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-2022 to 31-Dec-2022
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-2022 to 31-Dec-2022 (Data Lock Point, DLP).

The THS uses a heat-not-burn technology that generates an aerosol from heating tobacco rather than burning it. The EHTP is commercialized under the brand name *Marlboro HeatSticks*™ or *HEETS*™, depending on the market, and is specifically designed to be used with the *IQOS*™ device. In August 2021, a new THS was launched under brand name of *IQOS ILUMA*™ with *TEREA*™ or *SENTIA*™ tobacco sticks.

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 worldwide for the THS, was 04-Nov-2014.

Up to the DLP of this SUR (31-Dec-2022), the THS had been marketed in 71 markets worldwide: Albania, Andorra, Armenia, Austria, Aruba, Bahrain, Belarus, Bosnia & Herzegovina, Bulgaria, Canada, Canary Islands, Colombia, Costa Rica, Croatia, Curacao, Czech Republic, Denmark, Dominican Republic, 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, Palestine, Philippines, Poland, Portugal, Reunion, Romania, Russia, Saudi Arabia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, 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 interval for clinical studies and post-marketing safety surveillance was the Summary of Product Information (SPI) version 7.0 for THS (dated 10-May-2022).

The estimated cumulative subject exposure in clinical studies from the DIBD (30-Apr-2013) until the DLP of this SUR was 2,344 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 18,986,271 for the reporting period and 92,768,759 cumulatively for THD from the IBD, and 101,743,803,565 for the reporting period and 400,195,056,205 cumulatively for EHTP from the IBD.

During this reporting interval, 3 PMI-sponsored clinical studies were ongoing (P1-AAA-02-JP, P1-COPD-04-INT, and P1-REXC-10). No studies were closed during this reporting period.

During this reporting interval, no signals were open or closed.

New information received during the reporting interval of this SUR and cumulatively since the IBD up until the DLP was evaluated regarding the important identified risks of Hypersensitivity, Accidental exposure to product by child, and Burning sensation as well as the important potential risk of Thermal burn and the exposure to the THS during pregnancy and lactation.

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, 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 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
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COT	Commercial Offer Test
DIBD	Development International Birth Date
DLP	Data Lock Point
EC	Electronic Cigarette
EHTP	Electrically Heated Tobacco Product
HCP	Health Care Professional
HNBC	Heat-Not-Burn Cigarette
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
NEISS	National Electronic Injury Surveillance System
NR	Not Randomized
NRT	Nicotine Replacement Therapy
OR	Odds Ratio

PBA	Perception and Behaviour Assessment
PHQ	Patient Health Questionnaire
PMI	Philip Morris International
PT	Preferred Term
RRP	Reduced-Risk Product
RSI	Reference Safety Information
SA	Smoking Abstinence
SAE	Serious Adverse Event
SGA	Small for Gestational Age
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

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-2022 to 31-Dec-2022 (Data Lock Point, DLP).

The THS uses a heat-not-burn technology that generates an aerosol by heating tobacco rather than burning it. This technology is part of the Philip Morris International (PMI) Reduced-Risk Products (RRPs) portfolio. The RRPs 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 RRPs 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[1] 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, or induction technology where a metal strip, referred to as the susceptor, is integrated into the tobacco stick. Product technical specifications and constituents, as well as product user instructions, are described in the Summary of Product Information (SPI) for THS version 7.0 (Appendix 1) dated 10-May-2022.

The EHTP is commercialized under the brand name *Marlboro HeatSticks*™ or *HEETS*™ depending on the market and is specifically designed to be used with the *IQOS*™ device. 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 worldwide for the THS, was 04-Nov-2014.

[1] In selected markets alu-wrapper paper is used instead of non-flammable paper.

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-2022), the THS had been marketed in 71 markets worldwide: Albania, Andorra, Armenia, Austria, Aruba, Bahrain, Belarus, Bosnia & Herzegovina, Bulgaria, Canada, Canary Islands, Colombia, Costa Rica, Croatia, Curacao, Czech Republic, Denmark, Dominican Republic, 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, Palestine, Philippines, Poland, Portugal, Reunion, Romania, Russia, Saudi Arabia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Tunisia, Turkish Cyprus, Ukraine, United Arab Emirates, United Kingdom, United States (U.S.), and Uzbekistan.

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

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

4 CHANGES TO REFERENCE SAFETY INFORMATION

The SPI for THS version 6.0 was updated during the reporting period to version 7.0 (dated 10-May-2022) (Appendix 1). The update included addition of Preferred Term (PT) Tremor to the list of class effect risks with nicotine use.

The SPI verion 7.0 was used as Reference Safety Information (RSI) for all the clinical studies initiated in countries where the THS is marketed under the brand name *IQOS*™, as well as for post-marketing safety surveillance.

5 ESTIMATED EXPOSURE

5.1 Cumulative Subject Exposure in Clinical Studies

Cumulatively, up to the DLP of this SUR, a total of 12 PMI-sponsored open-label randomized controlled clinical studies had been completed, with 3 studies 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[1]	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[2]	Closed	6 Months	179	87	85	0	0	7
ZRHR-ERS-09-EXT-US	Closed	Up to 1-year	672[3]	309	363	0	0	0
P1-EXC-01-EU	Closed	3 Months	94	40	26	0	27	1
P1-AAA-02-JP[2]	Ongoing	Up to 3-years	48	16	16	0	16	0
P1-COPD-04-INT	Ongoing	Up to 3-years	0	0	0	0	0	0
P1-REXC-10	Ongoing	5 Days	45	29	10	0	0	6

Study Title	Study Status	Exposure Duration	Safety Population[1]	EHTP	CC	NRT	SA	NR
Total Exposure	**NA**	**NA**	**2,344**	**1,226**	**973**	**72**	**201**	**120**

[1]The overall safety population does not sum up the total of subjects in studies arms due to PK/PD crossover studies.
[2]Actual number of subjects enrolled at the DLP.
[3]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.

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
Gender	Male	1,338
	Female	958
	Total	**2,296**[1]
Race	Caucasian (White)	1,316[2]
	Asian (Japanese)	706[2]
	Black or African American	275
	Native Hawaiian or Other Pacific Islander	14
	American Indian or Alaska Native	7
	Other	26
	Total	**2,344**

[1]The total does not include data from ongoing study P1-AAA-02-JP.
[2]The subtotal includes the actual number of subjects enrolled in the ongoing studies at the DLP (31-Dec-2022).

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

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 7 pre-market studies (Blend Tests (BT), Whole Offer Tests (WOT), Commercial Offer Test (COT)), and 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 (31-Dec-2022), 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
Total Exposure	**NA**	**6,298**	**4,191**	**1,973**	**834**	**NA**

N=Number of subjects

5.3 Cumulative and Interval Consumer Exposure from Post-Marketing Experience

It is difficult to estimate a proper "Defined Daily Dose" to which consumers are exposed because the daily dose 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 interval for THD and EHTP is presented in Table 5-4 below.

Table 5-4 Interval and Cumulative Consumer Exposure

	Interval (n)	Cumulative (n)
THD	18,986,271	92,768,759
EHTP	101,743,803,565	400,195,056,205

n=number of units sold

(b) (4)

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 Adverse Events (AEs) was performed using the Medical Dictionary for Regulatory Activities (MedDRA) versions effective at the time of AE processing (latest version used 25.1).

The seriousness of the AEs corresponds to the seriousness assigned to events included in the Individual Case Safety Reports (ICSRs) using the criteria established in ICH-E2A (Clinical safety data management: Definitions and standards for expedited reporting).[2] 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, the majority 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 (31-Dec-2022) are presented in Appendix 2a. The summary tabulations are presented by MedDRA System Organ Class (SOC) for both the THS and the comparator arm CC.

The cumulative summary tabulations present 75 SAEs reported in 56 ICSRs. A total of 29 SAEs were reported in the THS arms, 31 SAEs in the CC arm, and 15 SAEs in the SA arm.

The most represented SOCs in the THS arms were Infections and infestations (n=7) and Injury, poisoning and procedural complications (n=7). All but 3 SAEs were assessed by principal investigators and by PMI as having no causal relationship to THS use. In case of 3 SAEs, the principal investigator was unable to assess whether they were related to THS use. These SAE concerned 1 consumer who enrolled to 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 on Ongoing Clinical Studies.

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 (31-Dec-2022) are presented in Appendix 2b. The summary tabulations are presented by MedDRA SOC for the THS.

(b) (4)

The cumulative summary tabulations present 25 SAEs reported in a total of 11 ICSRs. None of the SAEs were assessed by the principal investigators and by PMI as causally related to THS, and in the case of one SAE, the assessment was not provided by the principal investigator. The most represented SOCs were 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 25.1. 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 a 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 and 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 show 49,482 AEs (837 serious and 48,645 non-serious) from 31,512 ICSRs. The most represented SOCs (>5%) were: *Respiratory, thoracic and mediastinal disorders* (37.03%, n=18,322; 81 serious and 18,241 non-serious), *Gastrointestinal disorders* (17.45%, n=8,678; 55 serious and 8,623 non-serious), *Nervous system disorders* (11.96%, n=5,919; 76 serious and 5,843 non-serious), *Injury, poisoning and procedural complications* (10.30%, n=5,096; 44 serious and 5,052 non-serious), and *General disorders and administration site conditions* (9.33%, n=4,618; 22 serious and 4,596 non-serious).

  The most frequently reported events (>5%) were *Cough* (12.99%, n=6,426; 10 serious and 6,416 non-serious), *Headache* (7.10%, n=3,515; 8 serious and 3,507 non-serious), *Throat irritation* (5.51%, n=2,728; all non-serious), and *Oropharyngeal pain* (5.16%, n=2,551; 3 serious and 2,548 non-serious).

  Out of the total 837 SAEs, the most frequently reported (>5%) were: *Angina pectoris* (29.99%, n=251), *Arrhythmia* (8%, n=67), and *Pneumonia* (5.02%, n=42).

  Concerning the 251 serious events of *Angina pectoris*, the most frequently reported verbatim (>5%) was "heart pain(s)", "heartache, pain in the heart area, pain in the heart, acute pain in the heart, and heart hurts", all of which correspond to the

MedDRA coding "*Angina pectoris*". None of these cases of *Angina pectoris* were medically confirmed. In most of these cases, the consumers' medical history was not provided. The mean age of the consumers was 33.63 years. Out of these 251 events, two events of *Angina pectoris* led to hospitalization. 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, 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 (≥1/1,000, <1/100).

