reduced	0	3	0	0	0	3
Visual field defect	0	1	0	0	0	1
Visual impairment	10	92	0	1	10	93
Vitreous floaters	1	2	0	0	1	2
Xerophthalmia	0	1	0	1	0	2
<b>Gastrointestinal disorders</b>	<b>9718</b>	<b>59633</b>	<b>73</b>	<b>347</b>	<b>9791</b>	<b>59980</b>
Abdominal discomfort	220	1804	1	9	221	1813
Abdominal distension	111	505	0	2	111	507
Abdominal mass	1	1	0	0	1	1
Abdominal pain	171	638	2	4	173	642
Abdominal pain lower	2	24	0	0	2	24
Abdominal pain upper	769	3928	2	12	771	3940
Abdominal rigidity	2	7	0	0	2	7
Abdominal tenderness	1	1	0	0	1	1
Abnormal faeces	1	8	0	1	1	9
Aerophagia	1	3	0	0	1	3
Allergic stomatitis	0	2	0	0	0	2
Anaesthesia oral	0	10	0	0	0	10
Anal incontinence	0	2	0	0	0	2
Anal pruritus	1	1	0	0	1	1
Angular cheilitis	4	6	0	0	4	6

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Anorectal discomfort	3	7	0	0	3	7
Aphthous ulcer	39	368	0	0	39	368
Aptyalism	4	30	0	0	4	30
Barrett's oesophagus	0	0	0	1	0	1
Bile acid malabsorption	0	1	0	0	0	1
Bowel movement irregularity	0	12	0	0	0	12
Breath odour	32	180	0	1	32	181
Burning mouth syndrome	1	8	0	0	1	8
Cardiospasm	0	5	0	0	0	5
Change of bowel habit	0	2	0	0	0	2
Chapped lips	31	268	0	0	31	268
Cheilitis	35	364	0	0	35	364
Chronic gastritis	0	2	0	0	0	2
Coating in mouth	20	55	0	0	20	55
Coeliac disease	0	0	1	1	1	1
Colitis	15	27	1	2	16	29
Colitis ulcerative	0	0	0	3	0	3
Constipation	16	111	0	0	16	111
Crohn's disease	0	0	0	1	0	1
Defaecation disorder	1	1	0	0	1	1
Defaecation urgency	1	1	0	0	1	1
Dental caries	9	37	0	1	9	38
Dental discomfort	7	73	0	0	7	73
Dental paraesthesia	4	25	0	0	4	25
Dental plaque	7	46	0	0	7	46
Diaphragmatic hernia	0	1	0	0	0	1
Diarrhoea	104	626	0	7	104	633
Discoloured vomit	0	2	0	0	0	2
Dry mouth	646	3718	0	3	646	3721
Duodenal ulcer	0	0	0	4	0	4
Duodenitis	0	3	0	0	0	3
Dysbiosis	0	1	0	0	0	1
Dyschezia	1	3	0	0	1	3
Dyspepsia	470	3084	1	7	471	3091
Dysphagia	66	370	1	5	67	375
Enamel anomaly	0	1	0	0	0	1
Enlarged uvula	3	18	1	1	4	19
Enteritis	0	2	0	0	0	2
Enterocolitis	0	0	0	1	0	1
Epigastric discomfort	4	25	0	0	4	25
Erosive duodenitis	0	0	0	1	0	1
Eructation	7	73	0	0	7	73
Faeces discoloured	0	5	0	0	0	5
Faeces hard	0	1	0	0	0	1
Faeces soft	1	3	0	0	1	3

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Flatulence	54	173	0	1	54	174
Food poisoning	0	6	0	0	0	6
Frequent bowel movements	0	18	0	0	0	18
Functional gastrointestinal disorder	0	2	0	0	0	2
Gastric cyst	0	1	0	0	0	1
Gastric dilatation	0	3	0	0	0	3
Gastric hypermotility	1	1	0	0	1	1
Gastric perforation	0	1	0	1	0	2
Gastric ulcer	0	1	8	38	8	39
Gastric ulcer perforation	0	0	0	1	0	1
Gastritis	48	160	1	2	49	162
Gastritis erosive	0	0	0	1	0	1
Gastrointestinal disorder	43	292	4	9	47	301
Gastrointestinal hypermotility	0	1	0	0	0	1
Gastrointestinal inflammation	0	6	0	0	0	6
Gastrointestinal motility disorder	1	5	0	0	1	5
Gastrointestinal oedema	0	0	0	2	0	2
Gastrointestinal pain	31	60	0	1	31	61
Gastrointestinal sounds abnormal	2	8	0	0	2	8
Gastrointestinal tract irritation	2	7	0	0	2	7
Gastrointestinal ulcer	0	1	0	0	0	1
Gastroesophageal reflux disease	80	295	0	2	80	297
Gastroesophageal sphincter insufficiency	0	1	0	0	0	1
Gingival atrophy	1	1	0	0	1	1
Gingival bleeding	439	2684	0	9	439	2693
Gingival blister	2	29	0	0	2	29
Gingival cyst	1	1	0	0	1	1
Gingival discolouration	8	37	0	0	8	37
Gingival discomfort	56	269	1	2	57	271
Gingival disorder	18	237	0	2	18	239
Gingival erosion	1	7	0	0	1	7
Gingival erythema	6	39	0	0	6	39
Gingival pain	139	888	1	1	140	889
Gingival pruritus	2	26	0	0	2	26
Gingival recession	15	87	0	2	15	89
Gingival scar	0	1	0	0	0	1
Gingival swelling	53	623	0	2	53	625
Gingival ulceration	2	13	0	0	2	13
Glossitis	27	277	0	0	27	277
Glossodynia	96	935	0	0	96	935

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Haematemesis	0	0	5	17	5	17
Haematochezia	0	0	4	8	4	8
Haemorrhoids	3	10	0	0	3	10
Hiatus hernia	0	1	0	0	0	1
Hyperaesthesia teeth	37	286	0	0	37	286
Hyperchlorhydria	21	48	0	1	21	49
Hypertrophy of tongue papillae	2	4	0	0	2	4
Hypoaesthesia oral	58	545	0	1	58	546
Hypoaesthesia teeth	0	9	0	0	0	9
Intestinal ulcer	0	0	0	1	0	1
Irritable bowel syndrome	8	19	0	0	8	19
Large intestinal ulcer	0	0	1	2	1	2
Large intestine perforation	0	0	0	1	0	1
Leukoplakia oral	0	0	0	1	0	1
Lip blister	55	849	0	0	55	849
Lip discolouration	10	124	0	0	10	124
Lip disorder	5	61	0	0	5	61
Lip dry	101	488	0	0	101	488
Lip erosion	0	2	0	0	0	2
Lip erythema	8	251	0	0	8	251
Lip exfoliation	9	295	0	0	9	295
Lip haematoma	0	1	0	0	0	1
Lip haemorrhage	1	64	0	0	1	64
Lip oedema	0	3	0	0	0	3
Lip pain	87	881	0	1	87	882
Lip pruritus	10	34	0	0	10	34
Lip scab	1	4	0	0	1	4
Lip swelling	45	549	0	3	45	552
Lip ulceration	5	51	0	0	5	51
Loose tooth	4	43	0	0	4	43
Malpositioned teeth	0	1	0	0	0	1
Melaena	0	0	2	2	2	2
Mouth cyst	1	3	0	0	1	3
Mouth haemorrhage	19	182	0	1	19	183
Mouth swelling	13	151	0	1	13	152
Mouth ulceration	80	505	0	2	80	507
Nausea	1633	11146	5	34	1638	11180
Nicotinic stomatitis	0	2	0	0	0	2
Noninfective gingivitis	86	471	0	1	86	472
Noninfective sialoadenitis	3	5	0	0	3	5
Odynophagia	9	97	0	1	9	98
Oesophageal dilatation	0	1	0	0	0	1
Oesophageal discomfort	3	20	0	0	3	20
Oesophageal disorder	6	21	0	0	6	21
Oesophageal irritation	3	13	0	0	3	13

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Oesophageal obstruction	0	0	0	1	0	1
Oesophageal oedema	0	0	0	1	0	1
Oesophageal pain	13	55	0	1	13	56
Oesophageal rupture	0	1	0	0	0	1
Oesophageal spasm	0	1	0	0	0	1
Oesophagitis	5	40	0	2	5	42
Oral blood blister	0	1	0	0	0	1
Oral cavity fistula	0	1	0	0	0	1
Oral discharge	0	2	0	0	0	2
Oral discomfort	1945	7039	0	5	1945	7044
Oral disorder	5	136	0	0	5	136
Oral mucosa erosion	0	2	0	0	0	2
Oral mucosal blistering	33	354	0	0	33	354
Oral mucosal discolouration	3	46	0	0	3	46
Oral mucosal eruption	6	67	0	0	6	67
Oral mucosal erythema	3	53	0	0	3	53
Oral mucosal exfoliation	5	103	0	0	5	103
Oral mucosal roughening	2	17	0	0	2	17
Oral pain	87	824	1	3	88	827
Oral papule	1	4	0	0	1	4
Oral pigmentation	0	7	0	0	0	7
Oral pruritus	16	64	0	0	16	64
Palatal disorder	3	27	0	0	3	27
Palatal oedema	0	2	0	0	0	2
Palatal swelling	8	59	0	1	8	60
Palatal ulcer	0	4	0	0	0	4
Pancreatic disorder	3	24	0	1	3	25
Pancreatitis	0	0	3	13	3	13
Pancreatitis acute	0	0	1	3	1	3
Paraesthesia oral	50	340	0	1	50	341
Peptic ulcer	1	2	0	0	1	2
Periodontal disease	1	16	0	0	1	16
Pigmentation lip	0	9	0	0	0	9
Plicated tongue	6	44	0	1	6	45
Proctalgia	0	1	0	0	0	1
Rectal discharge	0	1	0	0	0	1
Rectal ulcer	0	0	1	1	1	1
Reflux gastritis	1	11	0	0	1	11
Regurgitation	1	8	0	0	1	8
Retching	57	446	1	1	58	447
Saliva altered	5	19	0	0	5	19
Saliva discolouration	11	35	0	1	11	36
Salivary duct stenosis	0	1	0	0	0	1
Salivary gland disorder	0	4	0	0	0	4
Salivary gland enlargement	1	8	0	0	1	8

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Salivary gland pain	0	7	0	0	0	7
Salivary hypersecretion	17	137	0	0	17	137
Scalloped tongue	0	1	0	0	0	1
Small intestinal obstruction	0	0	0	1	0	1
Stiff tongue	0	5	0	0	0	5
Stomatitis	187	2107	0	7	187	2114
Stomatitis haemorrhagic	0	1	0	0	0	1
Swollen tongue	36	200	0	1	36	201
Teeth brittle	0	5	0	0	0	5
Teething	0	4	0	0	0	4
Tongue blistering	16	120	0	0	16	120
Tongue coated	3	158	0	1	3	159
Tongue discolouration	12	80	0	0	12	80
Tongue discomfort	155	683	1	1	156	684
Tongue disorder	7	110	0	0	7	110
Tongue dry	28	100	0	0	28	100
Tongue erosion	1	1	0	0	1	1
Tongue eruption	6	69	0	1	6	70
Tongue erythema	6	74	0	0	6	74
Tongue exfoliation	3	16	0	0	3	16
Tongue geographic	1	1	0	0	1	1
Tongue haematoma	1	1	0	0	1	1
Tongue haemorrhage	2	25	0	1	2	26
Tongue movement disturbance	0	3	0	0	0	3
Tongue necrosis	0	0	0	1	0	1
Tongue oedema	0	1	0	0	0	1
Tongue pigmentation	1	1	0	0	1	1
Tongue pruritus	15	38	0	0	15	38
Tongue rough	2	26	0	0	2	26
Tongue spasm	0	1	0	0	0	1
Tongue thrust	0	1	0	0	0	1
Tongue ulceration	19	104	0	0	19	104
Tooth deposit	2	33	0	0	2	33
Tooth discolouration	13	92	0	1	13	93
Tooth disorder	6	126	0	1	6	127
Tooth erosion	0	7	0	0	0	7
Tooth loss	9	29	0	1	9	30
Tooth pulp haemorrhage	0	4	0	0	0	4
Tooth socket haemorrhage	1	5	0	0	1	5
Toothache	127	909	0	4	127	913
Trichoglossia	0	19	0	0	0	19
Varicose veins sublingual	0	1	0	0	0	1
Vomiting	505	3515	23	69	528	3584
<b>General disorders and administration site conditions</b>	<b>5012</b>	<b>37378</b>	<b>44</b>	<b>235</b>	<b>5056</b>	<b>37613</b>