Concerning the 67 serious events of *Arrhythmia*, the most frequently reported verbatim (>5%) was "arrhythmia". None of these cases of *Arrhythmia* were medically confirmed. In most of these cases, the consumers' medical history was not provided. The mean age of the consumers was 39.04 years. All the events of *Arrhythmia* were considered medically important and none of the events led to hospitalization or death. As per SPI version 7.0, arrhythmia supraventricular is listed.

Concerning the 42 serious events of *Pneumonia*, the most frequently reported verbatim (>5%) was "pneumonia". None of these cases of *Pneumonia* were medically confirmed. In most of these cases, the consumers' medical history was not provided. The mean age of the consumers was 37.1 years. Out of these 42 events, 7 events of *Pneumonia* led to hospitalization. None of the cases reported a fatal outcome. Out of 7 cases that led to hospitalization, in 4 cases, consumer was a smoker/ex-smoker and in 1 of the cases history of asthma was reported. In the remaining 3 cases, there was a limited information regarding either time to onset, medical history, concomitant medications, or investigations for further assessment. Pneumonia was considered as an unlisted event according to the SPI version 7.0.

- Cumulative summary tabulations of non-serious AEs and SAEs from post-marketing experience show 288,060 AEs (4,993 serious and 283,067 non-serious) from 165,190 ICSRs. The most represented SOCs (>5%) were: *Respiratory, thoracic and mediastinal disorders* (29.38%, n=84,629; 669 serious and 83,960 non-serious), *Gastrointestinal disorders* (17.44%, n=50,247; 280 serious and 49,967 non-serious), *Injury, poisoning and procedural complications* (11.83%, n=34,081; 209 serious and 33,872 non-serious), *Nervous system disorders* (11.37%, n=32,759; 430 serious and 32,329 non-serious), *General disorders and administration site conditions* (11.34%, n=32,668; 196 serious and 32,472 non-serious), and *Product issues* (8.40%, n=24,206; 5 serious and 24,201 non-serious).

  The most frequently reported events (>5%) were *Cough* (9.13%, n=26,290; 59 serious and 26,231 non-serious), *Thermal burn* (6.33%, n=18,248; 21 serious and 18,227 non-serious), and *Headache* (6.02%, n=17,340; 43 serious and 17,297 non-serious).

(b) (4)

Of the total 4,993 SAEs reported, the most frequently reported (>5%) were: *Angina pectoris* (19.83%, n=990) and *Hypersensitivity* (17.50%, n=874).

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

Concerning the 990 serious events of *Angina pectoris*, the most frequently reported verbatim (>5%) was "heart pain" and "heartache in the heart", both corresponding to the MedDRA coding "*Angina pectoris*". None of these cases of *Angina pectoris* were medically confirmed. In most of these cases, the consumers' medical history was not provided. The mean age of the consumers was 33.79 years. Of these 990 events, 11 events of *Angina pectoris* led to hospitalization, and one 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". 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 (≥1/1,000, <1/100).

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

7.1 Completed Clinical Studies

No PMI-sponsored clinical studies were completed during the period covered by this SUR.

7.2 Ongoing Clinical Studies

Three PMI-sponsored clinical studies (P1-AAA-02-JP, P1-COPD-04-INT, and P1-REXC-10) for the THS were ongoing 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. In total, 26 SAEs have been reported in 20 subjects up to 31-Dec-2022.

Six SAEs in 5 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 smoking history of 20 cigarettes/day. The subject was randomized to the THS arm on 30-Nov-2018. On 09-Sep-2019, the subject fell and broke his patella and was hospitalized. On 08-Nov-2020, the subject passed away. An image autopsy was performed with the findings 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. The sponsor assessed that there was no reasonable causal relationship between SAE of *Death* and THS use. The principal investigator considered these SAEs as unable to be assessed as having a causal relationship to THS use. The events of *Patella fracture* (that occurred as well in the same subject mentioned previously), *Lumbar spinal stenosis, Atrial fibrillation*, and *Femoral neck fracture* were assessed as not related to THS use by both the principal investigator and the sponsor.

Six SAEs in 6 subjects have been reported in Cigarette arm (*Cerebral haemorrhage, Angina unstable, Cataract, Inflammatory pseudotumour, Large intestinal polyp,* and *Tarsal tunnel syndrome*). The first case concerns a 79-year-old male subject with 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. On 16-Dec-2020, the subject 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. The events of *Inflammatory pseudotumour* and *Tarsal tunnel syndrome*, reported in the two cases, were assessed as not related to cigarettes by both the principal investigator and the sponsor. 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 last two events of *Angina unstable* and *Large intestinal polyp* were assessed as related to cigarettes.

(b) (4)

Fourteen SAEs in 9 subjects were reported in smoking cessation arm (4 SAEs of *Large intestine polyp*, and 1 SAE of each event *Acute myocardial infarction, Angina pectoris*, *Appendicitis*, *Cardiac failure*, *Gastroenteritis*, *Ileus*, *Inguinal hernia*, *Myocardial ischaemia*, *Peripheral arterial occlusive disease*, and *Pneumonia*) where the assessment of causal relationship to the products is not applicable.

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 cigarette smoking to the THS in mild to moderate Chronic Obstructive Pulmonary Disease (COPD) subjects with a history of chronic bronchitis symptoms. First subject screened in this study was in December 2022.

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. Study started in November 2022.

No SAEs were reported from studies P1-COPD-04-INT and P1-REXC-10 up to 31-Dec-2022.

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.

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

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. Study ABOUT-HF-ND-PV-06-INT is a multi-country quantitative study to evaluate the psychometric properties of the ABOUT™-Health and Functioning questionnaire for adult users of tobacco and/or nicotine products. The study was conducted in the U.S., Europe (Germany, Italy, and Russia) and Asia (Japan).

It was an online survey conducted for the validation of the ABOUT™-Health and Functioning questionnaire. The study is closed now. The first subject completed the survey on 25-Aug-2021 and the last subject completed the survey on 15-Dec-2021. There were about N=571 *IQOS™* users who completed the survey at Time 1 and N=410 at Time 2. No AEs were reported.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

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

Study APM-PMI IIS is a five-year cohort observational clinical study to assess possible harm-reduction effects of the THS in comparison with combustible cigarettes. This study is being conducted by the Academy of Preventive Medicine of Kazakhstan and was presented in the last SUR covering the period from 01-Jan-2021 to 31-Dec-2021.

The goal of this study is 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.

A total of 1,200 participants were recruited: 800 in the CC arm and 400 in THS arm until the DLP of this SUR. A total of 74 SAEs in 40 subjects were reported in THS arm up to 31-Dec-2022. No new participants were enrolled during the interval (01-Jan-2022 to 31-Dec-2022). Among these 74 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 69 SAEs.

As reported during the previous reporting period, none of the fatal SAEs of *Cardiac failure acute* and *Myocardial ischemia* were assessed as related to THS.

As reported during the previous reporting period, the life-threatening SAE of *Acute myocardial infarction* was considered not related to THS.

Study HW-001-DE in Germany 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 THS for 6 months in adult smokers who have been diagnosed with inflammatory bowel disease and are under treatment. This study was conducted on subjects with ulcerative colitis/Chron's diseases. Study is aiming to recruit about 100 subjects distributed on THS, CC and SA arms. The total number of subjects enrolled under the SC arm were 16 (9 with Chron's disease and 7 with ulcerative colitis), 14 under smoker arm (7 each with Chron's disease and ulcerative colitis) and 16 under THS arm (10 with Chron disease and 6 with ulcerative colitis). No SAEs were reported in subjects from this study up to 31-Dec-2022.

10 NON-CLINICAL DATA

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

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])

- **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 ((teeps W/2 26obaccoo)) OR ALL ((hnb AND tobacco)) OR ALL ((ths 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 product*' OR (lil NEAR/2 tobacco) OR (teeps NEAR/2 tobacco) OR (hnb:ti,ab,kw AND tobacco:ti,ab,kw)

- **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

- **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"

This comprehensive library was screened for publications containing new safety information associated with the THS products published during the reporting interval from 01-Jan-2022 to 31-Dec-2022 inclusive.

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

The first article by Young-Gyun Seo et al[4] states that the relationship between mental health and HTPs use remains unclear. The authors obtained data from the Korea National Health and Nutrition Examination Survey (2018–2020) on 18,231 participants aged ≥ 19 years and examined the association between participants' type of tobacco use (non-tobacco, CC only, or HTP use [with or without CCs]) and their mental health using logistic regression analysis. Among 18,231 participants, 18.41% were current tobacco users and 38.32% were lifetime tobacco users. Approximately 18.38% (18.14%) current (lifetime) tobacco users were current (lifetime) HTP users. Lifetime HTP users had higher odds of reporting perceived stress (adjusted odds ratio (OR): 1.91, 95% confidence interval (CI): [1.61–2.25]), depressive mood (1.79 [1.17–2.73]), suicidal ideation (2.09 [1.08–4.04]), Patient Health Questionnaire-9 (PHQ-9) ≥ 10 (3.68 [2.38–5.71]), and doctor-diagnosed depression (2.52 [1.75–3.62]) than non-tobacco users, and reporting perceived stress (1.18 [1.004–1.38]), depressive mood (1.53 [1.03–2.26], and PHQ-9 ≥ 10 (1.67 [1.12–2.49]) than lifetime CC only users. Finally, lifetime HTP only users had increased odds of doctor-diagnosed depression (4.30 [1.41–13.16]) than lifetime CC only users. Lifetime HTP users are more likely to experience poor mental status than non-tobacco and CC only users.

PMI comment: In above study, authors evaluated the relationship between mental health and HTP use. Study concluded that lifetime HTP users are more likely to experience poor mental status than non-tobacco and CC only users. This study had some limitations. First, it used a cross-sectional research design; therefore, authors could not provide causal

interpretations. Second, the results could be biased because the survey data were self-reported. The trajectory of tobacco use has become complicated since the introduction of novel tobacco products in Korea. Respondents, especially tobacco users, tend to underreport socially undesirable behaviors, even though smoking statistics are relatively accurate in Korea owing to the adoption of urine cotinine-based biochemical validation. Third, some potential confounding factors may have not been accounted for. Finally, the study had a small number of current HTP only users, with most HTP users in Korea being dual (CC and HTP) or triple users (CC, HTP and electronic cigarette (EC)). Hence, authors could not clarify the characteristics of the exclusive use of HTPs in Korea. Considering the high prevalence of tobacco use among Korean adults and the aggressive marketing of HTPs to young adults by the tobacco industry, this result calls for evaluation and intervention for mental health amid the expansion of HTP use in Korean adults. Further research is also needed to determine whether long-term use of HTPs only is related to poorer mental health conditions compared to using only CCs.