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Administration site dryness	0	1	0	0	0	1
Administration site irritation	0	3	0	0	0	3
Adverse drug reaction	1	16	0	0	1	16
Adverse event	12	224	14	19	26	243
Adverse reaction	0	43	0	0	0	43
Alcohol interaction	0	9	0	0	0	9
Application site acne	0	7	0	0	0	7
Application site alopecia	0	3	0	0	0	3
Application site burn	0	1	0	0	0	1
Application site coldness	0	1	0	0	0	1
Application site discolouration	0	1	0	0	0	1
Application site discomfort	0	3	0	0	0	3
Application site dryness	0	5	0	0	0	5
Application site erythema	0	3	0	0	0	3
Application site hypersensitivity	0	3	0	0	0	3
Application site inflammation	0	2	0	0	0	2
Application site irritation	0	1	0	0	0	1
Application site joint pain	0	1	0	0	0	1
Application site pain	2	11	0	0	2	11
Application site paraesthesia	0	8	0	0	0	8
Application site pruritus	0	1	0	0	0	1
Application site rash	0	4	0	0	0	4
Application site reaction	0	3	0	0	0	3
Application site swelling	0	3	0	0	0	3
Application site ulcer	0	1	0	0	0	1
Application site warmth	0	1	0	0	0	1
Asthenia	112	918	1	12	113	930
Axillary pain	0	1	0	0	0	1
Chest discomfort	686	4315	5	22	691	4337
Chest pain	1074	5038	4	21	1078	5059
Chills	15	103	0	0	15	103
Condition aggravated	15	186	2	8	17	194
Crepitations	0	4	0	0	0	4
Critical illness	0	0	0	1	0	1
Crying	14	79	1	2	15	81
Cyst	0	12	0	2	0	14
Death	0	0	3	13	3	13
Decreased activity	2	5	0	0	2	5
Device intolerance	1	9	0	0	1	9
Discharge	1	15	0	0	1	15
Discomfort	156	1414	0	2	156	1416
Disease complication	0	1	0	0	0	1
Disease susceptibility	0	1	0	0	0	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Drug ineffective	11	19	0	0	11	19
Drug interaction	0	2	0	0	0	2
Drug intolerance	1	13	0	0	1	13
Drug-device interaction	0	1	0	0	0	1
Electrocution	4	4	0	0	4	4
Enanthema	0	1	0	0	0	1
Energy increased	1	4	0	0	1	4
Exercise tolerance decreased	1	3	0	0	1	3
Face oedema	0	3	0	0	0	3
Facial discomfort	1	3	0	0	1	3
Facial pain	15	82	0	0	15	82
Fatigue	138	805	2	9	140	814
Feeling abnormal	146	1359	0	2	146	1361
Feeling cold	5	38	0	0	5	38
Feeling drunk	0	14	0	1	0	15
Feeling hot	77	1248	0	1	77	1249
Feeling jittery	2	8	0	0	2	8
Feeling of body temperature change	0	5	0	0	0	5
Feeling of relaxation	1	3	0	0	1	3
Foaming at mouth	2	4	0	0	2	4
Food interaction	0	4	0	0	0	4
Gait disturbance	6	35	0	0	6	35
Gait inability	1	14	0	0	1	14
General physical health deterioration	57	348	1	9	58	357
Generalised oedema	0	3	0	1	0	4
Glassy eyes	0	1	0	0	0	1
Granuloma	1	1	0	0	1	1
Hangover	1	17	0	0	1	17
Hernia	0	1	0	0	0	1
Hunger	6	41	0	0	6	41
Hyperplasia	0	1	0	0	0	1
Hyperthermia	0	2	0	0	0	2
Hypothermia	0	0	0	1	0	1
Idiopathic environmental intolerance	0	2	0	1	0	3
Ill-defined disorder	10	162	0	6	10	168
Illness	122	1343	0	12	122	1355
Impaired healing	0	3	0	0	0	3
Induration	0	1	0	0	0	1
Inflammation	14	161	1	4	15	165
Influenza like illness	5	15	0	2	5	17
Infusion site swelling	1	1	0	0	1	1
Injection site discomfort	0	1	0	0	0	1
Injection site hypersensitivity	0	1	0	0	0	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Injection site mass	0	1	0	0	0	1
Injection site pain	0	1	0	0	0	1
Injection site urticaria	0	1	0	0	0	1
Injection site vesicles	0	2	0	0	0	2
Injury associated with device	0	3	0	1	0	4
Localised oedema	0	2	0	0	0	2
Malaise	764	8620	1	22	765	8642
Mass	1	6	0	0	1	6
Medical device pain	1	1	0	0	1	1
Mucosa vesicle	0	1	0	0	0	1
Mucosal atrophy	0	1	0	0	0	1
Mucosal discolouration	1	3	0	0	1	3
Mucosal disorder	8	56	0	0	8	56
Mucosal dryness	31	213	0	0	31	213
Mucosal erosion	0	7	0	0	0	7
Mucosal haemorrhage	2	4	0	0	2	4
Mucosal hypertrophy	0	1	0	0	0	1
Mucosal induration	0	1	0	0	0	1
Mucosal inflammation	3	43	0	1	3	44
Mucosal membrane hyperplasia	0	1	0	0	0	1
Mucosal pain	0	6	0	0	0	6
Mucosal pigmentation	0	1	0	0	0	1
Mucosal ulceration	0	1	0	0	0	1
No adverse event	975	5707	4	6	979	5713
Nodule	0	5	0	1	0	6
Non-cardiac chest pain	0	5	0	0	0	5
Nonspecific reaction	0	1	0	0	0	1
Obstruction	0	3	0	0	0	3
Oedema	4	21	0	1	4	22
Oedema mucosal	3	15	0	2	3	17
Oedema peripheral	0	5	0	0	0	5
Organ failure	0	0	0	1	0	1
Pain	95	1061	0	5	95	1066
Performance status decreased	0	1	0	0	0	1
Peripheral swelling	5	99	0	0	5	99
Physical deconditioning	0	1	0	0	0	1
Polyp	1	10	0	0	1	10
Pre-existing condition improved	0	1	0	0	0	1
Product intolerance	7	330	0	0	7	330
Pyrexia	86	376	4	27	90	403
Rebound effect	1	2	0	0	1	2
Screaming	0	1	0	0	0	1
Secretion discharge	55	170	0	1	55	171
Sensation of blood flow	1	2	0	0	1	2

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Sensation of foreign body	99	1130	0	4	99	1134
Sense of oppression	0	5	0	0	0	5
Sensitivity to weather change	0	1	0	0	0	1
Sluggishness	12	40	0	0	12	40
Swelling	30	229	0	5	30	234
Swelling face	15	142	1	1	16	143
Temperature intolerance	0	18	0	0	0	18
Temperature regulation disorder	0	3	0	0	0	3
Tenderness	1	6	0	0	1	6
Therapeutic response increased	0	1	0	0	0	1
Therapeutic response unexpected	0	23	0	0	0	23
Therapy non-responder	1	1	0	0	1	1
Thirst	67	462	0	1	67	463
Thirst decreased	0	2	0	0	0	2
Tobacco interaction	0	3	0	0	0	3
Ulcer	17	68	0	2	17	70
Ulcer haemorrhage	0	0	0	1	0	1
Unevaluable event	1	190	0	1	1	191
Visceral pain	1	2	0	0	1	2
Withdrawal syndrome	3	20	0	1	3	21
Xerosis	1	3	0	0	1	3
<b>Hepatobiliary disorders</b>	<b>9</b>	<b>89</b>	<b>5</b>	<b>14</b>	<b>14</b>	<b>103</b>
Biliary colic	2	9	0	1	2	10
Cholelithiasis	0	3	0	0	0	3
Gallbladder disorder	0	7	0	0	0	7
Hepatic cirrhosis	0	0	1	1	1	1
Hepatic failure	0	0	0	2	0	2
Hepatic function abnormal	1	1	0	0	1	1
Hepatic pain	5	43	0	0	5	43
Hepatitis	0	0	2	4	2	4
Hepatitis toxic	0	0	0	1	0	1
Hepatomegaly	0	2	0	0	0	2
Hepatotoxicity	0	0	1	2	1	2
Liver disorder	0	22	0	1	0	23
Liver injury	0	0	1	2	1	2
Ocular icterus	1	2	0	0	1	2
<b>Immune system disorders</b>	<b>455</b>	<b>3134</b>	<b>3</b>	<b>899</b>	<b>458</b>	<b>4033</b>
Allergic oedema	0	1	0	0	0	1
Allergic reaction to excipient	0	23	0	0	0	23
Allergy to animal	0	1	0	0	0	1
Allergy to chemicals	0	34	0	1	0	35
Allergy to metals	9	24	0	1	9	25
Allergy to plants	0	1	0	0	0	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Anaphylactic reaction	0	0	0	1	0	1
Anaphylactic shock	0	0	0	10	0	10
Anaphylactoid reaction	0	0	0	1	0	1
Atopy	0	7	0	0	0	7
Autoimmune disorder	0	0	1	4	1	4
Decreased immune responsiveness	1	5	0	0	1	5
Device allergy	0	4	0	0	0	4
Drug hypersensitivity	0	4	0	0	0	4
Dust allergy	0	2	0	0	0	2
Food allergy	1	2	0	0	1	2
Hypersensitivity	439	2987	1	875	440	3862
Immune system disorder	1	10	0	2	1	12
Immunosuppression	0	1	0	1	0	2
Milk allergy	0	1	0	0	0	1
Mycotic allergy	0	1	0	0	0	1
Nicotine allergy	1	1	0	0	1	1
Reaction to excipient	0	5	0	0	0	5
Sarcoidosis	0	0	0	2	0	2
Seasonal allergy	1	8	1	1	2	9
Sensitisation	2	9	0	0	2	9
Smoke sensitivity	0	3	0	0	0	3
<b>Infections and infestations</b>	<b>421</b>	<b>2685</b>	<b>65</b>	<b>385</b>	<b>486</b>	<b>3070</b>
Abscess	1	7	0	2	1	9
Abscess oral	1	6	0	0	1	6
Acarodermatitis	0	5	0	0	0	5
Acne pustular	0	8	0	0	0	8
Acute sinusitis	0	1	0	1	0	2
Adenoiditis	1	2	0	0	1	2
Anal fungal infection	1	1	0	0	1	1
Appendicitis	0	0	0	1	0	1
Appendicitis perforated	0	0	0	1	0	1
Arthropod-borne disease	1	1	0	0	1	1
Bacterial allergy	0	1	0	0	0	1
Bacterial food poisoning	1	1	0	0	1	1
Bacterial infection	1	3	0	0	1	3
Bacterial rhinitis	0	0	0	1	0	1
Blister infected	1	8	0	0	1	8
Bronchiolitis	0	1	0	0	0	1
Bronchitis	42	240	2	16	44	256
Bronchitis bacterial	0	0	1	1	1	1
Burn infection	0	1	0	1	0	2
Candida infection	1	30	0	0	1	30
Cholecystitis infective	0	0	0	1	0	1
Chorioretinitis	0	0	0	1	0	1
Chronic sinusitis	1	2	0	0	1	2

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Chronic tonsillitis	0	2	2	15	2	17
Complicated appendicitis	0	0	0	1	0	1
Conjunctivitis	2	12	0	1	2	13
Coronavirus infection	0	6	0	2	0	8
COVID-19	1	10	0	6	1	16
COVID-19 pneumonia	0	0	0	12	0	12
Creutzfeldt-Jakob disease	0	0	0	1	0	1
Croup infectious	0	0	1	1	1	1
Cystitis	1	5	0	1	1	6
Dermatitis infected	0	1	0	0	0	1
Disseminated tuberculosis	0	0	0	1	0	1
Diverticulitis	0	0	0	2	0	2
Dysentery	0	0	1	2	1	2
Ear infection	2	5	0	1	2	6
Ear infection staphylococcal	0	0	1	1	1	1
Empyema	0	0	0	1	0	1
Endocarditis	0	0	0	1	0	1
Epiglottitis	0	0	2	3	2	3
Erythema induratum	0	1	0	0	0	1
Eye infection	0	1	1	1	1	2
Folliculitis	0	9	0	0	0	9
Fungal infection	2	11	0	0	2	11
Fungal pharyngitis	0	0	0	2	0	2
Furuncle	5	47	1	2	6	49
Gangrene	0	0	0	2	0	2
Gastric infection	1	1	0	0	1	1
Gastroenteritis	3	13	0	0	3	13
Gastroenteritis viral	1	6	0	0	1	6
Gastrointestinal infection	1	2	0	0	1	2
Genital infection fungal	1	1	0	0	1	1
Gingival abscess	0	3	0	5	0	8
Gingivitis	32	155	0	1	32	156
Helicobacter infection	0	1	1	1	1	2
Herpes dermatitis	0	2	0	0	0	2
Herpes virus infection	4	24	0	0	4	24
Herpes zoster	0	7	0	0	0	7
Hordeolum	0	7	0	0	0	7
Infected skin ulcer	0	0	0	1	0	1
Infection	4	51	0	4	4	55
Infection susceptibility increased	0	0	0	1	0	1
Infectious thyroiditis	1	1	0	0	1	1
Infective glossitis	0	10	0	1	0	11
Influenza	26	80	1	2	27	82
Injection site infection	0	1	0	0	0	1
Labyrinthitis	1	2	0	0	1	2

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Laryngitis	17	107	0	3	17	110
Laryngopharyngitis	1	10	0	0	1	10
Lip infection	1	11	0	0	1	11
Localised infection	0	1	0	0	0	1
Lower respiratory tract infection	4	6	2	17	6	23
Lower respiratory tract infection fungal	0	0	0	2	0	2
Lung abscess	0	0	0	1	0	1
Mastitis	0	0	0	1	0	1
Meningitis	0	0	0	1	0	1
Mucosal infection	1	1	0	0	1	1
Mumps	2	8	0	0	2	8
Myringitis	0	0	0	1	0	1
Nasopharyngitis	67	375	0	1	67	376
Oral bacterial infection	0	0	0	1	0	1
Oral candidiasis	5	33	0	0	5	33
Oral fungal infection	2	16	0	0	2	16
Oral herpes	10	172	0	0	10	172
Oral infection	5	107	0	1	5	108
Oral pustule	0	7	0	1	0	8
Osteomyelitis	0	0	0	4	0	4
Otitis externa	0	2	0	0	0	2
Otitis media	1	3	0	0	1	3
Parotitis	1	1	0	0	1	1
Periodontitis	5	59	0	1	5	60
Periorbital infection	0	0	0	1	0	1
Peritonitis	0	0	0	2	0	2
Peritonsillar abscess	0	0	0	7	0	7
Pertussis	0	0	0	2	0	2
Pharyngeal abscess	0	0	0	1	0	1
Pharyngitis	67	330	1	5	68	335
Pharyngitis bacterial	0	0	0	5	0	5
Pharyngitis streptococcal	2	5	0	0	2	5
Pharyngotonsillitis	0	0	0	1	0	1
Pneumonia	0	0	46	186	46	186
Pneumonia bacterial	0	0	0	1	0	1
Pneumonia fungal	0	0	0	1	0	1
Pneumonia klebsiella	0	0	0	1	0	1
Pneumonia pneumococcal	0	0	0	1	0	1
Pneumonia viral	0	0	0	1	0	1
Pulmonary tuberculosis	0	0	0	1	0	1
Pulpitis dental	2	7	0	0	2	7
Purulence	0	2	0	0	0	2
Purulent discharge	1	14	0	0	1	14
Pustule	1	18	0	1	1	19

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Rash pustular	1	15	0	0	1	15
Respiratory tract infection	3	5	1	8	4	13
Respiratory tract infection viral	0	1	0	2	0	3
Rhinitis	11	95	0	0	11	95
Sepsis	0	0	0	1	0	1
Sialoadenitis	0	0	0	1	0	1
Sinusitis	20	90	0	3	20	93
Skin infection	0	8	0	0	0	8
Sputum purulent	2	5	0	1	2	6
Streptococcal infection	0	1	0	0	0	1
Subcutaneous abscess	0	3	0	0	0	3
Suspected COVID-19	0	1	0	0	0	1
Tetanus	0	0	0	1	0	1
Tinea infection	0	3	0	0	0	3
Tongue abscess	0	1	0	0	0	1
Tongue fungal infection	1	5	0	0	1	5
Tonsillitis	36	307	1	4	37	311
Tonsillitis bacterial	0	0	0	6	0	6
Tooth abscess	0	3	0	0	0	3
Tooth infection	1	5	0	0	1	5
Tracheitis	8	21	0	0	8	21
Tracheobronchitis	0	1	0	0	0	1
Tuberculosis	0	0	0	3	0	3
Upper respiratory fungal infection	0	0	0	1	0	1
Upper respiratory tract infection	1	8	0	0	1	8
Urinary tract infection	0	2	0	0	0	2
Vestibular neuronitis	0	1	0	0	0	1
Viral infection	2	12	0	1	2	13
Viral pharyngitis	0	2	0	0	0	2
<b>Injury, poisoning and procedural complications</b>	<b>3588</b>	<b>37346</b>	<b>65</b>	<b>263</b>	<b>3653</b>	<b>37609</b>
Abdominal injury	1	1	0	0	1	1
Accident	0	1	0	1	0	2
Accidental exposure to product	107	613	2	6	109	619
Accidental exposure to product by child	848	6548	49	127	897	6675
Accidental overdose	0	2	0	0	0	2
Airway burns	4	73	1	2	5	75
Alcohol poisoning	0	2	0	0	0	2
Ankle fracture	0	0	0	1	0	1
Arthropod sting	1	3	0	0	1	3
Back injury	0	2	0	0	0	2
Bite	0	4	0	0	0	4
Blast injury	0	4	0	1	0	5

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Burn oesophageal	4	42	0	0	4	42
Burn of internal organs	0	2	0	0	0	2
Burn oral cavity	609	5223	0	3	609	5226
Burns first degree	1	18	0	0	1	18
Burns second degree	0	184	0	0	0	184
Burns third degree	0	0	1	6	1	6
Carbon monoxide poisoning	2	3	0	0	2	3
Carcinogenicity	0	1	0	0	0	1
Chemical burn	0	11	0	0	0	11
Chemical burn of oral cavity	0	2	0	0	0	2
Chemical burn of respiratory tract	0	0	0	3	0	3
Chemical poisoning	0	0	0	4	0	4
Chillblains	0	2	0	0	0	2
Clavicle fracture	0	0	0	1	0	1
Cold burn	2	12	0	0	2	12
Colon injury	0	1	0	0	0	1
Comminuted fracture	0	0	0	1	0	1
Concussion	0	1	0	1	0	2
Contraindicated product administered	1	1	0	0	1	1
Contusion	2	20	0	1	2	21
Corneal laceration	1	1	0	0	1	1
Dental restoration failure	1	4	0	0	1	4
Device difficult to use	27	971	0	0	27	971
Device maintenance issue	0	2	0	0	0	2
Device use error	0	9	0	0	0	9
Device use issue	3	24	0	0	3	24
Dislocation of vertebra	0	0	1	1	1	1
Ear injury	0	1	0	0	0	1
Electric injury	1	1	0	0	1	1
Electric shock	21	94	0	0	21	94
Electrical burn	3	5	0	0	3	5
Expired product administered	0	2	0	0	0	2
Exposure during pregnancy	292	526	1	2	293	528
Exposure to household chemicals	1	1	0	0	1	1
Exposure to SARS-CoV-2	0	2	0	0	0	2
Exposure to tobacco	0	1	0	0	0	1
Exposure to toxic agent	0	3	0	0	0	3
Exposure via breast milk	11	13	0	0	11	13
Exposure via eye contact	0	2	0	0	0	2
Exposure via inhalation	0	5	0	0	0	5
Eye contusion	0	2	0	0	0	2
Eye injury	1	4	0	0	1	4
Face injury	1	8	0	0	1	8

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Fall	5	46	0	5	5	51
Foreign body	0	2	0	0	0	2
Foreign body in eye	0	2	0	0	0	2
Foreign body in gastrointestinal tract	1	2	0	0	1	2
Foreign body in mouth	0	6	0	0	0	6
Foreign body in respiratory tract	0	8	0	1	0	9
Foreign body in throat	0	5	0	2	0	7
Fracture	0	1	0	0	0	1
Fracture displacement	0	0	0	1	0	1
Gas poisoning	0	1	0	0	0	1
Gastrointestinal injury	0	0	1	1	1	1
Gingival injury	1	15	0	0	1	15
Hair injury	0	1	0	0	0	1
Head injury	0	3	0	1	0	4
Heat stroke	1	2	0	0	1	2
Inappropriate schedule of product administration	1	1	0	0	1	1
Incorrect dose administered	1	1	0	0	1	1
Incorrect route of product administration	3	5	0	0	3	5
Inflammation of wound	0	1	0	0	0	1
Injury	4	29	0	0	4	29
Injury corneal	0	0	0	1	0	1
Intentional device misuse	0	5	0	0	0	5
Intentional overdose	0	2	0	1	0	3
Intentional product misuse	609	2490	1	3	610	2493
Intentional product misuse to child	0	1	0	0	0	1
Intentional product use issue	0	6	0	0	0	6
Intercepted wrong patient selected	0	1	0	0	0	1
Jaw fracture	0	0	0	3	0	3
Joint dislocation	0	1	0	2	0	3
Joint injury	0	2	0	1	0	3
Lack of administration site rotation	0	1	0	0	0	1
Laryngeal injury	0	0	0	1	0	1
Ligament rupture	0	0	0	1	0	1
Ligament sprain	1	2	0	1	1	3
Limb injury	6	38	0	1	6	39
Limb traumatic amputation	0	0	0	1	0	1
Lip injury	19	84	0	1	19	85
Lower limb fracture	0	0	0	1	0	1
Maternal exposure before pregnancy	0	1	0	0	0	1
Maternal exposure during breast feeding	8	11	0	0	8	11

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Maternal exposure during pregnancy	7	125	0	0	7	125
Maternal exposure timing unspecified	0	2	0	0	0	2
Metal poisoning	0	0	1	3	1	3
Mouth injury	8	54	1	1	9	55
Mucosal excoriation	0	2	0	0	0	2
Multiple injuries	0	0	0	1	0	1
Muscle injury	0	1	0	1	0	2
Muscle strain	3	16	0	1	3	17
Nail injury	0	6	0	0	0	6
Nasal injury	3	9	0	0	3	9
Nerve injury	1	5	0	1	1	6
Nervous system injury	0	1	0	0	0	1
Occupational exposure to product	0	6	0	0	0	6
Oesophageal injury	0	1	1	1	1	2
Oesophagitis chemical	0	0	0	1	0	1
Off label use	4	5	0	0	4	5
Oral contusion	2	13	0	0	2	13
Overdose	2	14	0	0	2	14
Palate injury	0	15	0	0	0	15
Pancreatic duct rupture	0	0	0	1	0	1
Paternal exposure during pregnancy	2	2	0	0	2	2
Pharyngeal contusion	1	1	0	0	1	1
Pharyngeal injury	0	3	0	2	0	5
Plaque shift	0	2	0	0	0	2
Pleural injury	0	0	1	1	1	1
Pneumoconiosis	0	0	0	1	0	1
Pneumonitis chemical	0	0	0	1	0	1
Poisoning	0	11	0	13	0	24
Poor quality product administered	0	1	0	0	0	1
Post procedural complication	0	1	0	0	0	1
Procedural dizziness	1	1	0	0	1	1
Product administration error	0	2	0	0	0	2
Product preparation error	0	1	0	0	0	1
Product storage error	0	0	0	1	0	1
Product use complaint	1	35	0	0	1	35
Product use issue	0	16	0	0	0	16
Respiratory fume inhalation disorder	0	3	0	0	0	3
Retinal injury	0	0	0	1	0	1
Rib fracture	0	1	0	2	0	3
Road traffic accident	0	2	0	2	0	4
Scar	3	42	0	0	3	42
Scratch	13	82	0	0	13	82