The second article by Yoshihiki Kosokawa at el[5] focuses on the impact of CC smoking on fetal growth during pregnancy and how the risk associated with HTPs remains unclear. This nationwide cross-sectional study investigated whether HTP use during pregnancy is associated with small for gestational age (SGA) outcomes among 5,647 post-delivery women with singleton pregnancies, which were divided into 4 groups: (1) lifetime never-smokers, (2) former smokers before pregnancy, and current smokers for each of the tobacco products during pregnancy ((3) sole HTP and (4) sole CC smokers). Information on the prevalence of SGA, defined as birth weight and height below the 10th percentile, was retrieved from the Maternal and Child Health Handbooks of post-delivery women. Using logistic regression, the association between sole HTP smokers during pregnancy and SGA, adjusted for covariates, with lifetime never-smokers as reference, was investigated. The prevalence was: current sole HTP smokers during pregnancy, 1.8% (102/5647); and SGA, 2.9% (164/5647). Sole HTP smokers during pregnancy had a higher prevalence of SGA (5.9% [6/102] vs. 2.7% [111/4144]) with an adjusted OR of 2.50 (95% CI, 1.03–6.05) than lifetime never-smokers. Among sole combustion smokers, the adjusted OR for SGA was 1.95 (95% CI, 0.81–4.67). In Japan, HTP smoking during pregnancy may be associated with an increased risk for SGA.

PMI comment: In above study, authors evaluated association between HTP use during pregnancy and fetal growth in Japan. The study concluded that smoking during pregnancy may be associated with an increased risk for SGA. The effect of THS use during pregnancy and lactation was recognized as missing information and is closely monitored by PMI. According to the *IQOS*™ SPI, women who are pregnant, breastfeeding, or think they may be pregnant, should quit tobacco and nicotine use altogether.

The third article by Masayoshi Zaitsu et al[6] presents a study that aimed to determine whether maternal HTP smoking is associated with allergy in their offspring and to evaluate the potential dose–response association. In total, 2.4% women smoked HTPs during pregnancy. Allergy occurred in 7.8% of the infants. The prevalence of allergy increased among the offspring of current HTP smokers during pregnancy at 15.2% (PR = 1.98, 95% CI 1.28–3.05); this association was the most pronounced during the first trimester but attenuated

before pregnancy and postpartum. Dose–response associations were observed, for example a one-unit increase in daily maternal HTP use during pregnancy was associated with a 5% increase in allergy onset. Sub-group analyses excluding CC smokers during pregnancy and sensitivity analyses using the International Study of Asthma and Allergies in Childhood questionnaire showed a similar pattern. Maternal HTP smoking during pregnancy is associated with allergy in the offspring.

PMI comment: In above study, authors evaluated whether maternal HTP smoking is associated with allergy in offspring and to evaluate the potential dose-response association. It was seen that the prevalence of allergy increased among the offspring of current HTP smokers during pregnancy and this association was the most pronounced during the first trimester but attenuated before pregnancy and postpartum. The dose-response associations suggested that a one-unit increase in daily maternal HTP use during pregnancy was associated with a 5% increase in allergy onset. The effect of THS use during pregnancy and lactation was recognized as missing information and is closely monitored by PMI. According to the *IQOS*™ SPI, women who are pregnant, breastfeeding, or think they may be pregnant, should quit tobacco and nicotine use altogether.

The fourth article by Huan Hu et al[7] presents a study that included 40,291 participants (mean age, 46.6 years; men, 84.3%), where about half of the current tobacco related product users reported using HTPs. Study used data from the Japan Epidemiology Collaboration on Occupational Health Study, which is an ongoing multi-company study of workers in Japan. The details of the Japan Epidemiology Collaboration on Occupational Health Study have been described elsewhere. In phase 3, between April 2018 and March 2021, 5 companies participated in a questionnaire survey on the use of new tobacco-related products (Study I). In another large company, information on the use of new tobacco-related products was available from the 2019 health checkup (Study II). Exclusive HTP users had higher odds of prediabetes (pooled OR 1.36; 95% CI 1.25–1.47) and diabetes (1.68; 95% CI 1.45–1.94) than never smokers. Similarly, dual users also had increased odds of prediabetes (pooled OR, 1.26; 95% CI 1.13–1.39) and diabetes (1.93; 95% CI 1.63–2.29). The strength of these associations was comparable to that of CC smokers. The authors observed significantly higher HbA1c and fasting blood glucose levels among both exclusive HTP users and dual users compared to never smokers. HTP use was associated with an increased likelihood of prediabetes and diabetes. Prospective studies are warranted to confirm the cross-sectional association.

PMI comment: In above study, authors assessed the cross-sectional association of HTP use with prediabetes and diabetes. Study observed significantly higher HbA1c and fasting blood glucose levels among both exclusive HTP users and dual users compared to never smokers. The study however had certain limitations. First, given the cross-sectional design of the study, it is not possible to establish causality between HTP use and diabetes. Second, the smoking habits were ascertained via a questionnaire but not biologically verified (e.g., exhaled carbon monoxide or salivary cotinine). Third, the relatively small number of female participants included and the inability to evaluate sex effects. Fourth, authors defined the study outcome using one-time measurement of HbA1c and fasting blood glucose, which is

subject to random error. Fifth, the questionnaire used in Study II does not allow the study to distinguish between HTPs and ECs. Nevertheless, the association of HTP use and abnormal glucose metabolism was similar between Study I and Study II, suggesting little impact of the difference in tobacco use questions on results. Last, the study is based on a Japanese working population; therefore, findings may not be generalizable to the general population or other racial/ ethnic groups. From the perspective of preventing diabetes, the study results did not support that HTPs are less harmful alternatives to CCs. Future prospective cohort studies are required to confirm the findings.

The fifth article by Sato Eri et al[8] suggests that the amount of HTPs used as an alternative to CCs has increased, and reports of lung damage have gradually increased. This case was thought to be an HTP-related interstitial lung disease that was incidentally discovered before the onset of clinical symptoms. Early detection may prevent irreversible disease progression. Although the composition of mainstream *Ploom TECH*® (heated tobacco) smoke differs from that of CCs, it contains harmful substances that cause smoking related interstitial lung disease. When an abnormal lung shadow is seen, it is important to conduct an interview and examination, including a history of use of HTPs.

PMI comment: In above study, authors assessed a case report of interstitial lung disease and its relation to HTP. It was thought to be an HTP-related interstitial lung disease that was incidentally discovered before the onset of clinical symptoms and it was concluded that when an abnormal lung shadow is seen, it is important to conduct an interview and examination, including a history of use of HTP as early detection may prevent irreversible disease progression. Due to lack of information related to concomitant medications, details on product use, exogeneous exposure to other potential sources, non-evocative temporal relationship, it is currently not possible to assess the causal relationship between the use of the product and the reported AE. Further studies are needed for a better understanding of the pathophysiological underlying mechanisms in this case.

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

12 OTHER PERIODIC REPORTS

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

13 LATE-BREAKING INFORMATION

No potentially important safety findings concerning THS products were identified after the DLP (31-Dec-2022) and until the date of release of this SUR.

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 three 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 (PMI-sponsored clinical, post-market research studies, and passive surveillance pre-market studies) and during the assessment of information derived from unsolicited sources such as: literature monitoring, call centres, poison centres, 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 interval, no signals were open or closed.

15 SIGNAL AND RISK EVALUATION

15.1 Summary of Safety Concerns

A summary of the safety concerns at the beginning of the reporting interval of this SUR is presented in Table 15-1 below. New information received during the period covered by this SUR (01-Jan-2022 to 31-Dec-2022) has been evaluated regarding: a) three important identified risks of *Hypersensitivity*, *Accidental exposure to product by child*, and *Burning sensation*; b) one 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-New Information at the Beginning of the Reporting Interval

	Risk	Search criteria for Risk Assessment	Interval Retrieved AEs within Safety Database
Important Identified Risks	Hypersensitivity	Standardised MedDRA Query (SMQ) Hypersensitivity (Narrow)	1,627 AEs of hypersensitivity retrieved: Most reported AEs (>1%): - Hypersensitivity, n=738 - Rash, n=301 - Pharyngeal swelling, n=113 - Gingival swelling, n=84 - Urticaria, n=62 - Rash macular, n=57 - Lip swelling, n=49 - Swelling tongue, n=26 - Swollen face, n=22 - Eczema, n=19 - Allergic cough, n=17
	Accidental exposure to product by child	Selected PTs: - Accidental exposure to product by child; - Accidental exposure to product packaging by child; - Accidental exposure to product Selected age groups: - Adolescent - Child - Infant - Neonate Selected age units: - Months - Years	913 AEs retrieved: - Accidental exposure to product by child, n=913 Co-reported AEs representing at least 1% of the total: - Vomiting, n=180 - Pallor, n=18 - Nausea, n=18 - Cough, n=17 - Crying, n=15 - Mood altered, n=14 - Respiratory tract irritation, n=10 - Hiccups, n=9 - Somnolence, n=8 - Retching, n=6 - Asthenia, n=6

	Risk	Search criteria for Risk Assessment	Interval Retrieved AEs within Safety Database
			- Choking sensation, n=6 - Drooling,n=5 - Illness, n=5 - Mouth haemorrhage, n=5
	Burning sensation	Customized search of MedDRA PTs and *Lowest Level Terms (LLTs)*: - Burning sensation - Burning sensation mucosal - Skin burning sensation - Oral discomfort (only the following *LLTs* are included in the risk assessment): - *Burning corner of mouth* - *Burning lips* - *Burning mouth* - *Burning oral sensation* - *Lip burning sensation of* - *Oral hot feeling* - *Oral mucosal burning sensation)*	1,282 AEs retrieved: - Burning sensation, n=267 - Burning sensation mucosal, n=2 - Skin burning sensation, n=3 - Oral discomfort*, n=1010 (only the following selected *LLTs* under the PT Oral discomfort are included in the risk assessment: - *Burning lips, n=423* - *Lip burning sensation of, n=404* - *Burning mouth, n=146* - *Burning oral sensation, n=20* - *Oral hot feeling, n=10* - *Oral mucosal burning sensation, n=7* * note that the total number of AEs under the PT Oral discomfort is 1,071 out of which 1,010 were included in the risk assessment. The following *LLTs* have been excluded from the risk assessment: - *Oral discomfort (n=29)* - *Discomfort in mouth (n=15)* - *Lip discomfort (n=12)* - *Oral cavity discomfort (n=5)*
Important Potential Risks	Thermal burn	Customized search of MedDRA PTs: - Airway burns - Burn oral cavity - Burns first degree - Burns second degree - Burns third degree - Burns fourth degree - Thermal burn - Thermal burns of eye	2,595 AEs retrieved: - Thermal burn, n=1,933 - Burn oral cavity, n=644 - Airway burns, n=12 - Burns second degree, n=6