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Silicosis	0	1	0	0	0	1
Skeletal injury	0	0	0	1	0	1
Skin abrasion	2	6	0	2	2	8
Skin injury	0	7	0	0	0	7
Skin laceration	5	16	0	0	5	16
Skin wound	0	4	0	0	0	4
Soft tissue foreign body	0	1	0	0	0	1
Spinal column injury	0	1	0	0	0	1
Stab wound	1	1	0	0	1	1
Sunburn	0	1	0	0	0	1
Thermal burn	883	19106	1	22	884	19128
Thermal burns of eye	0	1	1	2	1	3
Tibia fracture	0	0	0	2	0	2
Tissue injury	0	1	0	0	0	1
Tobacco poisoning	22	241	2	6	24	247
Tongue injury	7	27	0	0	7	27
Tooth fracture	0	4	0	1	0	5
Tooth injury	4	46	0	1	4	47
Toxicity to various agents	0	11	0	0	0	11
Tracheal injury	0	2	0	0	0	2
Traumatic lung injury	0	10	0	0	0	10
Upper limb fracture	0	1	0	0	0	1
Vascular injury	0	1	0	0	0	1
Wound	6	103	0	1	6	104
Wound complication	0	3	0	0	0	3
Wound haemorrhage	1	15	0	0	1	15
Wound secretion	1	6	0	0	1	6
Wrong technique in device usage process	0	7	0	0	0	7
Wrong technique in product usage process	0	9	0	0	0	9
<b>Investigations</b>	<b>714</b>	<b>4143</b>	<b>10</b>	<b>58</b>	<b>724</b>	<b>4201</b>
Alanine aminotransferase increased	0	5	0	0	0	5
Allergy test positive	0	1	0	0	0	1
Amino acid level increased	0	1	0	0	0	1
Aspartate aminotransferase	0	1	0	0	0	1
Aspartate aminotransferase increased	0	3	0	0	0	3
Biopsy palate abnormal	0	1	0	0	0	1
Biopsy prostate abnormal	0	1	0	0	0	1
Blood aluminium increased	0	2	0	0	0	2
Blood bilirubin increased	0	2	0	0	0	2
Blood carbon monoxide	0	1	0	0	0	1
Blood carbon monoxide increased	0	1	0	0	0	1
Blood cholesterol	1	1	0	0	1	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Blood cholesterol increased	1	11	0	0	1	11
Blood creatinine increased	0	1	0	0	0	1
Blood glucose	0	2	0	0	0	2
Blood glucose abnormal	0	2	0	0	0	2
Blood glucose decreased	0	5	0	0	0	5
Blood glucose increased	12	59	0	0	12	59
Blood growth hormone	0	1	0	0	0	1
Blood immunoglobulin E increased	0	1	0	0	0	1
Blood magnesium increased	0	1	0	0	0	1
Blood mercury abnormal	0	1	0	0	0	1
Blood pressure abnormal	29	133	0	0	29	133
Blood pressure decreased	30	219	0	2	30	221
Blood pressure immeasurable	0	1	0	0	0	1
Blood pressure increased	151	1183	2	16	153	1199
Blood pressure systolic decreased	0	1	0	0	0	1
Blood pressure systolic increased	0	2	0	0	0	2
Blood test abnormal	1	3	0	0	1	3
Blood triglycerides increased	0	1	0	0	0	1
Blood uric acid abnormal	0	1	0	0	0	1
Blood urine	0	1	0	0	0	1
Blood urine present	0	3	0	0	0	3
Body mass index increased	0	1	0	0	0	1
Body temperature	2	2	0	0	2	2
Body temperature abnormal	1	5	0	0	1	5
Body temperature decreased	0	6	0	0	0	6
Body temperature fluctuation	0	6	0	0	0	6
Body temperature increased	4	94	0	5	4	99
Breath sounds	2	8	0	0	2	8
Breath sounds abnormal	8	31	0	2	8	33
Breath sounds absent	0	1	0	0	0	1
Bronchial arteriography	1	1	0	0	1	1
Cardiac murmur	0	1	0	0	0	1
Cells in urine	0	1	0	0	0	1
Chest X-ray abnormal	0	1	0	0	0	1
Clostridium test positive	0	1	0	0	0	1
C-reactive protein increased	1	1	0	1	1	2
Drug level	0	1	0	0	0	1
Electrocardiogram abnormal	0	1	0	0	0	1
Endoscopy upper gastrointestinal tract	0	2	0	0	0	2
Epinephrine increased	0	3	0	0	0	3
Full blood count abnormal	0	1	0	0	0	1
Gamma-glutamyltransferase increased	0	1	0	0	0	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Gastric pH decreased	5	29	0	1	5	30
General physical condition abnormal	1	13	0	2	1	15
Haemoglobin increased	1	3	0	0	1	3
Heart rate	3	17	0	0	3	17
Heart rate abnormal	6	27	0	0	6	27
Heart rate decreased	2	21	0	2	2	23
Heart rate increased	367	1331	6	15	373	1346
Heart rate irregular	19	67	0	1	19	68
Hepatic enzyme increased	1	4	0	0	1	4
Histamine level increased	0	1	0	0	0	1
Hormone level abnormal	3	8	0	0	3	8
Immunoglobulins increased	0	1	0	0	0	1
Inflammatory marker test	0	1	0	0	0	1
Inspiratory capacity decreased	0	1	0	0	0	1
Intraocular pressure increased	2	6	0	0	2	6
Intraocular pressure test	1	4	0	0	1	4
Investigation abnormal	0	2	0	0	0	2
Laboratory test abnormal	0	1	0	0	0	1
Laryngoscopy	0	1	0	0	0	1
Liver function test abnormal	0	3	0	0	0	3
Liver function test increased	2	3	0	0	2	3
Lumbar puncture	0	1	0	0	0	1
Lymph node palpable	0	3	0	0	0	3
Magnetic resonance imaging abnormal	0	1	0	0	0	1
Myocardial necrosis marker increased	0	0	1	1	1	1
Nicotine test	0	1	0	0	0	1
Occult blood negative	0	1	0	0	0	1
Oxygen consumption decreased	1	15	0	0	1	15
Oxygen consumption increased	0	1	0	0	0	1
Oxygen saturation decreased	4	12	0	2	4	14
Oxygen saturation increased	0	1	0	0	0	1
Physical examination abnormal	0	1	0	0	0	1
Platelet count decreased	0	0	0	1	0	1
Product residue present	0	5	0	0	0	5
Pulmonary arterial pressure	0	1	0	0	0	1
Pulmonary function test decreased	0	4	0	0	0	4
Pulse abnormal	4	11	0	0	4	11
Pulse pressure abnormal	1	1	0	0	1	1
Pulse pressure increased	1	3	0	0	1	3
Quality of life decreased	0	1	0	0	0	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Red blood cell count increased	1	1	0	0	1	1
Respiratory rate decreased	0	3	1	2	1	5
Respiratory rate increased	4	24	0	0	4	24
Rheumatoid factor	0	1	0	0	0	1
SARS-CoV-2 test negative	0	1	0	0	0	1
SARS-CoV-2 test positive	0	1	0	0	0	1
Sperm concentration abnormal	1	1	0	0	1	1
Spermatozoa abnormal	1	1	0	0	1	1
Sputum abnormal	0	5	0	0	0	5
Thyroid function test abnormal	0	1	0	0	0	1
Thyroid hormones increased	0	1	0	0	0	1
Total lung capacity abnormal	1	1	0	0	1	1
Total lung capacity decreased	4	24	0	0	4	24
Transaminases increased	1	2	0	0	1	2
Urine viscosity increased	0	1	0	0	0	1
Vital capacity	1	1	0	0	1	1
Vital capacity decreased	0	1	0	0	0	1
Weight	2	2	0	0	2	2
Weight abnormal	0	3	0	0	0	3
Weight decreased	4	41	0	1	4	42
Weight increased	26	595	0	1	26	596
White blood cell count decreased	0	2	0	2	0	4
White blood cell count increased	0	1	0	1	0	2
X-ray abnormal	0	1	0	0	0	1
<b>Metabolism and nutrition disorders</b>	<b>69</b>	<b>483</b>	<b>3</b>	<b>45</b>	<b>72</b>	<b>528</b>
Acidosis	0	2	0	0	0	2
Appetite disorder	0	8	0	0	0	8
Dairy intolerance	0	1	0	0	0	1
Decreased appetite	36	210	0	2	36	212
Dehydration	14	108	0	0	14	108
Diabetes mellitus	0	0	3	27	3	27
Diabetes mellitus inadequate control	0	0	0	13	0	13
Diabetic complication	0	1	0	0	0	1
Diet refusal	0	1	0	0	0	1
Eating disorder symptom	0	1	0	0	0	1
Electrolyte imbalance	1	1	0	0	1	1
Feeding disorder	4	20	0	0	4	20
Fluid intake reduced	0	1	0	0	0	1
Fluid retention	3	14	0	0	3	14
Food aversion	2	2	0	0	2	2
Food craving	0	1	0	0	0	1

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Food intolerance	0	1	0	0	0	1
Food refusal	1	1	0	0	1	1
Glucose tolerance impaired	0	1	0	0	0	1
Hyperglycaemia	0	2	0	0	0	2
Hyperinsulinaemia	0	1	0	0	0	1
Hyperlipidaemia	0	1	0	0	0	1
Hyperphagia	1	4	0	0	1	4
Hypervolaemia	0	1	0	0	0	1
Hypoglycaemia	0	3	0	0	0	3
Hypovitaminosis	0	1	0	0	0	1
Increased appetite	5	61	0	0	5	61
Ketoacidosis	0	0	0	1	0	1
Lactose intolerance	0	2	0	0	0	2
Metabolic disorder	1	3	0	0	1	3
Obesity	0	1	0	1	0	2
Polydipsia	0	13	0	0	0	13
Poor feeding infant	0	1	0	0	0	1
Tetany	1	1	0	0	1	1
Type 2 diabetes mellitus	0	0	0	1	0	1
Vitamin D deficiency	0	1	0	0	0	1
Weight fluctuation	0	11	0	0	0	11
Weight gain poor	0	1	0	0	0	1
Weight loss poor	0	1	0	0	0	1
<b>Musculoskeletal and connective tissue disorders</b>	<b>232</b>	<b>1366</b>	<b>2</b>	<b>24</b>	<b>234</b>	<b>1390</b>
Antisynthetase syndrome	0	1	0	0	0	1
Arthralgia	26	107	0	2	26	109
Arthritis	2	6	0	0	2	6
Arthropathy	0	3	0	0	0	3
Back disorder	0	1	0	0	0	1
Back pain	29	140	0	1	29	141
Bone disorder	1	2	0	1	1	3
Bone loss	0	1	0	0	0	1
Bone pain	4	23	0	0	4	23
Costochondritis	0	1	0	0	0	1
Fibromyalgia	0	1	0	0	0	1
Flank pain	1	24	0	0	1	24
Fracture pain	0	1	0	0	0	1
Groin pain	0	1	0	0	0	1
Growth retardation	0	0	1	1	1	1
Intervertebral disc protrusion	0	1	0	0	0	1
Jaw disorder	0	6	0	0	0	6
Joint contracture	0	1	0	0	0	1
Joint noise	0	1	0	0	0	1
Joint stiffness	0	3	0	1	0	4
Joint swelling	2	6	0	0	2	6

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Knee deformity	0	1	0	0	0	1
Ligament disorder	0	1	0	0	0	1
Limb discomfort	6	30	0	1	6	31
Mastication disorder	2	16	0	1	2	17
Mobility decreased	0	1	0	0	0	1
Muscle contracture	0	2	0	0	0	2
Muscle discomfort	0	3	0	0	0	3
Muscle disorder	0	2	0	0	0	2
Muscle spasms	16	141	0	0	16	141
Muscle tightness	2	8	0	1	2	9
Muscle twitching	1	16	0	1	1	17
Muscular weakness	4	42	0	0	4	42
Musculoskeletal chest pain	3	36	0	0	3	36
Musculoskeletal discomfort	10	46	0	1	10	47
Musculoskeletal disorder	0	1	0	0	0	1
Musculoskeletal pain	0	9	0	0	0	9
Musculoskeletal stiffness	6	51	0	0	6	51
Myalgia	6	55	0	0	6	55
Myokymia	0	1	0	0	0	1
Myositis	1	3	0	0	1	3
Neck mass	0	1	0	0	0	1
Neck pain	42	177	1	4	43	181
Osteitis	2	4	0	0	2	4
Osteoarthritis	0	1	0	0	0	1
Osteochondrosis	0	0	0	4	0	4
Pain in extremity	46	203	0	0	46	203
Pain in jaw	17	169	0	2	17	171
Periarthritis	1	1	0	0	1	1
Plantar fasciitis	0	1	0	0	0	1
Posture abnormal	0	1	0	0	0	1
Rheumatoid arthritis	0	0	0	1	0	1
Spinal disorder	0	1	0	1	0	2
Spinal pain	0	3	0	1	0	4
Tendon pain	0	2	0	0	0	2
Tendonitis	1	2	0	0	1	2
Trigger points	1	1	0	0	1	1
Trismus	0	4	0	0	0	4
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	<b>4</b>	<b>43</b>	<b>28</b>	<b>145</b>	<b>32</b>	<b>188</b>
Adenoma benign	0	1	0	0	0	1
Benign neoplasm	0	2	0	0	0	2
Bladder cancer	0	0	1	1	1	1
Brain neoplasm	0	0	1	3	1	3
Brain neoplasm malignant	0	0	0	1	0	1
Cancer in remission	0	1	0	0	0	1

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(b) (4)

MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Cancer pain	0	0	0	1	0	1
Fibroma	0	1	0	0	0	1
Hepatic neoplasm	0	0	0	1	0	1
Laryngeal cancer	0	0	0	1	0	1
Laryngeal papilloma	0	1	0	0	0	1
Leukaemia	0	0	1	2	1	2
Lipoma	0	2	0	0	0	2
Lung adenocarcinoma	0	0	0	1	0	1
Lung adenocarcinoma stage II	0	0	0	1	0	1
Lung cancer metastatic	0	0	0	1	0	1
Lung neoplasm	0	4	1	2	1	6
Lung neoplasm malignant	0	1	12	50	12	51
Lymphoma	0	0	0	2	0	2
Melanocytic naevus	0	2	0	0	0	2
Metastases to bladder	0	0	0	1	0	1
Metastases to central nervous system	0	0	0	2	0	2
Metastases to liver	0	0	0	1	0	1
Metastases to lung	0	0	0	1	0	1
Metastases to lymph nodes	0	0	0	1	0	1
Neoplasm	1	5	0	0	1	5
Neoplasm malignant	0	0	8	53	8	53
Neoplasm skin	0	1	0	0	0	1
Oral neoplasm	0	0	0	1	0	1
Pancreatic carcinoma	0	0	0	1	0	1
Papilloma	0	15	0	0	0	15
Pharyngeal neoplasm	0	0	0	1	0	1
Prostate cancer	0	0	0	1	0	1
Rectal cancer	0	0	0	1	0	1
Recurrent cancer	0	0	0	1	0	1
Renal cancer	0	0	1	1	1	1
Skin papilloma	0	2	0	0	0	2
Small intestine carcinoma	0	0	0	1	0	1
Testis cancer	0	0	0	1	0	1
Throat cancer	0	0	2	5	2	5
Thyroid cancer	0	0	0	2	0	2
Tongue neoplasm	2	4	0	1	2	5
Tongue neoplasm malignant stage unspecified	0	0	1	2	1	2
Tonsillar neoplasm	1	1	0	0	1	1
<b>Nervous system disorders</b>	<b>6050</b>	<b>38381</b>	<b>75</b>	<b>498</b>	<b>6125</b>	<b>38879</b>
Ageusia	30	132	0	1	30	133
Akathisia	0	1	0	0	0	1
Altered state of consciousness	0	1	0	2	0	3
Amnesia	1	10	0	0	1	10

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(b) (4)

MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Anosmia	15	61	0	0	15	61
Aphasia	3	16	0	0	3	16
Ataxia	0	1	0	0	0	1
Autonomic nervous system imbalance	0	7	0	3	0	10
Balance disorder	6	36	0	1	6	37
Bradykinesia	2	4	0	0	2	4
Brain fog	8	45	0	0	8	45
Brain hypoxia	0	0	1	1	1	1
Brain stem infarction	0	0	0	1	0	1
Burning sensation	844	2480	0	2	844	2482
Burning sensation mucosal	2	33	0	0	2	33
Carotid artery stenosis	0	0	0	1	0	1
Cerebral cyst	1	1	0	0	1	1
Cerebral disorder	1	8	0	0	1	8
Cerebral haemorrhage	0	0	1	4	1	4
Cerebral hypoperfusion	0	0	0	1	0	1
Cerebral infarction	0	0	1	6	1	6
Cerebral microinfarction	0	0	0	1	0	1
Cerebral thrombosis	0	0	1	1	1	1
Cerebral vasoconstriction	0	0	0	2	0	2
Cerebrovascular accident	0	0	7	32	7	32
Cerebrovascular disorder	0	1	0	1	0	2
Cervicogenic headache	0	1	0	0	0	1
Circadian rhythm sleep disorder	0	1	0	0	0	1
Clumsiness	0	1	0	0	0	1
Cluster headache	1	5	0	0	1	5
Cognitive disorder	0	2	0	0	0	2
Cold-stimulus headache	0	1	0	0	0	1
Coma	0	0	0	2	0	2
Coordination abnormal	1	10	1	1	2	11
Depressed level of consciousness	0	1	2	11	2	12
Disturbance in attention	8	49	1	1	9	50
Dizziness	1430	10299	8	48	1438	10347
Dizziness exertional	0	1	0	0	0	1
Dizziness postural	1	17	0	0	1	17
Dreamy state	0	2	0	0	0	2
Drizzling	6	23	1	3	7	26
Dysarthria	2	14	0	1	2	15
Dysgeusia	184	1462	0	0	184	1462
Dysgraphia	0	1	0	0	0	1
Dyskinesia	0	3	0	0	0	3
Dyslalia	1	1	0	0	1	1
Dysstasia	3	23	0	1	3	24