	Risk	Search criteria for Risk Assessment	Interval Retrieved AEs within Safety Database
Missing Information	Pregnancy and lactation	MedDRA SOC: - "Pregnancy, puerperium and perinatal conditions" 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"	178 AEs retrieved: - Maternal exposure during pregnancy, n=83 - Exposure during pregnancy, n=78 - Morning sickness, n=5 - Pregnancy, n=2 - Multigravida, n=2 - Abortion spontaneous, n=1 - Somatic symptom disorder of pregnancy, n=1 - Maternal exposure during breast feeding, n=1 - Exposure via breast milk, n=1 - Umbilical cord around neck, n=1 - Maternal exposure before pregnancy, n=1 - Pre-eclampsia, n=1 - Live birth, n=1 Co-reported AEs representing at least 1% of the total: - Passive smoking, n=19 - Nicotine dependence, n=10 - Malaise, n=6 - Anxiety, n=5 - Nausea, n=5 - Dyspnoea, n=5 - Product odour abnormal, n=4 - Headache, n=4 - Illness, n=4 - Vomiting, n=3 - Pain, n=2 - Fatigue, n=2 - Throat irritation, n=2

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-2022 up to the DLP of this SUR (31-Dec-2022) 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 carried out using the MedDRA SMQ Hypersensitivity (narrow scope).

A total of 1,627 AEs of hypersensitivity-related events with THS use (24 serious and 1,603 non-serious) were received in 1,458 ICSRs. The most reported AEs (>1%) were: *Hypersensitivity* (45.36%, n=738; 2 serious and 736 non-serious), *Rash* (18.50%, n=301; all non-serious), *Pharyngeal swelling* (6.95%; n=113; all non-serious), *Gingival swelling* (5.16%, n=84; all non-serious), *Urticaria* (3.81%, n=62; 1 serious and 61 non-serious), *Rash macular* (3.50%, n=57; 1 serious and 56 non-serious), *Lip swelling* (3.01%, n=49; all non-serious), *Swollen tongue* (1.60%, n=26; all non-serious), *Swelling face* (1.35%, n=22; all non-serious), *Eczema* (1.17%, n=19; all non-serious), and *Allergic cough* (1.04%, n=17; all non-serious).

The most reported SAEs (>1%) were: *Angioedema* (45.83%, n=11, 8 recovered/resolved and 3 with unknown outcome), *Laryngeal oedema* (16.67%, n=4, 2 recovered/resolved and 2 with unknown outcome), *Hypersensitivity* (8.33%, n=2, 1 resolved/resolved and 1 with unknown outcome), *Oropharyngeal blistering* (8.33%, n=2, 1 not resolved and 1 with unknown outcome), *Shock symptom* (4.17%, n=1, resolved), *Anaphylactic shock* (4.17%, n=1, with unknown outcome), *Urticaria* (4.17%, n=1, resolved), *Rash macular* (4.17%, n=1, not resolved), and *Shock* (4.17%, n=1, with unknown outcome).

As per the current RSI *Anaphylactic shock*, *Laryngeal oedema*, and *Oropharyngeal blistering* are unlisted, whereas *Hypersensitivity*, and *Angioedema* are listed.

The AEs belonging to the MedDRA SMQ Hypersensitivity represented 3.29% (1,627/49,482) of the total AEs received during the period covered by this SUR.

During the reporting interval of the current SUR, the number of cases under the MedDRA SMQ Hypersensitivity per 1 million users was estimated to be 76.79. This calculation is based on the number of cases falling under the MedDRA SMQ Hypersensitivity and reported during the reporting interval of this SUR (n=1,458). The calculation also includes the number of users during this period, which is estimated to be 18.5 million (based on EHTP PMI's sales data and the assumption that a consumer uses 15 *HeatSticks*™ per day during the reporting interval of this SUR). Taking into consideration an under-reporting of 90% specific to a spontaneous AE reporting system,[9] the reporting frequency rate for cases falling into the MedDRA SMQ Hypersensitivity was estimated to be 0.08 per 100 users, following 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 (≥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.

The evaluation of new information received during the SUR reporting interval does not support a revision of the risk characterization of *Hypersensitivity* at this point. 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.

15.3.1.2 Accidental exposure to product by Child

A search covering the reporting interval of this SUR (01-Jan-2022 to 31-Dec-2022) 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*, *Accidental exposure to product packaging by child*, and *Accidental exposure*). The selected age groups were adolescent, child, infant, and neonate. The selected age units were months and years.

A total of 913 events of *Accidental exposure to product by child* (27 serious and 886 non-serious) were received in 913 ICSRs. A total of 400 AEs were co-reported. In 69.22% of ICSRs concerning accidental exposure by children, no health-related events were co-reported (*No adverse event*, n=632). In the remaining cases, the most frequent (>1%) co-reported events were: *Vomiting* (n=180; 16 serious and 164 non-serious, 45%), *Pallor* (n=18; 1 serious and 17 non-serious, 4.50%), *Nausea* (n=18; 1 serious and 17 non-serious, 4.50%), *Cough* (n=17; 1 serious and 16 non-serious, 4.25%), *Crying* (n=15; all non-serious, 3.75%), *Mood altered* (n=14; 1 serious and 13 non-serious, 3.50%), *Respiratory tract irritation* (n=10; all non-serious, 2.50%), *Hiccups* (n=9; all non-serious, 2.25%), *Somnolence* (n=8; 1 serious and 7 non-serious, 2%), *Retching* (n=6; all non-serious, 1.50%), *Asthenia* (n=6; all non-serious, 1.50%), *Choking sensation* (n=6; all non-serious, 1.50%), *Drooling* (n=5; all non-serious, 1.25%), *Illness* (n=5; all non-serious, 1.25%), and *Mouth haemorrhage* (n=5; 1 serious and 4 non-serious, 1.25%).

The evaluation of the new information received during the SUR reporting interval 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-2022 up to the DLP of this SUR (31-Dec-2022) 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 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 1,282 (1 serious and 1,281 non-serious) AEs were received in 1,264 ICSRs. In 1 serious event reported of *Burning mouth*, the consumer was hospitalized for longer than 24 hours. Outcome of event was unknown. The retrieved AEs among the selected PT list were: *Burning sensation* (n=267; all non-serious), *Burning sensation mucosal* (n=2; all non-serious), *Oral discomfort* (n=1010; 1 serious and 1009 non-serious), and *Skin burning sensation* (n=3; all non-serious). The AEs retrieved among the selected LLTs under the PT *Oral discomfort* were: *Burning lips* (n=423), *Lip burning sensation of* (n=404), *Burning mouth* (n=146), *Burning oral sensation* (n=20), *Oral hot feeling* (n=10), and *Oral mucosal burning sensation* (n=7). Of note, the total number of AEs under the PT *Oral discomfort* was 1,071; out of which 1,010 were included in the risk assessment. The LLTs excluded from the risk assessment were: *Oral discomfort* (n=29), *Discomfort in mouth* (n=15), *Lip discomfort* (n=12), and *Oral cavity discomfort* (n=5).

The evaluation of the new information received during the SUR reporting interval 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-2022 up to the DLP of this SUR (31-Dec-2022) 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 and 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 2,595 AEs (3 serious and 2,592 non-serious) were received in 2,534 ICSRs: *Thermal burn* (n=1,933; 3 serious and 1,930 non-serious), *Burn oral cavity* (n=644; all non-serious), *Airway burns* (n=12; all non-serious), and *Burns second degree* (n=6; all non-serious),

There were 3 serious cases identified, reporting a serious event of *Thermal burn*. All 3 serious events involved hospitalization. The reported events concerned lips and fingers. In 1 out of 3 cases, the patient underwent a treatment. The event outcome was reported as resolving for 2 events and resolved for the remaining event.

In about 64.43% of cases, the consumer reported the oral cavity (including mouth, lips, and tongue) as the body site affected. In about 14.41% of the cases, the reported body site were fingers and/or hands. In 20.35% of cases, the affected body site was not specified.

The evaluation of the new information received during the period covered by this SUR does not support an update of the characterization of the risk of *Thermal burn*. PMI will continue to perform regular review of the *Thermal burn* events upon the THS use to ensure the ongoing evaluation of new safety information.

15.3.3 Update on missing information

15.3.3.1 Pregnancy and Lactation

A search covering the period from 01-Jan-2022 to the DLP of this SUR (31-Dec-2022) 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 178 (2 serious and 176 non-serious) pregnancy related AEs were received in 167 ICSRs: *Maternal exposure during pregnancy* (n=83; all non-serious), *Exposure during pregnancy* (n=78; 1 serious and 77 non-serious), *Morning sickness* (n=5; all non-serious), *Pregnancy* (n=2; all non-serious), *Multigravida* (n=2; all non-serious), *Abortion spontaneous* (n=1; serious), *Somatic symptom disorder of pregnancy* (n=1; non-serious), *Maternal exposure during breast feeding* (n=1; non-serious), *Exposure via breast milk* (n=1; non-serious), *Umbilical cord around neck* (n=1; non-serious), *Maternal exposure before pregnancy* (n=1; non-serious), *Pre-eclampsia* (n=1; non-serious), and *Live birth* (n=1; non-serious).

There were 2 SAEs concerning pregnancy reported in 2 cases that were identified during the review period. One case reported an event of *Abortion spontaneous*. The case provided no additional data. The second case reported a serious event of *Exposure during pregnancy*. The consumer started using *IQOS*™ 2.4 and *IQOS* consumable (unspecified). Consumer was hospitalized, reporting drug exposure during pregnancy followed by asthma, dyspnoea and headache 6 months later. She had medical history of asthma and was an ex-smoker smoking on average 3 to 4 CCs per day for unspecified duration. Final action taken with the product's use following the events' occurrence was product use withdrawal. It was reported that the events were resolved after stopping product use, and returned after product use was resumed. The outcome of the events asthma, dyspnoea and headache was reported as not resolved, and the outcome of the event exposure during pregnancy was reported as unknown. Asthma and exposure during pregnancy are considered as unlisted events and dyspnoea, headache are

considered as listed events according to the SPI THS version 7.0. Asthma could be explained due to underlying history of asthma in this case.

The co-reported AEs representing >1% of the total included: *Passive smoking* (n=19; all non-serious), *Nicotine dependence* (n=10; all non-serious), *Malaise* (n=6; all non-serious), *Anxiety* (n=5; all non-serious), *Nausea* (n=5; all non-serious), *Dyspnoea* (n=5; 1 serious and 4 non-serious), *Product odour* abnormal (n=4; all non-serious), *Headache* (n=4; 1 serious and 3 non-serious), *Illness* (n=4; all non-serious), *Vomiting* (n=3; all non-serious), *Pain* (n=2; all non-serious), *Fatigue* (n=2; all non-serious), *and Throat irritation* (n=2; all non-serious).

The information received on the risk associated to the exposure during Pregnancy and lactation to the THS during the reporting interval 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.[10,11] One possible reason for such an increase may be the changing exposure to known and unknown risk factors[12] 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, as well as to some outdoor allergens such as pollen.[13] Smoking augments nasal responses to allergen in atopic subjects and increases IgE, immunoglobulin G4, and postallergen histamine levels in nasal lavage fluid.[14,15] Tobacco smoke has a number of harmful effects on the immune system,[16] *e.g.* on humoral and cellular immunity. The putative direct effect of tobacco smoke on the skin is unclear,[17] but smoke might directly impair skin-barrier function via the effects of reactive oxygen species on keratinocytes.[18,19]. Several studies have assessed the association between smoking exposure and allergic diseases.[20] Nicotine replacement therapies based on nasal inhalation of nicotine also showed *Hypersensitivity* as a common (≥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.[21]

The SPI version 7.0 dated 10-May-2022, 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 (31-Dec-2022) 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 carried out under the MedDRA SMQ Hypersensitivity (narrow).

Cumulatively, 10,081 hypersensitivity-related AEs with THS use (1,068 serious and 9,013 non-serious) were received in 8,728 ICSRs. The most reported AEs (>1%) were: *Hypersensitivity* (33.92%, n=3,419; 874 serious and 2,545 non-serious), *Rash* (22.17%, n=2,235; 27 serious and 2,208 non-serious), *Pharyngeal swelling* (8.37%, n=844; 5 serious and 839 non-serious), *Gingival swelling* (5.66%, n=571; 2 serious and 569 non-serious), *Rash macular* (5.42%, n=546; 6 serious and 540 non-serious), *Lip swelling* (5.04%, n=508; 3 serious and 505 non-serious), *Urticaria* (4.64%, n=468; 5 serious and 463 non-serious), *Swollen tongue* (1.64%, n=165; 1 serious and 164 non-serious), *Mouth swelling* (1.38%, n=139; 1 serious and 138 non-serious), *Swelling face* (1.25%, n=126; all non-serious), and *Rash pruritic* (1.15%, n=116; 2 serious and 114 non-serious).

The most reported SAEs (>1%) were: *Hypersensitivity* (81.84%, n=874, 511 resolved or resolving, 236 with unknown outcome, and 127 not resolved), *Angioedema* (4.78%, n=51, 34 resolved or resolving, 13 with unknown outcome, and 4 not resolved), *Oropharyngeal blistering* (2.90%, n=31, 13 with unknown outcome, 11 not resolved, and 7 resolved or resolving), *Laryngeal oedema* (2.62%, n=28, 11 not resolved, 10 resolved or resolving, and 7 with unknown outcome), and *Rash* (2.53%, n=27, 20 resolved or resolving, 6 not resolved, and 1 with unknown outcome).

As mentioned in section 15.3.1.1, the reporting frequency rate of cases of *Hypersensitivity* is estimated to be 0.08 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 (≥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.

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 major 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[22] in 2017. Out of 277 incidents analysed, unintentional exposure was the most frequently cited type of exposure (71.3%). Among all analysed poisoning incidents, 42.7% were among the children population. Exposure via ingestion was more frequent among paediatric patients (≤5 years) compared with children of 6–18 years and adults (87.0% vs. 59.3% vs. 57.6% $p < 0.001$).[22]

Similar results have been shown by a retrospective analysis of exposures associated with nicotine and tobacco products (including e-liquid, CC) among children younger than 6 years old conducted in the U.S.[23,24] Chewing tobacco (67.3%) and snuff (25.0%) accounted for most of the other tobacco product exposures.[23] Most children were exposed through ingestion (95.5%) or multiple routes including ingestion (2.8%), and only 1.7% through non-ingestion routes.[23]A recent study aiming to analyse cases of acute exposure to ECs, e-liquids, and heat-not-burn cigarette (HNBC) products containing nicotine based on toxicological consultations at the Czech Republic poisons control centre during a 7-year period (2012–2018) showed similar results.[25] From 119,229 consultations, 148 cases concerned acute exposure to ECs. 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 129 (87%) cases, inhalation in 9 (6%) cases, ocular in 6 (4%) cases, and intravenous administration in 3 (2%) cases. The sources of exposure were: the cartridge with e-liquid (107 cases; 72%), refillable tank (29 cases; 20%), and HNBC refill (9 cases, 6%).[25]

Infants are susceptible to accidental tobacco ingestion because of a natural curiosity and a tendency for oral exploration.[26,27] Ingestion of as little as 1mg of nicotine by a small child can produce symptoms such as nausea and vomiting.[28] Severe toxic effects of nicotine ingestion may include weakness, convulsions, unresponsiveness, and impaired respiration, and ultimately, may lead to respiratory arrest and death.[28]

As described in SPI version 7.0 for THS (dated 10-May-2022), 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, 5–6mg of nicotine. The accidental ingestion of EHTP may potentially cause signs and symptoms of nicotine intoxication such as: nausea, hyper-salivation, abdominal pain, vomiting, diarrhoea, 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, a physician should be contacted immediately.

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 (31-Dec-2022) 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*, *Accidental exposure to product packaging by child*, and *Accidental exposure*. The selected age groups were adolescent, child, infant, and neonate. The selected age units were months and years.

Cumulatively, 5,845 (81 serious and 5,764 non-serious) events of *Accidental exposure to product by child* were received in 5,845 ICSRs. In 75.84% of ICSRs reporting Accidental exposure to product by children, no health-related events were co-reported (*No adverse event*, n=4,433). In the remaining cases there were a total of 1,911 co-reported events (92 serious and 1,819 non-serious).

The most frequently (>1%) co-reported AEs were: *Vomiting* (43.85%, n=838; 32 serious and 806 non-serious), *Pallor* (5.34%, n=102; 9 serious and 93 non-serious), *Cough* (4.81%, n=92;

1 serious and 91 non-serious), *Nausea* (4.40%, n=84; 2 serious and 82 non-serious), *Irritability* (3.24%, n=62; all non-serious), *Mood altered* (3.14%, n=60; 1 serious and 59 non-serious), *Crying* (2.67%, n=51; 1 serious and 50 non-serious), *Asthenia* (2.15%, n=41; 1 serious and 40 non-serious), *Malaise* (1.73%, n=33; 1 serious and 32 non-serious), *Hiccups* (1.73%, n=33; all non-serious), *Respiratory tract irritation* (1.47%, n=28; all non-serious), *Somnolence* (1.47%, n=28; 1 serious and 27 non-serious), *Retching* (1.26%, n=24; all non-serious), *Pyrexia* (1.10%, n=21; 2 serious and 19 non-serious), and *Fatigue* (1.05%, n=20; all non-serious).

Eighteen events of *Choking* (14 serious and 4 non-serious) were received in 18 ICSRs. All the children (age range 6 to 24 months) introduced EHTPs, parts of them, or leachate of EHTP into their mouths. The co-reported events reported more than once included: *Cough* (n=9), *Vomiting* (n=7), *Respiratory tract irritation* (n=6), *Pyrexia* (n=2), and *Respiratory disorder* (n=2), all non-serious AEs. No medical intervention was deemed necessary in all 18 ICSRs. The event outcome of *Choking* was reported as resolving or resolved for 5 events (3 serious and 2 non-serious) and was unknown for the remaining 13 events. Taking into consideration that none of these cases led to hospitalization and that no medical intervention was necessary, it is unlikely that these refer to cases of airway obstruction.

Induction based THS was launch first in Japan in August 2021. Up to date, AEs associated with accidental exposure to EHTP by children are similar in nature and frequency between the blade and the induction based THS. PMI will continue to monitor closely cases of accidental exposure to EHTP by children for blade and induction based THS.

Cumulatively, the information received on the accidental exposure by children to the EHTP did not show a modified trend in the number of cases, or 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.

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 (31-Dec-2022) 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 excluded being 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, 6,270 AEs (7 serious and 6,263 non-serious) were received in 6,177 ICSRs. The retrieved AEs among the selected PT list were: *Burning sensation* (n=1,664; 3 serious and 1,661 non-serious), *Burning sensation mucosal* (n=31; all non-serious), *Oral discomfort* (n=4,557; 4 serious and 4,553 non-serious), and *Skin burning sensation* (n=18; all non-serious). The AEs retrieved among the selected LLTs under the PT *Oral discomfort* were: *Lip burning sensation of* (n=2,559; 2 serious and 2,557 non-serious), *Burning lips* (n=1,032; 1 serious and 1,031 non-serious), *Burning mouth* (n=558; 1 serious and 557 non-serious), *Burning oral sensation* (n=154; all non-serious), *Oral mucosal burning sensation* (n=127; all non-serious), and *Oral hot feeling* (n=127; all non-serious). Of note, the total number of AEs under the PT *Oral discomfort* was 5,100, out of which 4,557 AEs were included in the risk assessment. The LLTs excluded from the risk assessment were: *Oral discomfort* (n=233), *Lip discomfort* (n=176), *Discomfort in mouth* (n=110), and *Oral cavity discomfort* (n=24).

Among the 3 serious events of *Burning sensation*, 2 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.

Concerning the 4 serious events of Oral discomfort, 3 of them concerned burning/ burning sensation of lips, and one concerned burning mouth. All 4 were assessed as serious as they involved hospitalization.