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Dystonia	0	0	2	3	2	3
Electric shock sensation	3	45	0	1	3	46
Epilepsy	0	1	5	19	5	20
Exaggerated startle response	0	1	0	0	0	1
Facial paralysis	0	0	1	5	1	5
Facial paresis	0	1	0	0	0	1
Facial spasm	0	5	0	0	0	5
Formication	0	4	0	0	0	4
Freezing phenomenon	0	1	0	0	0	1
Glossopharyngeal neuralgia	0	1	0	0	0	1
Haemorrhage intracranial	0	0	0	1	0	1
Hand-eye coordination impaired	0	1	0	0	0	1
Head discomfort	46	379	0	2	46	381
Head titubation	0	2	0	0	0	2
Headache	3096	20392	8	50	3104	20442
Hemihypoesthesia	0	0	0	1	0	1
Hemiplegia	0	0	0	2	0	2
Hyperaesthesia	0	6	0	0	0	6
Hypersomnia	6	11	0	0	6	11
Hypertonia	0	1	0	0	0	1
Hypoaesthesia	54	368	0	7	54	375
Hypogeusia	0	13	0	0	0	13
Hypokinesia	2	8	0	0	2	8
Hyporeflexia	0	1	0	0	0	1
Hyposmia	0	13	0	0	0	13
Hypotonia	3	6	0	0	3	6
Infant irritability	0	1	0	0	0	1
Intracranial hypotension	1	1	0	0	1	1
Intracranial pressure increased	0	0	2	12	2	12
Judgement impaired	0	1	0	0	0	1
Lethargy	14	76	0	2	14	78
Loss of consciousness	0	3	11	106	11	109
Memory impairment	1	19	1	2	2	21
Meningeal disorder	0	1	0	0	0	1
Mental impairment	0	2	0	6	0	8
Migraine	64	418	0	3	64	421
Migraine with aura	0	1	0	0	0	1
Monoplegia	0	0	0	2	0	2
Motor dysfunction	0	3	0	0	0	3
Movement disorder	2	9	0	0	2	9
Myoclonus	0	1	0	0	0	1
Nervous system disorder	6	23	0	0	6	23
Neuralgia	1	11	0	1	1	12
Neuritis	1	1	0	0	1	1

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(b) (4)

MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Neurological symptom	0	1	0	0	0	1
Neurotoxicity	0	0	0	1	0	1
Nystagmus	0	1	0	0	0	1
Occipital neuralgia	0	1	0	0	0	1
Paraesthesia	29	243	0	2	29	245
Paraesthesia mucosal	0	1	0	0	0	1
Paraparesis	0	0	0	5	0	5
Parosmia	6	109	0	0	6	109
Patient elopement	1	3	0	1	1	4
Post-traumatic epilepsy	0	1	0	0	0	1
Presyncope	20	118	0	0	20	118
Pseudostroke	0	0	1	1	1	1
Psychomotor hyperactivity	0	2	0	0	0	2
Reflexes abnormal	2	5	0	0	2	5
Sedation	0	2	0	0	0	2
Seizure	0	2	6	18	6	20
Seizure like phenomena	0	0	1	1	1	1
Sensory disturbance	1	20	0	0	1	20
Sensory loss	1	9	0	0	1	9
Sensory processing disorder	0	1	0	0	0	1
Sinus headache	1	5	0	0	1	5
Sleep deficit	1	6	0	0	1	6
Slow speech	1	2	0	0	1	2
Somnolence	39	232	0	1	39	233
Speech disorder	6	53	0	2	6	55
Speech disorder developmental	0	1	0	0	0	1
Stupor	0	1	0	0	0	1
Syncope	0	22	11	100	11	122
Taste disorder	47	613	0	0	47	613
Tension headache	2	30	0	0	2	30
Thermohypoaesthesia	0	2	0	0	0	2
Tongue biting	3	3	0	0	3	3
Tongue paralysis	0	0	1	5	1	5
Transient ischaemic attack	0	0	1	5	1	5
Tremor	39	299	0	2	39	301
Unresponsive to stimuli	0	0	0	1	0	1
Uvular spasm	0	1	0	0	0	1
Vestibular migraine	1	1	0	0	1	1
Vibratory sense increased	0	1	0	0	0	1
Visual perseveration	0	1	0	0	0	1
Visuospatial deficit	0	1	0	0	0	1
Vocal cord paralysis	0	3	0	0	0	3
<b>Pregnancy, puerperium and perinatal conditions</b>	<b>17</b>	<b>38</b>	<b>7</b>	<b>13</b>	<b>24</b>	<b>51</b>

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(b) (4)

MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Abortion of ectopic pregnancy	0	0	0	1	0	1
Abortion spontaneous	0	0	3	6	3	6
Ectopic pregnancy	0	0	0	1	0	1
Foetal growth restriction	0	0	1	1	1	1
Gestational diabetes	0	0	1	1	1	1
Imminent abortion	0	0	0	1	0	1
Increased foetal movements	1	1	0	0	1	1
Live birth	0	1	0	0	0	1
Morning sickness	3	15	0	0	3	15
Normal newborn	0	1	0	0	0	1
Placenta praevia	0	0	1	1	1	1
Pre-eclampsia	1	2	0	0	1	2
Pregnancy	12	15	0	0	12	15
Somatic symptom disorder of pregnancy	0	1	0	0	0	1
Stillbirth	0	0	1	1	1	1
Umbilical cord around neck	0	1	0	0	0	1
Unintended pregnancy	0	1	0	0	0	1
<b>Product issues</b>	<b>1122</b>	<b>25308</b>	<b>1</b>	<b>5</b>	<b>1123</b>	<b>25313</b>
Device battery explosion	0	2	0	0	0	2
Device breakage	18	192	1	3	19	195
Device catching fire	12	53	0	0	12	53
Device colour issue	0	8	0	0	0	8
Device connection issue	0	1	0	0	0	1
Device defective	1	30	0	0	1	30
Device delivery system issue	0	5	0	0	0	5
Device deposit issue	0	2	0	0	0	2
Device electrical finding	0	9	0	0	0	9
Device failure	0	5	0	0	0	5
Device inappropriate shock delivery	0	1	0	0	0	1
Device ineffective	0	1	0	0	0	1
Device issue	44	1221	0	0	44	1221
Device leakage	4	70	0	0	4	70
Device malfunction	36	1332	0	1	36	1333
Device material issue	0	1	0	0	0	1
Device occlusion	0	2	0	0	0	2
Device pacing issue	0	1	0	0	0	1
Device physical property issue	495	12129	0	1	495	12130
Device power source issue	0	17	0	0	0	17
Device temperature issue	2	30	0	0	2	30
Manufacturing issue	0	1	0	0	0	1
Manufacturing production issue	0	1	0	0	0	1
Out of specification test results	0	1	0	0	0	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Physical product label issue	0	2	0	0	0	2
Product adhesion issue	0	1	0	0	0	1
Product after taste	0	5	0	0	0	5
Product availability issue	0	1	0	0	0	1
Product caught fire	1	28	0	0	1	28
Product coating issue	0	1	0	0	0	1
Product colour issue	0	10	0	0	0	10
Product complaint	5	2521	0	0	5	2521
Product contamination	0	1	0	0	0	1
Product deposit	0	3	0	0	0	3
Product distribution issue	0	1	0	0	0	1
Product label issue	1	2	0	0	1	2
Product leakage	1	3	0	0	1	3
Product odour abnormal	116	1119	0	0	116	1119
Product physical consistency issue	0	15	0	0	0	15
Product physical issue	154	4198	0	0	154	4198
Product quality issue	12	739	0	0	12	739
Product size issue	0	2	0	0	0	2
Product substitution issue	0	3	0	0	0	3
Product taste abnormal	220	1530	0	0	220	1530
Suspected counterfeit product	0	1	0	0	0	1
Suspected product quality issue	0	5	0	0	0	5
Undersensing	0	2	0	0	0	2
<b>Psychiatric disorders</b>	<b>503</b>	<b>2643</b>	<b>4</b>	<b>36</b>	<b>507</b>	<b>2679</b>
Abnormal behaviour	1	1	0	0	1	1
Abnormal dreams	0	3	0	0	0	3
Adjustment disorder	0	1	0	0	0	1
Adjustment disorder with depressed mood	0	1	0	0	0	1
Affect lability	1	3	0	0	1	3
Affective disorder	1	9	0	0	1	9
Aggression	0	6	0	0	0	6
Agitation	16	68	0	1	16	69
Anger	4	12	0	1	4	13
Anhedonia	0	2	0	0	0	2
Anxiety	117	421	0	1	117	422
Anxiety disorder	0	3	0	0	0	3
Apathy	2	18	0	0	2	18
Attention deficit hyperactivity disorder	0	1	0	0	0	1
Aversion	0	8	0	0	0	8
Behaviour disorder	1	1	0	0	1	1
Behavioural addiction	0	1	0	0	0	1
Bipolar disorder	0	0	0	1	0	1
Bradyphrenia	0	2	0	0	0	2

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Breath holding	1	2	0	0	1	2
Breathing-related sleep disorder	0	1	0	0	0	1
Bruxism	0	5	0	0	0	5
Completed suicide	0	0	0	1	0	1
Confusional state	3	43	0	0	3	43
Daydreaming	0	8	0	0	0	8
Decreased eye contact	0	1	0	1	0	2
Decreased interest	1	3	0	0	1	3
Dependence	0	12	0	1	0	13
Depressed mood	8	49	0	0	8	49
Depression	6	37	0	0	6	37
Depressive symptom	0	1	0	0	0	1
Derealisation	1	1	0	0	1	1
Disinhibition	0	1	0	0	0	1
Disorientation	6	32	0	0	6	32
Dissociation	1	1	0	0	1	1
Distractibility	1	4	0	0	1	4
Drug dependence	0	1	0	0	0	1
Dysphemia	0	2	0	0	0	2
Dysphoria	0	10	0	0	0	10
Eating disorder	1	22	0	0	1	22
Emotional disorder	0	1	0	0	0	1
Emotional distress	2	11	0	0	2	11
Emotional poverty	0	3	0	0	0	3
Euphoric mood	0	19	0	0	0	19
Factitious disorder	0	1	0	0	0	1
Fear	1	40	0	0	1	40
Fear of death	4	10	0	1	4	11
Feeling guilty	0	2	0	0	0	2
Feeling of despair	0	1	0	0	0	1
Feelings of worthlessness	0	1	0	0	0	1
Frustration tolerance decreased	1	5	0	0	1	5
Hallucination	0	2	1	7	1	9
Hallucination, auditory	0	1	1	2	1	3
Hallucination, visual	0	0	0	1	0	1
Illness anxiety disorder	1	2	0	0	1	2
Impatience	0	1	0	0	0	1
Imperception	1	1	0	0	1	1
Inappropriate affect	2	4	0	0	2	4
Indifference	0	1	0	0	0	1
Initial insomnia	1	17	0	0	1	17
Insomnia	60	416	1	3	61	419
Intentional self-injury	0	0	0	1	0	1
Irritability	40	293	0	1	40	294

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Laziness	1	8	0	0	1	8
Libido decreased	1	8	0	0	1	8
Listless	0	12	0	1	0	13
Loss of libido	0	1	0	0	0	1
Mental disorder	2	15	0	1	2	16
Mental fatigue	0	2	0	0	0	2
Mental status changes	0	5	0	0	0	5
Middle insomnia	2	9	0	0	2	9
Mood altered	32	118	1	2	33	120
Mood swings	2	7	0	0	2	7
Morbid thoughts	1	5	0	0	1	5
Morose	0	1	0	0	0	1
Nervousness	7	90	0	0	7	90
Neurosis	0	2	0	0	0	2
Nicotine dependence	98	295	0	0	98	295
Nightmare	0	7	0	0	0	7
Obsessive-compulsive disorder	0	1	0	0	0	1
Panic attack	26	142	0	3	26	145
Panic disorder	0	9	0	1	0	10
Panic reaction	2	19	0	0	2	19
Paranoia	0	2	0	0	0	2
Personality change	0	1	0	0	0	1
Poor quality sleep	0	25	0	1	0	26
Premature ejaculation	1	2	0	0	1	2
Psychotic disorder	0	2	0	0	0	2
Purging	1	1	0	0	1	1
Restlessness	2	18	0	0	2	18
Self esteem decreased	0	1	0	0	0	1
Sleep disorder	13	68	0	1	13	69
Sleep disorder due to general medical condition, insomnia type	0	1	0	0	0	1
Speech sound disorder	0	1	0	0	0	1
Stress	20	74	0	0	20	74
Suicidal ideation	0	0	0	2	0	2
Suicide attempt	0	0	0	1	0	1
Tearfulness	0	2	0	0	0	2
Tension	4	29	0	0	4	29
Terminal insomnia	0	1	0	0	0	1
Thinking abnormal	2	7	0	0	2	7
Thought blocking	0	1	0	0	0	1
Tic	0	2	0	0	0	2
Tobacco abuse	1	15	0	0	1	15
Tobacco withdrawal symptoms	0	5	0	0	0	5
<b>Renal and urinary disorders</b>	<b>15</b>	<b>114</b>	<b>2</b>	<b>11</b>	<b>17</b>	<b>125</b>