Cumulatively, the information received on this risk did not show a different trend in the number of cases, or impact on the individual or public health throughout the IBD and the DLP of this SUR. 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

Thermal burns defined as skin injuries caused by exposure to heat may occur while using EC. Concerning the burn severity, it can be determined by burn depth, size, location, and patient age.[29] The burns reported with the EC use vary from small skin blisters to serious fourth degree burns that may occur with the explosion of the EC. The mechanism of the explosions is attributed to the battery. Lithium-ion batteries are the most common batteries in EC as they are lighter in weight and more powerful compared to other batteries.[30] However, the lithium-ion battery is susceptible to a thermal runaway process that can generate massive amounts of energy with temperatures reaching up to 903°C causing spontaneous explosions.[31] The failure rate of lithium batteries established during the manufacturing is 1 in 10 million.[32]

The study by Corey et al. 2018[33] analyzed the data provided in the National Electronic Injury Surveillance System (NEISS) to estimate the number of emergency department visits for burn injuries associated with EC batteries in the U.S. In 2016, 26 EC battery-related burn cases were captured by NEISS, which translates to a national estimate of 1,007 (95% CI: 357–1657) injuries presenting in U.S. emergency departments. Thermal burns made for 80.4% of all injuries and occurred mainly to the upper leg/lower trunk (77.3%). Examination of the case narrative showed that at least 20 of the burn injuries occurred while EC batteries were held in the user's pocket. A later study by Dohnalek et al.[34] analyzed information from a national database of emergency department visits looking for EC related injuries over a 10-year period. They found a total of 49 incidents recorded during the years 2008 to 2017, including 18 cases in 2017, 25 cases in 2016, 5 cases in 2015, and 1 case in 2013. Using statistical weights, the estimated annual national incidence is 835 cases. Most of the injuries were thermal burns to the lower extremity, followed by the upper extremity and hand. Additionally, according to the review by Rossheim et al.[35], there were an estimated 2,035 EC explosion and burn injuries presented to U.S. hospital emergency departments (95% CI 1107 to 2964) in years 2015 to 2017.

To characterize this risk, a cumulative search from the IBD (04-Nov-2014) to the DLP of this SUR (31-Dec-2022) 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, 23,143 AEs (31 serious and 23,112 non-serious) were received in 22,399ICSRs: *Thermal burn* (n=18,248; 21 serious and 18,227 non-serious), *Burn oral cavity* (n=4,618; 3 serious and 4,615 non-serious), *Burns second degree* (n=183; all non-serious), *Airway burns* (n=70; 1 serious and 69 non-serious), *Burns first degree* (n=17; all non-serious), *Burns third degree* (n=5; all serious), and *Thermal burns of eye* (n=2; 1 serious and 1 non-serious).

In about 73.25% of cases, the consumer reported the oral cavity (including mouth, lips, and tongue) as the body site affected. In about 7.05% of the cases, the reported body site were fingers and/or hands. In 19.08% of cases, the affected body site was not specified.

Among the 21 serious events of *Thermal burn*, 20 led to hospitalization. In the remaining case, the charger "caught on fire", and "possibly exploded", which led to hand burn. The respondent mentioned that he was hurt by debris of something and he got something stuck into his hand (not further explained) as his hand was smeared with ash (did not explain more about the burned issue). Regarding the charger, it was reported that "the charger caught fire and possibly exploded". A technical investigation had been conducted and showed that the device pieces were physically damaged due to external causes, including dismantling of the charger and the battery. Concerning the site of the burn, 16 cases reported a burn of lips or hand/fingers, in 3 cases, the burn site was provided as laryngeal mucosa, throat, voice box, and in remaining 2 cases the site was unspecified.

Among the 3 serious events of *Burn oral cavity*, two led to hospitalization. In the third case, the consumer experienced a disgusting feeling, along with the tongue burning. The consumer felt that his tongue was scorched, the taste perceptions was lost, and it did not improve after the product was stopped.

In the 1 serious event reported of *Airway burns* that led to hospitalization, the consumer reported that she had an anaphylactic shock, a spasm and burned bronchi after using *IQOS*$^{TM.}$

Among the 5 serious events of *Burns third degree*, 1 case reported a third degree burn to the hand due to an alleged explosion of the device, 1 case reported "very deep subcutaneous burn" of lips and salivary gland resection due to the burn, 1 case reported a burn on consumer's thumb resulting on the loss of the skin after having touched the lid of the device, 1 case reported a third degree burn inside the mouth, and the last case reported "burned my lower lip, to a stage 3 burn lip".

In 1 serious event reported of *Thermal burns of eye* that did not lead to hospitalization, the consumer experienced burned eye, burning sensation in the eye and eye infection. The consumer cleaned the holder with the cleaning stick, a piece of dirt flew into his eye and gave him a burning sensation in the eye and burned his eye. It was reported that now he had an infection that may require surgery.

Cumulatively, the information received on the risk of *Thermal burn* did not show a different trend in the number of cases, or impact on the individual or public health throughout the IBD and the DLP of this SUR. PMI will continue to perform regular evaluation of this risk to ensure the ongoing evaluation of new safety information.

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[36] as it is clear that maternal smoking affects fetal wellbeing and growth. Indeed, nicotine is able to cross the placenta, and therefore, may affect foetal development.[37] 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 7.0 for THS (dated 105-May-2022), 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 (31-Dec-2022) 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 delivery complications and risk factors (excl. abortions and stillbirth," "Fœtal disorders," "Functional lactation disorders," "Neonatal disorders," "Normal pregnancy conditions and outcomes," and "Termination of pregnancy and risk of abortion".

Cumulatively, 405 AEs (8 serious and 397 non-serious) were received in 385 ICSRs including *Exposure during pregnancy* (n=241; 1 serious and 240 non-serious), *Maternal exposure during pregnancy* (n=120; all non-serious), *Morning sickness* (n=12; all non-serious), *Abortion spontaneous* (n=3; all serious), *Pregnancy* (n=3; non-serious), *Maternal exposure during breast feeding* (n=3; all non-serious), *Primigravida* (n=2; all non-serious), *Exposure via breast milk* (n=2; all non-serious), *Multigravida* (n=2; all non-serious), *Maternal exposure timing unspecified* (n=2; all non-serious), *Imminent abortion* (n=1; serious), *Umbilical cord around neck* (n=1; non-serious), *Unintended pregnancy* (n=1; non-serious), *Somatic symptom disorder of pregnancy* (n=1; non-serious), *Live birth* (n=1; non-serious), *Mastitis* (n=1; serious), *Ectopic pregnancy* (n=1; serious), *Maternal exposure before pregnancy* (n=1, non-serious), *Respiratory disorder neonatal* (n=1; non-serious), *Normal newborn* (n=1; non-serious), *Suppressed lactation* (n=1; non-serious), *Poor feeding infant* (n=1; non-serious), *Abortion of ectopic pregnancy* (n=1; serious), *Pre-eclampsia* (n=1; non-serious), *Infant irritability* (n=1; non-serious).

Cumulatively, there were 8 SAEs concerning pregnancy reported in 7 ICSRs. Three cases reported an event of *Abortion spontaneous*. Two cases provided no additional data. The third case concerns a female partner of the *IQOS*™ consumer who has a medical history of miscarriage. The fourth case reported a serious event of *Imminent abortion* that concerns the wife of the consumer. The wife reported that "I really dislike how my husband smokes *IQOS* cigarettes even though I have an imminent abortion." The fact that her husband said he would quit once she got pregnant made her even more frustrated. The data provided in this case were limited. The fifth case reported SAE of *Ectopic pregnancy* and *Abortion of ectopic pregnancy*. The consumer reported that she had an ectopic pregnancy, and the baby did not make it. The sixth case reported a SAE of *Mastitis*. The consumer stopped using *IQOS* due to laryngitis symptoms and when she resumed using it, mastitis occurred. No additional data are available. The seventh case reported SAE of *Exposure during pregnancy*. In this case, the consumer started using *IQOS* 2.4 and *IQOS* consumable (unspecified) and reported drug exposure during pregnancy followed by asthma, dyspnoea and headache 6 months later. She had medical history of asthma and was an ex-smoker smoking on average 3 to 4 cigarettes per day for unspecified duration. Final action taken with the product's use following the events' occurrence was product use withdrawal. It was reported that the events were resolved after stopping product use and returned after product use was resumed. The outcome of the events asthma, dyspnoea, and headache was reported as not resolved, and the outcome of the event drug exposure during pregnancy was reported as resolved. Asthma and exposure during pregnancy are considered as unlisted events and dyspnoea and headache are considered as listed events according to the SPI THS version 7.0. Asthma could be explained due to underlying history of asthma in this case.

The 348 co-reported AEs were The most reported AEs representing at least 1% of the total included: *Passive smoking* (17.53%, n=61), *Malaise* (6.90%, n=24), *Nausea* (6.32%, n=22), *Nicotine dependence* (4.89%, n=17), *Product complaint* (3.74%, n=13), *No adverse event* (3.45%; n=12), *Product odour abnormal* (2.59%, n=9), *Anxiety* (2.01%; n=7), *Headache* (2.01%; n=7, 1 serious and 6 non-serious), *Illness* (2.01%; n=7), *Vomiting* (2.01%; n=7), *Throat irritation* (1.44%; n=5), *Accidental exposure to product by child* (1.44%; n=5), *Dizziness* (1.44%; n=5), *Dyspnoea* (1.44%; n=5, 1 serious and 4 non-serious), *Cough* (1.44%; n=5), *Pain* (1.15%; n=4), *Thermal burn* (1.15%; n=4), and *Abdominal pain upper* (1.15%; n=4).

Cumulatively, the information received on the risk associated to the exposure during Pregnancy and lactation to the THS did not show a modified trend in the number of cases, or 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.

(b) (4)

16 CONCLUSIONS AND ACTIONS

This SUR covers all relevant safety data related to THS products use received by PMI during the period from 01-Jan-2022 to 31-Dec-2022.

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 meticulously collect and evaluate all new safety information in order to guarantee adequate supervision of the safety of THS products and their impact on public health.

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(b) (4)

18 APPENDICES

18.1 Appendix 1: Reference Safety Information

THS SPI version 7.0 dated 10-May-2022

PMI RESEARCH & DEVELOPMENT

SUMMARY OF PRODUCT INFORMATION (SPI)

Tobacco Heating System (THS)

Company:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	7.0
Release Date:	10 May 2022
Replaces Previous Version:	Version 6.0

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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
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 producing combustion. The THS products generate on average 90% lower levels of HPHCs compared to cigarette smoke. The THS products are currently marketed as *IQOS™ with HeatSticks™/HEETS™, IQOS ILUMA™* with *TEREA ™* sticks, *lil™ SOLID with Fiit™*, and *lil™ HYBRID with MIIX™*.

The results of clinical studies conducted with the THS[1] have shown a consistent sustained reduction in the levels of biomarkers of exposure (BoExp) to selected HPHCs in smokers who used 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[1] were comparable to those observed when smokers stopped smoking cigarettes (1).

In addition, the results of the Exposure Response Studies, measuring the biological response of smokers who predominantly[2] switch to the THS[1] for six months (2) and for a prolonged period of 26 weeks (3) compared with individuals who continued to smoke cigarettes, demonstrated favorable changes in biomarkers of potential harm (also referred to as clinical risk endpoints) pointing in the direction of risk reduction in those who switched to the THS[3].

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 products should be used safely and effectively as well 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.

2 PRODUCT DESCRIPTION

The THS consists of two 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 two separate elements or one element.

The EHTP is designed to function with the holder and is composed of a tobacco plug, a hollow acetate tube (HAT), a polylactic acid (PLA) polymer-film filter, a mouthpiece filter, and of outer and mouth-end papers. Additionally, it contains non-flammable wrapping paper[4] 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

[1] IQOS™ with HeatSticks™/HEETS™.

[2] Switching to THS use at ≥70% on average.

[3] The information in this document pertaining to IQOS with HeatSticks/HEETS is considered also applicable to IQOS ILUMA with TEREA sticks, lil SOLID with Fiit and lil HYBRID with MIIX.

[4] In selected markets alu-wrapper paper is used instead of non-flammable paper.

(i) a heating blade[5] or heating pins[6] that is placed inside the THD; (ii) external heating;[7] (iii) or induction technology[8] where a metal strip, referred to as the susceptor, is integrated into the tobacco stick. The composition of EHTP is reported in Table 1. Each tobacco stick contains, on average, five (5) to six (6) milligrams of nicotine.

Figure 1 Schematic cross-sectional view of the EHTP

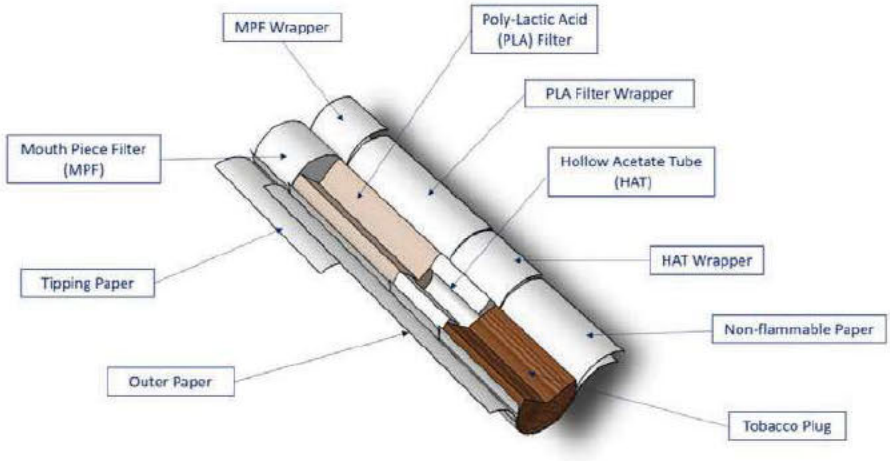
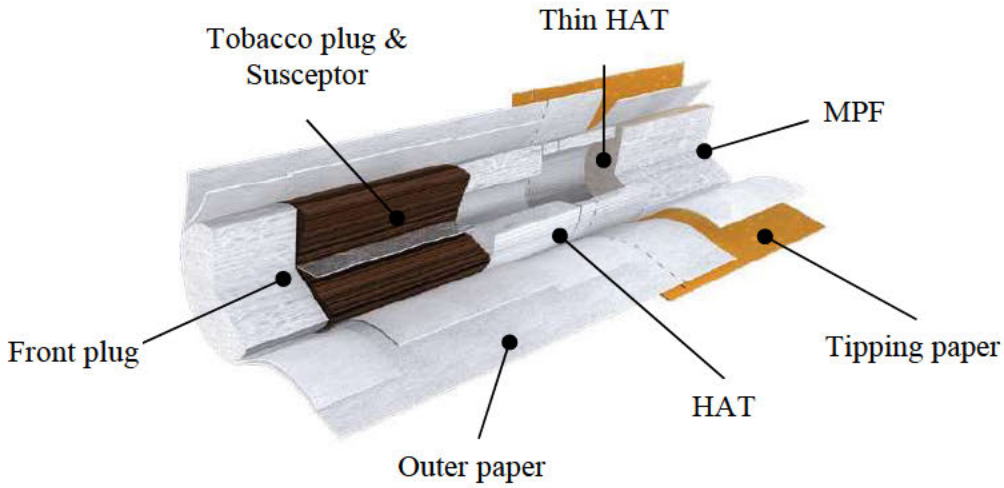


Figure 2 Schematic cross-sectional view of the EHTP with susceptor



[5] *IQOS™*

[6] *lil™ SOLID*

[7] *lil™ HYBRID*

[8] *IQOS ILUMA™*

Table 1 Ingredients contained in the EHTP, in addition to blended tobacco

* Only in *TEREA*™ sticks

Ingredients contained in the EHTP
Tobacco mixture (Tobacco, Glycerin, Water, Cellulose fibers, Guar gum, Menthol, Propylene glycol, Flavors)
Wrapper and adhesive
Hollow acetate tube (HAT)
Mouth-piece filter (MPF)
Front Filter Plug (FP)*
Outer paper
Mouth-end paper
Adhesives
Metal Strip (Susceptor)*

2.1 Product Name

The THD are marketed as *IQOS™*, *IQOS ILUMA™*, *lil™ SOLID*, and *lil™ HYBRID*. The EHTPs are marketed as *HeatSticks™/ HEETS™*, *TEREA ™* sticks, *Fiit™*, and *MIIX™* [9] Devices must only be used with the tobacco stick specifically designed for use with such device.

2.2 Product Variants

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

2.3 THS Aerosol

2.3.1.1 Aerosol Fractions Determined by International Organization for Standardization (ISO) and Health Canada Methods

Many countries require cigarette manufacturers to print the per cigarette yields of tar, nicotine, and carbon monoxide (CO) on the outside of the packaging. Per cigarette/tobacco stick tar, nicotine, and CO yields are normally determined by standardized test methods. The most widely used test method is ISO 4387. PMI has developed a modified version of this method, which improves the determination of tar in products with high water content, which is typical for heated tobacco products (4). Another method is the more intensive smoking method, Health Canada Intense (HCI)(5) .

Table 2 and Table 3 list HCI reported values for Regular and Menthol THS tobacco sticks:

Table 2 Reported Aerosol Fractions for the THS Tobacco Sticks (Regular)

Constituent (mg/THS Tobacco Stick)	ISO [10]	Health Canada Intense regimen [11]
NFDPM [12]	(b) (4)	
Nicotine		
Carbon monoxide		

[9] The Miix™ consumable consists of (b) (4)
(b) (4)

[10] International Organization for Standardization ISO machine-smoking regimen. The analytical method has been modified to avoid inaccuracies as a result of condensation from high water-content aerosols.

[11] Health Canada Intense machine-smoking regimen (55 mL puff volume, 2-second puff duration, 30-second inter-puff interval)5. Health Canada, Tobacco Control Programme. Determination of "tar", nicotine and carbon monoxide in mainstream tobacco smoke. T-115. 1999;Available from: http://edge.rit.edu/edge/P10056/public/Health%20Canada%20Nicotine (Accessed on 06 January 2016).. Data collected 11/11/2014, product reference CONS.01938.RD(2)/B-13063, blend Dorado II.

[12] NFDPM: nicotine free dry particulate matter

Table 3 Reported Aerosol Fractions for the THS Tobacco Sticks (Menthol)

Constituent (mg/THS Menthol Tobacco Stick)	ISO [13]	Health Canada Intense regime [14]
NFDPM [15]	(b) (4)	
Nicotine		
Carbon monoxide		

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 and 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.

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 Guide.

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.

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[13] International Organization for Standardization ISO machine-smoking regimen. The analytical method has been modified to avoid inaccuracies as a result of condensation from high water-content aerosols.

[14] Health Canada Intense machine-smoking regimen (55 mL puff volume, 2-second puff duration, 30-second inter-puff interval)5. Health Canada, Tobacco Control Programme. Determination of "tar", nicotine and carbon monoxide in mainstream tobacco smoke. T-115. 1999;Available from: http://edge.rit.edu/edge/P10056/public/Health%20Canada%20Nicotine (Accessed on 06 January 2016).. Data collected 19-23/01/2015, product reference CONS.01944.RD, blend Dorado I.

[15] NFDPM: nicotine free dry particulate matter.

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*^{TM} stick can cause serious injury to internal organs due small metal part with sharp edges.

3.3.1.3 Burning Sensation

Of note, PMI has found that 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. In some cases, this may result in thermal burns. 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 THS 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) (6). 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 as 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 a de-induction of CYP1A2, resulting from a decrease or absence of exposure to inducers such as PAHs. 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 4 and Table 5 are to be considered expected with THS use.

3.5.2.1 Identified Risks

Table 4 provides the list of identified risks associated with the use of THS based on clinical studies and post-market surveillance.

Table 4 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 Class Effect Risks

Table 5 provides the list of nicotine class effect risks with THS use, based on safety information included in the Summary of Product Characteristics (SPC) or label for Nicotine Replacement Therapies (NRTs). Based on Merck Manual online (7) 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 (8-10), nicotine lozenge (11-13), nicotine inhalator/inhaler (14, 15), and nicotine mouth spray (16) were selected as references for nicotine class effect risks.

AE terms mentioned in the SPCs/label for nicotine gum (8-10), nicotine lozenge (11-13), nicotine inhalator/inhaler (14, 15), and nicotine mouth spray (16), which are not Preferred Terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA), were coded to match corresponding PTs in MedDRA.

Table 5 List of Class Effect Risks with Nicotine Use

System Organ Class	Risk (Preferred Term)
Immune System Disorders	- Anaphylactic reaction
	- Hypersensitivity
Psychiatric disorders	- Abnormal dreams
	- Agitation
	- Anxiety
	- Disturbance in attention
	- Insomnia
	- Mood altered
	- Irritability
	- Nervousness
	- Depression
Nervous System Disorders	- Headache
	- Dizziness

System Organ Class	Risk (Preferred Term)
	- 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
	- Stomatitis
	- Hiccups
	- Abdominal pain
	- Diarrhoea
	- Dry mouth
	- Dyspepsia
	- Gastritis
	- Oesophagitis
	- Flatulence
	- Salivary hypersecretion
	- Vomiting
	- Eructation

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

3.6 Other Effects

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

Quitting smoking has been associated with an increased gum bleeding due to an increase in blood flow in gum tissues (17). This effect is transient and seen particularly during the first months after quitting (18).

Because THS heats tobacco instead of burning it, switching to THS reduces the exposure to toxicants/HPHCs, which are associated with cigarette smoking, by over 90% compared to continued smoking (1). 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 accurate estimate of the acute lethal oral dose in adults (19). One EHTP contains, in average, five to six milligrams 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 (20) 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 commonly seen in acute nicotine intoxication cases (21, 22), 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 (23).