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Bladder irritation	0	1	0	0	0	1
Bladder leukoplakia	0	0	0	1	0	1
Calculus urinary	0	0	0	1	0	1
Chromaturia	0	8	0	0	0	8
Dysuria	1	10	0	0	1	10
Haematuria	0	1	0	0	0	1
Incontinence	0	1	0	0	0	1
Micturition disorder	0	3	0	0	0	3
Micturition urgency	1	2	0	1	1	3
Nephritis	0	0	2	2	2	2
Nephrolithiasis	0	0	0	1	0	1
Nocturia	1	1	0	0	1	1
Pollakiuria	0	7	0	0	0	7
Polyuria	0	2	0	0	0	2
Renal disorder	1	9	0	0	1	9
Renal failure	0	0	0	1	0	1
Renal pain	4	44	0	1	4	45
Urinary incontinence	2	3	0	1	2	4
Urinary retention	0	0	0	2	0	2
Urinary tract discomfort	0	2	0	0	0	2
Urinary tract disorder	1	1	0	0	1	1
Urine odour abnormal	4	19	0	0	4	19
<b>Reproductive system and breast disorders</b>	<b>15</b>	<b>79</b>	<b>5</b>	<b>44</b>	<b>20</b>	<b>123</b>
Adnexa uteri pain	0	1	0	0	0	1
Breast discomfort	1	2	0	0	1	2
Breast enlargement	0	1	0	0	0	1
Breast fibrosis	1	1	0	0	1	1
Breast inflammation	0	1	0	0	0	1
Breast pain	2	14	0	0	2	14
Breast tenderness	0	2	0	0	0	2
Cervical friability	0	1	0	0	0	1
Dysmenorrhoea	0	1	0	0	0	1
Erectile dysfunction	0	5	5	43	5	48
Erection increased	0	1	0	0	0	1
Female reproductive tract disorder	1	1	0	0	1	1
Genital discomfort	0	1	0	0	0	1
Genital disorder	0	1	0	0	0	1
Genital paraesthesia	1	1	0	0	1	1
Gynaecomastia	1	1	0	0	1	1
Heavy menstrual bleeding	2	4	0	0	2	4
Lactation insufficiency	0	1	0	0	0	1
Menometrorrhagia	0	1	0	0	0	1
Menstrual disorder	0	4	0	0	0	4
Menstruation delayed	1	3	0	0	1	3

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Menstruation irregular	2	4	0	0	2	4
Nipple swelling	0	1	0	0	0	1
Oligomenorrhoea	0	2	0	0	0	2
Organic erectile dysfunction	0	1	0	0	0	1
Pelvic pain	0	2	0	0	0	2
Penile discharge	0	1	0	0	0	1
Prostatic disorder	1	2	0	0	1	2
Prostatitis	0	1	0	0	0	1
Sexual dysfunction	2	12	0	0	2	12
Spontaneous penile erection	0	1	0	0	0	1
Testicular swelling	0	1	0	0	0	1
Uterine disorder	0	1	0	0	0	1
Uterine haemorrhage	0	0	0	1	0	1
Uterine polyp	0	1	0	0	0	1
Vaginal flatulence	0	1	0	0	0	1
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>22726</b>	<b>106635</b>	<b>110</b>	<b>779</b>	<b>22836</b>	<b>107414</b>
Adductor vocal cord weakness	1	1	0	0	1	1
Adenoidal hypertrophy	0	1	0	0	0	1
Allergic bronchitis	0	1	0	0	0	1
Allergic cough	2	56	0	0	2	56
Allergic respiratory disease	0	1	0	0	0	1
Allergic respiratory symptom	1	1	0	0	1	1
Allergic sinusitis	1	3	0	0	1	3
Alveolar proteinosis	0	0	0	1	0	1
Alveolitis	0	1	0	0	0	1
Anoxia	0	0	0	1	0	1
Aphonia	94	558	0	3	94	561
Apnoea	0	0	2	9	2	9
Apnoeic attack	0	0	0	1	0	1
Asphyxia	0	2	0	21	0	23
Aspiration	0	0	0	1	0	1
Asthma	119	688	3	28	122	716
Asthmatic crisis	0	0	0	2	0	2
Bronchial disorder	16	121	0	2	16	123
Bronchial hyperreactivity	0	3	0	0	0	3
Bronchial irritation	5	52	0	0	5	52
Bronchial obstruction	0	0	0	1	0	1
Bronchial oedema	0	1	0	3	0	4
Bronchial secretion retention	0	4	0	0	0	4
Bronchial varices	0	1	0	0	0	1
Bronchiectasis	0	0	0	1	0	1
Bronchitis chronic	3	18	0	1	3	19
Bronchospasm	9	73	0	4	9	77
Bronchostenosis	0	0	0	1	0	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Catarrh	22	83	0	0	22	83
Childhood asthma	0	1	0	0	0	1
Choking	0	17	0	19	0	36
Choking sensation	942	3468	1	5	943	3473
Chronic obstructive pulmonary disease	2	22	1	3	3	25
Chronic respiratory disease	1	3	0	0	1	3
Cough	7948	34158	19	78	7967	34236
Cough decreased	0	7	0	0	0	7
Cough variant asthma	0	6	0	0	0	6
Cystic lung disease	0	1	0	0	0	1
Decreased bronchial secretion	0	1	0	0	0	1
Diaphragmalgia	1	9	0	0	1	9
Diaphragmatic disorder	1	6	0	0	1	6
Dry throat	1381	6164	1	4	1382	6168
Dysphonia	284	1495	0	4	284	1499
Dyspnoea	1699	9493	17	108	1716	9601
Dyspnoea at rest	0	1	0	1	0	2
Dyspnoea exertional	0	35	0	0	0	35
Ear, nose and throat disorder	0	2	0	0	0	2
Emphysema	1	14	5	8	6	22
Eosinophilic pneumonia acute	0	0	0	4	0	4
Epiglottic cyst	0	1	0	0	0	1
Epistaxis	67	733	0	7	67	740
Haemoptysis	33	270	0	5	33	275
Hiccups	39	307	0	1	39	308
Hyperactive pharyngeal reflex	0	5	0	0	0	5
Hyperventilation	0	9	0	0	0	9
Hypopnoea	5	26	0	0	5	26
Hypoxia	0	0	2	9	2	9
Increased bronchial secretion	0	5	0	0	0	5
Increased upper airway secretion	14	62	0	0	14	62
Increased viscosity of bronchial secretion	0	8	0	0	0	8
Increased viscosity of upper respiratory secretion	1	9	0	0	1	9
Interstitial lung disease	0	0	1	2	1	2
Irregular breathing	1	7	0	0	1	7
Laryngeal discomfort	1	50	0	0	1	50
Laryngeal disorder	1	12	0	0	1	12
Laryngeal inflammation	1	12	0	0	1	12
Laryngeal obstruction	0	0	0	1	0	1
Laryngeal oedema	0	4	0	28	0	32
Laryngeal pain	10	75	0	0	10	75

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Laryngeal ulceration	0	1	0	0	0	1
Laryngitis allergic	0	1	0	0	0	1
Laryngospasm	0	12	0	0	0	12
Larynx irritation	7	27	0	1	7	28
Lower respiratory tract congestion	17	32	0	0	17	32
Lower respiratory tract inflammation	0	1	0	0	0	1
Lung disorder	119	760	2	16	121	776
Lung hyperinflation	0	1	0	0	0	1
Lung infiltration	1	3	0	0	1	3
Mouth breathing	0	2	0	0	0	2
Nasal congestion	92	740	0	1	92	741
Nasal crusting	0	13	0	0	0	13
Nasal cyst	0	1	0	0	0	1
Nasal discharge discolouration	0	5	0	0	0	5
Nasal discomfort	29	126	0	0	29	126
Nasal disorder	3	15	0	0	3	15
Nasal dryness	42	283	0	0	42	283
Nasal inflammation	6	32	0	0	6	32
Nasal mucosal blistering	0	1	0	0	0	1
Nasal mucosal discolouration	0	2	0	0	0	2
Nasal mucosal disorder	0	9	0	0	0	9
Nasal mucosal ulcer	0	2	0	0	0	2
Nasal obstruction	0	6	0	0	0	6
Nasal odour	0	1	0	0	0	1
Nasal oedema	0	18	0	0	0	18
Nasal polyps	1	5	0	0	1	5
Nasal pruritus	2	27	0	0	2	27
Nasal septum disorder	0	1	0	0	0	1
Nasal ulcer	0	4	0	0	0	4
Nocturnal dyspnoea	0	8	0	0	0	8
Obstructive airways disorder	5	32	0	1	5	33
Oropharyngeal blistering	0	3	1	32	1	35
Oropharyngeal discolouration	0	6	0	0	0	6
Oropharyngeal discomfort	698	2679	1	3	699	2682
Oropharyngeal pain	2943	17234	2	31	2945	17265
Oropharyngeal plaque	8	19	0	0	8	19
Oropharyngeal scar	0	1	0	0	0	1
Oropharyngeal spasm	4	23	0	1	4	24
Oropharyngeal swelling	1	6	0	0	1	6
Painful respiration	11	50	0	0	11	50
Paranasal sinus discomfort	1	3	0	0	1	3
Paranasal sinus hypersecretion	1	1	0	0	1	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Paranasal sinus hyposecretion	0	4	0	0	0	4
Paranasal sinus inflammation	0	5	0	0	0	5
Pharyngeal cyst	0	2	0	0	0	2
Pharyngeal disorder	4	77	0	1	4	78
Pharyngeal enanthema	0	2	0	0	0	2
Pharyngeal erythema	18	88	0	1	18	89
Pharyngeal exudate	0	2	0	1	0	3
Pharyngeal haemorrhage	0	0	5	82	5	82
Pharyngeal hypoaesthesia	7	33	0	0	7	33
Pharyngeal inflammation	16	141	0	3	16	144
Pharyngeal lesion	0	1	0	0	0	1
Pharyngeal mass	0	14	0	0	0	14
Pharyngeal oedema	1	18	0	0	1	18
Pharyngeal paraesthesia	39	131	0	1	39	132
Pharyngeal swelling	129	969	0	5	129	974
Pharyngeal ulceration	6	18	0	0	6	18
Pleural effusion	2	8	0	1	2	9
Pleural thickening	0	1	0	0	0	1
Pleurisy	0	1	0	1	0	2
Pleuritic pain	0	3	0	0	0	3
Pneumonitis	4	19	3	7	7	26
Pneumothorax	0	0	5	14	5	14
Pneumothorax spontaneous	0	0	1	3	1	3
Productive cough	545	2803	3	7	548	2810
Pulmonary calcification	0	3	0	0	0	3
Pulmonary congestion	0	8	1	17	1	25
Pulmonary embolism	0	0	0	5	0	5
Pulmonary fibrosis	0	0	4	7	4	7
Pulmonary haemorrhage	0	0	0	3	0	3
Pulmonary hypertension	0	0	1	1	1	1
Pulmonary infarction	0	0	0	1	0	1
Pulmonary mass	3	8	0	0	3	8
Pulmonary oedema	0	1	7	47	7	48
Pulmonary pain	338	2027	2	10	340	2037
Pulmonary sarcoidosis	0	0	0	2	0	2
Rales	2	14	0	1	2	15
Reflux laryngitis	3	5	0	0	3	5
Respiration abnormal	7	39	0	1	7	40
Respiratory acidosis	1	1	0	0	1	1
Respiratory arrest	0	0	0	2	0	2
Respiratory depression	0	0	0	1	0	1
Respiratory disorder	41	184	1	4	42	188
Respiratory disorder neonatal	0	1	0	0	0	1
Respiratory distress	0	1	0	4	0	5
Respiratory failure	0	0	5	17	5	17

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Respiratory fatigue	2	4	0	0	2	4
Respiratory muscle weakness	0	1	0	0	0	1
Respiratory paralysis	0	0	1	1	1	1
Respiratory symptom	0	2	0	0	0	2
Respiratory tract congestion	33	176	0	1	33	177
Respiratory tract inflammation	9	21	1	1	10	22
Respiratory tract irritation	27	235	0	1	27	236
Respiratory tract oedema	0	1	0	6	0	7
Respiratory tract ulceration	0	0	1	1	1	1
Rhinalgia	17	107	1	1	18	108
Rhinitis allergic	9	33	0	0	9	33
Rhinitis atrophic	0	1	0	0	0	1
Rhinorrhoea	55	493	1	6	56	499
Rhonchi	0	4	0	0	0	4
Sinonasal obstruction	1	1	1	1	2	2
Sinus congestion	4	19	0	0	4	19
Sinus disorder	10	36	0	0	10	36
Sinus pain	5	13	0	0	5	13
Sleep apnoea syndrome	4	6	0	0	4	6
Sneezing	40	310	0	2	40	312
Snoring	5	37	0	0	5	37
Sputum discoloured	20	148	1	1	21	149
Sputum increased	2	21	0	0	2	21
Sputum retention	0	14	0	0	0	14
Stridor	0	2	0	0	0	2
Suffocation feeling	392	1451	2	10	394	1461
Tachypnoea	0	2	0	0	0	2
Throat clearing	32	115	0	0	32	115
Throat irritation	3979	15026	2	23	3981	15049
Throat lesion	2	16	0	1	2	17
Throat tightness	83	461	0	1	83	462
Tonsillar cyst	0	2	0	1	0	3
Tonsillar disorder	6	51	0	0	6	51
Tonsillar erythema	2	7	0	0	2	7
Tonsillar exudate	0	4	0	0	0	4
Tonsillar haemorrhage	0	1	1	2	1	3
Tonsillar hypertrophy	26	174	0	0	26	174
Tonsillar inflammation	16	69	0	1	16	70
Tonsillar ulcer	0	4	0	0	0	4
Tonsillolith	2	5	0	0	2	5
Tracheal disorder	3	12	0	0	3	12
Tracheal inflammation	1	9	0	0	1	9
Tracheal oedema	0	0	1	4	1	4
Tracheal pain	2	34	0	0	2	34
Upper airway obstruction	0	0	0	1	0	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Upper respiratory tract congestion	25	110	1	1	26	111
Upper respiratory tract inflammation	3	14	0	2	3	16
Upper respiratory tract irritation	3	18	0	0	3	18
Upper-airway cough syndrome	2	5	0	0	2	5
Vasomotor rhinitis	1	2	0	0	1	2
Vocal cord atrophy	0	1	0	0	0	1
Vocal cord disorder	6	82	0	2	6	84
Vocal cord dysfunction	1	5	0	0	1	5
Vocal cord inflammation	5	21	0	0	5	21
Vocal cord polyp	0	2	0	0	0	2
Vocal cord thickening	0	5	0	1	0	6
Wheezing	26	234	0	4	26	238
Yawning	2	13	0	0	2	13
<b>Skin and subcutaneous tissue disorders</b>	<b>859</b>	<b>9151</b>	<b>7</b>	<b>135</b>	<b>866</b>	<b>9286</b>
Acne	55	682	0	4	55	686
Acne cystic	0	1	0	0	0	1
Acne varioliformis	0	1	0	0	0	1
Alopecia	11	59	0	1	11	60
Angioedema	0	0	5	55	5	55
Blister	55	662	0	3	55	665
Blister rupture	0	7	0	0	0	7
Blood blister	0	6	0	0	0	6
Cellulite	1	1	0	0	1	1
Circumoral oedema	0	1	0	0	0	1
Cold sweat	11	80	0	0	11	80
Cold urticaria	1	2	0	0	1	2
Dandruff	0	13	0	0	0	13
Decubitus ulcer	0	1	0	0	0	1
Dermal cyst	0	2	0	0	0	2
Dermatitis	7	79	0	0	7	79
Dermatitis acneiform	0	8	0	0	0	8
Dermatitis allergic	15	80	0	0	15	80
Dermatitis atopic	5	32	0	0	5	32
Dermatitis bullous	0	0	0	1	0	1
Dermatitis contact	2	11	0	0	2	11
Dilated pores	0	1	0	0	0	1
Dry skin	23	155	0	1	23	156
Dyshidrotic eczema	2	8	0	0	2	8
Eczema	17	75	0	0	17	75
Erythema	49	582	0	2	49	584
Erythema nodosum	0	1	0	1	0	2
Fingerprint loss	0	1	0	0	0	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Haemorrhage subcutaneous	0	0	0	2	0	2
Hair colour changes	0	3	0	0	0	3
Hair disorder	0	3	0	0	0	3
Hair texture abnormal	0	2	0	0	0	2
Hand dermatitis	2	3	0	0	2	3
Hidradenitis	0	1	0	0	0	1
Hyperhidrosis	41	261	0	1	41	262
Hyperkeratosis	0	6	0	0	0	6
Keratosis pilaris	0	1	0	0	0	1
Leukoplakia	2	5	0	0	2	5
Lichen planus	0	0	0	1	0	1
Lichenification	0	1	0	0	0	1
Lipoatrophy	1	1	0	0	1	1
Livedo reticularis	0	1	0	0	0	1
Madarosis	0	3	0	0	0	3
Mechanical urticaria	0	1	0	0	0	1
Melanos	0	1	0	0	0	1
Miliaria	2	4	0	0	2	4
Nail bed bleeding	0	1	0	0	0	1
Nail bed inflammation	0	1	0	0	0	1
Nail discolouration	1	4	0	0	1	4
Nail disorder	0	3	0	0	0	3
Nail hypertrophy	0	1	0	0	0	1
Neurodermatitis	0	1	0	0	0	1
Night sweats	1	2	0	0	1	2
Occupational dermatitis	0	1	0	0	0	1
Oedema blister	0	1	0	0	0	1
Onychoclasia	2	7	0	0	2	7
Onycholysis	0	1	0	0	0	1
Pain of skin	1	19	0	0	1	19
Palmar erythema	0	3	0	0	0	3
Palmoplantar pustulosis	1	3	0	0	1	3
Papule	0	3	0	0	0	3
Perioral dermatitis	0	5	0	0	0	5
Petechiae	0	2	0	0	0	2
Photosensitivity reaction	1	3	0	0	1	3
Pigmentation disorder	2	16	0	1	2	17
Piloerection	1	3	0	0	1	3
Pityriasis rosea	0	1	0	0	0	1
Pruritus	151	1480	0	9	151	1489
Pruritus allergic	0	2	0	0	0	2
Psoriasis	4	29	0	1	4	30
Purpura	0	3	0	0	0	3
Rash	178	2390	2	29	180	2419
Rash erythematous	6	100	0	1	6	101

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Rash follicular	0	1	0	0	0	1
Rash macular	42	581	0	6	42	587
Rash papular	1	22	0	1	1	23
Rash pruritic	9	123	0	2	9	125
Rash vesicular	0	7	0	0	0	7
Rosacea	0	1	0	0	0	1
Scab	3	56	0	0	3	56
Scar pain	0	1	0	0	0	1
Sebaceous gland disorder	0	2	0	0	0	2
Sebaceous glands overactivity	0	2	0	0	0	2
Seborrhoea	0	8	0	0	0	8
Seborrhoeic dermatitis	2	13	0	0	2	13
Sensitive skin	5	10	0	0	5	10
Skin atrophy	0	2	0	0	0	2
Skin burning sensation	5	46	0	1	5	47
Skin depigmentation	0	6	0	0	0	6
Skin discharge	1	1	0	0	1	1
Skin discolouration	7	76	0	1	7	77
Skin discomfort	1	6	0	0	1	6
Skin disorder	11	279	0	0	11	279
Skin exfoliation	8	182	0	1	8	183
Skin fissures	3	9	0	0	3	9
Skin haemorrhage	0	9	0	0	0	9
Skin hypertrophy	2	5	0	0	2	5
Skin induration	0	2	0	0	0	2
Skin irritation	13	104	0	1	13	105
Skin lesion	2	10	0	0	2	10
Skin mass	0	0	0	1	0	1
Skin necrosis	0	0	0	2	0	2
Skin odour abnormal	5	27	0	0	5	27
Skin plaque	0	1	0	0	0	1
Skin reaction	1	18	0	0	1	18
Skin striae	0	2	0	0	0	2
Skin swelling	2	18	0	0	2	18
Skin tightness	0	3	0	0	0	3
Skin ulcer	1	4	0	0	1	4
Skin weeping	0	5	0	0	0	5
Skin wrinkling	4	18	0	1	4	19
Solar lentigo	0	3	0	0	0	3
Spider naevus	0	1	0	0	0	1
Sticky skin	0	1	0	0	0	1
Telangiectasia	1	1	0	0	1	1
Urticaria	77	540	0	5	77	545
Urticaria chronic	0	1	0	0	0	1
Urticaria pressure	0	1	0	0	0	1

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Vascular skin disorder	1	1	0	0	1	1
Xeroderma	0	1	0	0	0	1
Yellow nail syndrome	0	1	0	0	0	1
Yellow skin	1	7	0	0	1	7
<b>Social circumstances</b>	<b>96</b>	<b>320</b>	<b>2</b>	<b>6</b>	<b>98</b>	<b>326</b>
Alcohol use	0	1	0	0	0	1
Bedridden	0	1	0	0	0	1
Breast feeding	5	6	0	0	5	6
Crime	0	1	0	0	0	1
Ex-tobacco user	1	6	0	0	1	6
Impaired driving ability	1	5	0	0	1	5
Impaired work ability	0	2	0	0	0	2
Life expectancy shortened	1	1	0	0	1	1
Loss of personal independence in daily activities	1	7	1	2	2	9
Multigravida	0	2	0	0	0	2
Non-tobacco user	1	5	0	0	1	5
Passive smoking	75	246	1	4	76	250
Patient dissatisfaction with device	0	1	0	0	0	1
Patient dissatisfaction with treatment	0	1	0	0	0	1
Patient uncooperative	0	1	0	0	0	1
Pollution	0	1	0	0	0	1
Primigravida	0	2	0	0	0	2
Substance use	1	1	0	0	1	1
Tobacco user	8	26	0	0	8	26
Unhealthy diet	0	1	0	0	0	1
Victim of child abuse	1	1	0	0	1	1
Water pollution	1	1	0	0	1	1
Wheelchair user	0	1	0	0	0	1
<b>Surgical and medical procedures</b>	<b>6</b>	<b>60</b>	<b>4</b>	<b>21</b>	<b>10</b>	<b>81</b>
Adenotonsillectomy	0	1	0	0	0	1
Bronchial anastomosis	1	1	0	0	1	1
Caesarean section	1	1	0	0	1	1
Cardiac operation	0	1	0	0	0	1
Cardioversion	0	2	0	0	0	2
Cholecystectomy	0	1	0	0	0	1
Dental disorder prophylaxis	0	1	0	0	0	1
Dental operation	0	1	0	0	0	1
Endodontic procedure	1	2	0	0	1	2
Gallbladder operation	0	1	0	0	0	1
Gastric operation	0	1	0	0	0	1
Gingival operation	0	1	0	0	0	1
Hospitalisation	1	2	3	12	4	14
Infusion	0	1	0	0	0	1

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Injection	0	1	0	0	0	1
Large intestine operation	0	0	0	1	0	1
Lung lobectomy	0	0	0	1	0	1
Lung operation	0	0	0	2	0	2
Lymphadenectomy	0	0	0	1	0	1
Mass excision	0	1	0	0	0	1
Mechanical ventilation	0	1	0	0	0	1
Nasal cavity packing	1	2	0	0	1	2
Nerve block	0	1	0	0	0	1
Oxygen therapy	0	1	0	0	0	1
Pancreatic operation	0	1	0	0	0	1
Pulmonary resection	0	0	1	1	1	1
Routine health maintenance	0	3	0	0	0	3
Salivary gland resection	0	0	0	1	0	1
Skin graft	0	2	0	0	0	2
Surgery	0	11	0	1	0	12
Therapy cessation	0	1	0	0	0	1
Thyroid operation	0	1	0	0	0	1
Tonsillectomy	0	0	0	1	0	1
Tooth extraction	1	12	0	0	1	12
Tooth restoration	0	1	0	0	0	1
Vocal cord operation	0	1	0	0	0	1
Wisdom teeth removal	0	2	0	0	0	2
Wound drainage	0	1	0	0	0	1
<b>Vascular disorders</b>	<b>372</b>	<b>1561</b>	<b>32</b>	<b>121</b>	<b>404</b>	<b>1682</b>
Aneurysm	0	1	0	2	0	3
Angiopathy	6	32	0	0	6	32
Aortic aneurysm	0	1	0	0	0	1
Arterial occlusive disease	0	0	0	1	0	1
Arterial rupture	0	0	0	1	0	1
Arterial spasm	0	1	0	0	0	1
Arteriosclerosis	3	4	0	0	3	4
Blood pressure fluctuation	7	74	0	2	7	76
Bloody discharge	0	5	0	0	0	5
Capillary disorder	1	3	0	0	1	3
Capillary fragility	0	3	0	0	0	3
Circulatory collapse	0	0	2	3	2	3
Cyanosis	0	12	0	0	0	12
Embolism	0	0	0	1	0	1
Flushing	2	48	0	2	2	50
Haematoma	1	4	0	0	1	4
Haemorrhage	1	3	6	28	7	31
Hot flush	5	35	0	0	5	35
Hyperaemia	1	3	0	0	1	3
Hypertension	272	867	6	20	278	887

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Hypertensive crisis	0	0	4	9	4	9
Hypotension	42	119	0	1	42	120
Infarction	0	0	1	8	1	8
Internal haemorrhage	0	0	0	2	0	2
Ischaemia	0	1	0	0	0	1
Jugular vein distension	0	1	0	0	0	1
Labile blood pressure	0	1	0	0	0	1
Lymphoedema	0	2	0	0	0	2
Orthostatic hypotension	0	1	0	0	0	1
Pallor	15	186	7	16	22	202
Peripheral artery occlusion	0	0	0	1	0	1
Peripheral coldness	8	30	0	0	8	30
Peripheral vascular disorder	0	17	0	1	0	18
Phlebitis	0	2	0	0	0	2
Poor peripheral circulation	1	4	0	0	1	4
Raynaud's phenomenon	1	3	0	0	1	3
Shock	0	1	1	2	1	3
Shock symptom	0	0	0	1	0	1
Superficial vein prominence	0	1	0	0	0	1
Thrombophlebitis	0	1	0	0	0	1
Thrombosis	0	0	4	16	4	16
Varicose vein	1	16	0	0	1	16
Vascular insufficiency	0	1	0	0	0	1
Vascular occlusion	0	8	0	1	0	9
Vascular pain	0	10	0	0	0	10
Vascular rupture	0	1	0	0	0	1
Vascular stenosis	0	3	0	0	0	3
Vasculitis	0	0	0	1	0	1
Vasoconstriction	2	34	1	1	3	35
Vasodilatation	1	4	0	0	1	4
Vasospasm	2	10	0	0	2	10
Vein disorder	0	4	0	0	0	4
Vein rupture	0	1	0	1	0	2
Venous occlusion	0	2	0	0	0	2
Vessel perforation	0	1	0	0	0	1
<b>Grand Total</b>	<b>53110</b>	<b>335835</b>	<b>834</b>	<b>5776</b>	<b>53944</b>	<b>341611</b>

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### 18.3 Appendix 3: Tabular Summary of Safety Signals

Signal term	Date opened	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation & summary of key data	Method of signal evaluation	Action(s) taken or planned
Acne	Dec 2017	Closed	December 2018	Global Safety Database	Increased reporting rate	Qualitative and quantitative	Monitoring activities
Chest discomfort	Dec 2017	Closed	December 2018	Global Safety Database	Increased reporting rate	Qualitative and quantitative	Monitoring activities
Rash	Dec 2017	Closed	December 2018	Global Safety Database	Increased reporting rate	Qualitative and quantitative	Monitoring activities
Chest pain	May 2018	Closed	December 2018	Global Safety Database	Increased reporting rate	Qualitative and quantitative	Monitoring activities
Urticaria	May 2018	Closed	December 2018	Global Safety Database	Increased reporting rate	Qualitative and quantitative	Monitoring activities
Epistaxis	May 2018	Closed	October 2019	Global Safety Database	Increased reporting rate	Qualitative and quantitative	Monitoring activities
Bacterial pneumonia	August 2018	Closed	August 2018	Scientific Literature	Increased Pneumococcal adhesion to nasal epithelial cells exposed to <i>IQOS</i> extract	Qualitative and quantitative	Monitoring activities
Acute Eosinophilic Pneumonia	January 2019	Closed	December 2019	Scientific Literature	Case report of acute eosinophilic pneumonia in a 16-year-old Japanese man who started using	Qualitative and quantitative	Monitoring activities

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Signal term	Date opened	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation & summary of key data	Method of signal evaluation	Action(s) taken or planned
					heated tobacco product 2 weeks before admission to hospital.		

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## 18.4 Appendix 4: Listing of Interventional and Non-Interventional Studies during the Reporting period

Study Protocol Number	Study title	Country	Study start	Status
P1-AAA-02-JP	A controlled, open-label, 3-arm parallel group, multi-center study to evaluate the Abdominal Aortic Aneurysm (AAA) growth rate in adult smoking patients randomized to either cigarette smoking or IQOS use and to compare with the AAA growth rate in patients who had stopped smoking.	Japan	03-Oct-2018 The study duration for each patient will be up to 3 years and 1 month.	Closed on 06-Apr-2023
P1-REXC-10	A randomized, controlled, open-label, 4 parallel arms study to demonstrate reductions in exposure to selected harmful and potentially harmful constituents (HPHC) of cigarette (CIG) smoke in healthy smokers switching to different versions of Tobacco Heating System (THS) compared to continuing CIG smoking, for 5 days in confinement	United Kingdom	04-Nov-2022 The entire study duration per subject will be 12 to 39 days.	Closed on 04-Feb-2023
P1-PK-12	A single-center, randomized, controlled, open-label study in smoking healthy subjects to investigate the nicotine pharmacokinetic profiles following single use of Tobacco Heating System (THS) with a regular or a menthol stick, compared to smoking of a single combustible cigarette (CIG)	United Kingdom	16-Feb-2023 The entire study per subject will last up to 34 days.	Closed on 02-Apr-2023
P1-PMTA I4-07-US	Actual Use Study of THS 3.0 – P1-PMTA I4-07-US	U.S.	19-Jan-2023 The entire study per subject will last up to 6 weeks.	Closed on 10-Apr-2023
P1-COPD-04-INT	A 3-year, 3-group, preference, multi-center study to demonstrate the slowing of disease	Europe, U.S., and Asia	December 2022 The entire study duration per subject	Ongoing

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Study Protocol Number	Study title	Country	Study start	Status
	progression when switching from cigarette smoking to the Tobacco Heating System (THS) in mild to moderate Chronic Obstructive Pulmonary Disease (COPD) subjects with a history of chronic bronchitis symptom		will be maximum 39 months.	

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## 18.5 Appendix 5: Market Specific Appendices

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## 18.5.1 Appendix 5a: U.S. Appendix

### 18.5.1.1 Cumulative and interval Summary Tabulations of Serious and Non-Serious Adverse Reactions from U.S. Post-Marketing Experience

On 15-May-2017, PMI submitted 3 Pre-Market Tobacco Product Applications for the IQOS™ THS with 3 variants of *Marlboro HeatSticks*™. The Marketing Orders for 3 variants of *Marlboro HeatSticks* (PM0000424, PM0000425 and PM0000426) and for the IQOS System Holder and Charger 2.4 (PM0000479) were issued on 30-Apr-2019. On 07-Dec-2020, the Marketing Order was issued for the IQOS System Holder and Charger 3.0 (PM0000634).

The global safety database was searched for serious and non-serious AEs received from unsolicited sources in the U.S. during the reporting period from 01-Jan-2023 to 31-Dec-2023 and cumulatively from 30-Apr-2019 to 31-Dec-2023. The summary tabulation of identified AEs organized by MedDRA SOC is presented in [Table 18-1](#). Of note, none of the spontaneous reports received by PMI during the reporting period were medically confirmed, i.e., they were received from consumers directly and not via HCPs.

A total of 23 non-serious AEs was received from 13 ICSRs in the U.S. during the reporting period. The AEs reported more than once included: *No adverse event* (13.04%, n=3); *Accidental exposure to product* (8.70%, n=2); *Throat irritation* (8.70%, n=2); *Accidental exposure to product by child* (8.70%, n=2); and *Nicotine dependence* (8.70%, n=2). No SAEs were received from the U.S. during the period covered by this SUR. As mentioned in the SPI version 8.0 for THS, *Throat irritation*, is a known class effect AEs associated with the use of nicotine-containing products, and *Accidental exposure to product by child* is an important identified risk for THS.

The SOCs reported more than once included: *Injury, poisoning and procedural complications* (26.09%, n=6); *General disorders and administration site conditions* (21.74%, n=5); *Respiratory, thoracic and mediastinal disorders* (17.39%, n=4), *Psychiatric disorders* (8.70%, n=2); and *Nervous system disorders* (8.70%, n=2).

Cumulatively, there were 245 non-serious AEs received from 102 ICSRs in the U.S. Cumulatively, no SAEs were received from the U.S.

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**Table 18-1 Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Experiences from U.S. Post-Marketing Experience**

MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
<b>Cardiac disorders</b>	<b>1</b>	<b>3</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>3</b>
Palpitations	0	2	0	0	0	2
Tachycardia	1	1	0	0	1	1
<b>Ear and labyrinth disorders</b>	<b>1</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>2</b>
Vertigo	1	2	0	0	1	2
<b>Gastrointestinal disorders</b>	<b>1</b>	<b>36</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>36</b>
Abdominal discomfort	0	4	0	0	0	4
Abdominal distension	0	1	0	0	0	1
Abdominal pain upper	0	1	0	0	0	1
Breath odour	0	1	0	0	0	1
Chapped lips	0	1	0	0	0	1
Cheilitis	0	1	0	0	0	1
Coating in mouth	0	1	0	0	0	1
Diarrhoea	0	1	0	0	0	1
Dry mouth	0	1	0	0	0	1
Dyspepsia	0	2	0	0	0	2
Dysphagia	0	1	0	0	0	1
Gingival bleeding	0	1	0	0	0	1
Glossitis	0	1	0	0	0	1
Nausea	0	10	0	0	0	10
Oral discomfort	0	3	0	0	0	3
Paraesthesia oral	1	1	0	0	1	1
Retching	0	1	0	0	0	1
Stomatitis	0	1	0	0	0	1
Swollen tongue	0	1	0	0	0	1
Tongue disorder	0	1	0	0	0	1
Vomiting	0	1	0	0	0	1
<b>General disorders and administration site conditions</b>	<b>5</b>	<b>18</b>	<b>0</b>	<b>0</b>	<b>5</b>	<b>18</b>
Chest discomfort	0	1	0	0	0	1
Chest pain	1	4	0	0	1	4
Fatigue	0	1	0	0	0	1
Feeling abnormal	0	1	0	0	0	1
Malaise	1	1	0	0	1	1
No adverse event	3	8	0	0	3	8
Pain	0	2	0	0	0	2
<b>Hepatobiliary disorders</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>
Hepatic pain	0	1	0	0	0	1
<b>Immune system disorders</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>2</b>
Device allergy	0	1	0	0	0	1
Hypersensitivity	0	1	0	0	0	1
<b>Infections and infestations</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Pharyngitis streptococcal	0	1	0	0	0	1
<b>Injury, poisoning and procedural complications</b>	<b>6</b>	<b>34</b>	<b>0</b>	<b>0</b>	<b>6</b>	<b>34</b>
Accidental exposure to product	2	2	0	0	2	2
Accidental exposure to product by child	2	8	0	0	2	8
Burn oral cavity	0	2	0	0	0	2
Device difficult to use	0	4	0	0	0	4
Exposure during pregnancy	1	3	0	0	1	3
Intentional product misuse	0	1	0	0	0	1
Occupational exposure to product	0	5	0	0	0	5
Thermal burn	1	9	0	0	1	9
<b>Investigations</b>	<b>0</b>	<b>4</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>4</b>
Blood pressure increased	0	1	0	0	0	1
Heart rate increased	0	1	0	0	0	1
Hormone level abnormal	0	1	0	0	0	1
Transaminases increased	0	1	0	0	0	1
<b>Nervous system disorders</b>	<b>2</b>	<b>29</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>29</b>
Anosmia	0	1	0	0	0	1
Burning sensation	0	1	0	0	0	1
Dizziness	0	4	0	0	0	4
Dysgeusia	0	2	0	0	0	2
Head discomfort	0	1	0	0	0	1
Headache	1	16	0	0	1	16
Hypoaesthesia	1	1	0	0	1	1
Somnolence	0	1	0	0	0	1
Taste disorder	0	2	0	0	0	2
<b>Product issues</b>	<b>0</b>	<b>55</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>55</b>
Device breakage	0	2	0	0	0	2
Device issue	0	3	0	0	0	3
Device malfunction	0	3	0	0	0	3
Device physical property issue	0	12	0	0	0	12
Product complaint	0	12	0	0	0	12
Product distribution issue	0	1	0	0	0	1
Product odour abnormal	0	5	0	0	0	5
Product physical issue	0	7	0	0	0	7
Product quality issue	0	3	0	0	0	3
Product taste abnormal	0	7	0	0	0	7
<b>Psychiatric disorders</b>	<b>2</b>	<b>10</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>10</b>
Agitation	0	1	0	0	0	1
Anxiety	0	2	0	0	0	2
Confusional state	0	1	0	0	0	1
Irritability	0	1	0	0	0	1
Nicotine dependence	2	3	0	0	2	3

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MedDRA SOC MedDRA PT	Interval Non- serious	Cumulative Non- serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Panic attack	0	1	0	0	0	1
Sleep disorder	0	1	0	0	0	1
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>4</b>	<b>48</b>	<b>0</b>	<b>0</b>	<b>4</b>	<b>48</b>
Asthma	0	1	0	0	0	1
Cough	1	15	0	0	1	15
Dysphonia	0	1	0	0	0	1
Dyspnoea	0	4	0	0	0	4
Epistaxis	0	1	0	0	0	1
Haemoptysis	0	1	0	0	0	1
Nasal discomfort	0	1	0	0	0	1
Oropharyngeal discomfort	0	1	0	0	0	1
Oropharyngeal pain	0	11	0	0	0	11
Productive cough	1	1	0	0	1	1
Respiratory tract irritation	0	1	0	0	0	1
Sneezing	0	1	0	0	0	1
Snoring	0	1	0	0	0	1
Throat irritation	2	7	0	0	2	7
Throat tightness	0	1	0	0	0	1
<b>Social circumstances</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>1</b>
Passive smoking	1	1	0	0	1	1
<b>Vascular disorders</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>
Cyanosis	0	1	0	0	0	1
<b>Grand Total</b>	<b>23</b>	<b>245</b>	<b>0</b>	<b>0</b>	<b>23</b>	<b>245</b>

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## 18.6 Appendix 6: Signatures

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## Safety Update Report

Period Covered: 01-Jan-2023 to 31-Dec-2023

*Electrically Heated Tobacco Product (EHTP) and Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS)*

Justification	Name/Title	Signature	Date
Author	Kamila Kowa/ Senior Safety Lead	(b) (6)	24-Apr-2024
Review	Brindusa Taranu/ Manager Medical Operations		24-Apr-2024
Approval	Marina Suvakov/ Global Head Safety Surveillance		24-Apr-2024
Approval	Patrick Picavet/ Chief Medical Officer		24-Apr-2024

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# IQOS SUR2023\_v1.0\_23Apr2024\_US

Final Audit Report

2024-04-24

Created:	2024-04-24
By:	Kamila Kowa (b) (6) @pmi.com
Status:	Signed
Transaction ID:	CBJCHBCAABAAwhRD0WCrRwD_37i6KibxSPJ6qazRUzQs

## "IQOS SUR2023\_v1.0\_23Apr2024\_US" History

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