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 several weeks.

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 (24, 25).

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 2.4).

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™ with HeatSticks™/HEETS™

August-2020 (Russia) for lil™ SOLID with Fiit™

October-2020 (Japan) for lil™ HYBRID with Miix™

September 2021 (Japan) for IQOS ILUMA™ with *TEREA* ™ sticks

6 DATE OF REVISION OF THE TEXT

10 May 2022

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18.2 Appendix 2: Cumulative and Interval Summary Tabulations

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
Blood and lymphatic system disorders	**0**	**0**	**0**	**1**	**0**	**1**
Anaemia	0	0	0	1	0	**1**
Cardiac disorders	**21**	**2**	**0**	**0**	**4**	**8**
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**
Cardiac failure	0	0	0	0	1	**1**
Myocardial ischaemia	0	0	0	0	1	**1**
Eye Disorders	**1**	**0**	**0**	**0**	**0**	**1**
Cataract	1	0	0	0	0	**1**
Gastrointestinal disorders	**2**	**0**	**0**	**0**	**6**	**8**
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**
General disorders and administration site conditions	**1**	**1**	**0**	**0**	**0**	**2**
Death	1	1	0	0	0	**2**
Infections and infestations	**5**	**0**	**1**	**6**	**3**	**15**
Appendicitis	0	0	0	1	1	**2**
Cellulitis	1	0	0	0	0	**1**
Cellulitis staphylococcal	1	0	0	0	0	**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**
Injury, poisoning and procedural complications	**4**	**2**	**0**	**5**	**0**	**11**
Clavicle fracture	1	0	0	0	0	**1**
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**
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**

MedDRA SOC MedDRA PT	CC	THS unspecified	THS Menthol	THS Regular	SA	Total
Metabolism and nutrition disorders	**0**	**0**	**1**	**0**	**0**	**1**
Diabetic ketoacidosis	0	0	1	0	0	**1**
Musculoskeletal and connective tissue disorders	**3**	**1**	**0**	**1**	**0**	**5**
Back pain	1	0	0	0	0	**1**
Costochondritis	0	0	0	1	0	**1**
Jaw cyst	1	0	0	0	0	**1**
Lumbar spine stenosis	0	1	0	0	0	**1**
Vertebral osteophyte	1	0	0	0	0	**1**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**1**	**0**	**1**	**1**	**6**
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**
Nervous system disorders	**4**	**0**	**0**	**1**	**0**	**5**
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**
Psychiatric disorders	**2**	**0**	**0**	**2**	**0**	**4**
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**
Renal and urinary disorders	**1**	**0**	**0**	**0**	**0**	**1**
Nephrolithiasis	1	0	0	0	0	**1**
Reproductive system and breast disorders	**0**	**1**	**0**	**1**	**0**	**2**
Heavy menstrual bleeding	0	0	0	1	0	**1**
Ovarian cyst	0	1	0	0	0	**1**
Respiratory, thoracic and mediastinal disorders	**1**	**0**	**0**	**1**	**0**	**2**
Pleural effusion	1	0	0	0	0	**1**
Pneumonia aspiration	0	0	0	1	0	**1**
Social circumstances	**1**	**0**	**0**	**0**	**0**	**1**
Bereavement	1	0	0	0	0	**1**
Vascular disorders	**1**	**0**	**0**	**0**	**1**	**2**
Peripheral arterial occlusive disease	0	0	0	0	1	**1**
Peripheral ischaemia	1	0	0	0	0	**1**
Total	**31**	**8**	**2**	**19**	**15**	**75**

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	
Total		**25**	**25**

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
Blood and lymphatic system disorders	**39**	**192**	**0**	**2**	**39**	**194**
Anaemia	5	13	0	1	5	14
Blood disorder	2	3	0	0	2	3
Coagulopathy	0	2	0	0	0	2
Lymph node pain	1	21	0	0	1	21
Lymphadenitis	5	18	0	0	5	18
Lymphadenopathy	26	135	0	1	26	136
Cardiac disorders	**524**	**2246**	**349**	**1360**	**873**	**3606**
Acute myocardial infarction	0	0	0	3	0	3
Angina pectoris	0	1	251	990	251	991
Angina unstable	0	0	3	6	3	6
Arrhythmia	0	0	67	219	67	219
Arteriospasm coronary	0	0	0	3	0	3
Atrial fibrillation	0	0	0	1	0	1
Atrioventricular block	1	2	0	0	1	2
Bradycardia	0	0	1	3	1	3
Cardiac arrest	0	0	0	2	0	2
Cardiac discomfort	20	104	0	1	20	105
Cardiac disorder	78	274	2	8	80	282
Cardiac dysfunction	0	0	0	1	0	1
Cardiac failure	0	0	2	5	2	5
Cardiac failure acute	0	0	0	1	0	1
Cardiac failure chronic	0	0	0	1	0	1
Cardiac fibrillation	0	0	0	2	0	2
Cardiac flutter	0	0	1	3	1	3
Cardiomegaly	0	2	0	0	0	2
Cardiopulmonary failure	0	0	0	1	0	1
Cardiovascular disorder	5	44	0	1	5	45
Carditis	0	0	0	1	0	1
Coronary artery disease	0	0	0	2	0	2
Coronary artery occlusion	0	0	0	1	0	1
Dressler's syndrome	0	1	0	0	0	1
Extrasystoles	11	20	0	0	11	20
Gastrocardiac syndrome	0	1	0	0	0	1
Left ventricular hypertrophy	0	2	0	0	0	2
Myocardial infarction	0	1	15	70	15	71

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Myocardial ischaemia	0	0	1	7	1	7
Palpitations	254	1092	1	12	255	1104
Pericardial effusion	0	0	0	1	0	1
Pericarditis	0	0	0	2	0	2
Sinus arrhythmia	1	2	0	1	1	3
Sinus tachycardia	2	3	0	1	2	4
Supraventricular extrasystoles	1	1	0	0	1	1
Tachyarrhythmia	0	1	0	1	0	2
Tachycardia	150	694	5	10	155	704
Tachycardia paroxysmal	1	1	0	0	1	1
Congenital, familial and genetic disorders	**2**	**6**	**0**	0	**2**	**6**
Albinism	0	1	0	0	0	1
Cystic fibrosis	1	1	0	0	1	1
Frenulum breve	1	1	0	0	1	1
Gastrointestinal disorder congenital	0	1	0	0	0	1
Kenny-Caffey syndrome	0	1	0	0	0	1
Protuberant ear	0	1	0	0	0	1
Ear and labyrinth disorders	**153**	**665**	**2**	**10**	**155**	**675**
Deafness	0	0	1	5	1	5
Deafness transitory	0	1	0	1	0	2
Ear congestion	5	27	0	0	5	27
Ear discomfort	7	52	0	0	7	52
Ear disorder	2	10	0	0	2	10
Ear haemorrhage	1	2	0	0	1	2
Ear inflammation	2	2	0	0	2	2
Ear pain	10	53	0	0	10	53
Ear pruritus	3	7	0	0	3	7
Ear swelling	0	5	0	0	0	5
Excessive cerumen production	1	2	0	0	1	2
External ear inflammation	1	1	0	0	1	1
Hypoacusis	2	16	0	1	2	17
Inner ear disorder	2	2	0	0	2	2
Inner ear inflammation	0	2	0	0	0	2
Meniere's disease	0	0	1	1	1	1
Middle ear inflammation	0	1	0	0	0	1
Motion sickness	2	26	0	0	2	26
Otorrhoea	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Sudden hearing loss	0	0	0	1	0	1
Tinnitus	17	96	0	0	17	96
Vertigo	97	357	0	1	97	358
Vertigo positional	1	2	0	0	1	2
Endocrine disorders	**11**	**61**	**1**	**4**	**12**	**65**
Autoimmune thyroid disorder	0	0	0	1	0	1
Goitre	3	10	0	0	3	10
Hyperthyroidism	0	0	1	3	1	3
Hypothyroidism	0	1	0	0	0	1
Thyroid cyst	0	1	0	0	0	1
Thyroid disorder	7	30	0	0	7	30
Thyroid mass	0	5	0	0	0	5
Thyroid pain	0	9	0	0	0	9
Thyroiditis	1	5	0	0	1	5
Eye disorders	**132**	**972**	**1**	**25**	**133**	**997**
Abnormal sensation in eye	0	1	0	0	0	1
Accommodation disorder	0	1	0	0	0	1
Asthenopia	1	10	0	0	1	10
Binocular eye movement disorder	1	1	0	0	1	1
Blepharospasm	0	6	0	0	0	6
Blindness	0	0	1	5	1	5
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	1	1	0	0	1	1
Dermatochalasis	1	1	0	0	1	1
Diplopia	0	4	0	0	0	4
Dry eye	1	91	0	0	1	91
Eczema eyelids	1	2	0	0	1	2
Erythema of eyelid	0	2	0	0	0	2
Excessive eye blinking	1	3	0	0	1	3
Exophthalmos	0	0	0	1	0	1
Eye allergy	2	5	0	0	2	5
Eye colour change	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Eye discharge	0	7	0	0	0	7
Eye disorder	4	21	0	0	4	21
Eye haemorrhage	0	1	0	2	0	3
Eye inflammation	2	5	0	1	2	6
Eye irritation	9	51	0	1	9	52
Eye movement disorder	0	4	0	0	0	4
Eye oedema	0	1	0	0	0	1
Eye pain	13	110	0	0	13	110
Eye paraesthesia	0	1	0	0	0	1
Eye pruritus	11	65	0	1	11	66
Eye swelling	6	65	0	3	6	68
Eyelid disorder	0	1	0	0	0	1
Eyelid function disorder	0	1	0	0	0	1
Eyelid irritation	1	3	0	0	1	3
Eyelid oedema	0	3	0	0	0	3
Eyelid ptosis	0	1	0	0	0	1
Eyelid rash	0	2	0	0	0	2
Eyelids pruritus	1	4	0	0	1	4
Foreign body sensation in eyes	1	2	0	0	1	2
Lacrimation increased	26	155	0	2	26	157
Maculopathy	0	1	0	0	0	1
Metamorphopsia	0	2	0	0	0	2
Mydriasis	0	4	0	0	0	4
Ocular discomfort	3	23	0	0	3	23
Ocular hyperaemia	11	75	0	0	11	75
Ocular hypertension	0	0	0	1	0	1
Periorbital pain	0	1	0	0	0	1
Periorbital swelling	1	7	0	0	1	7
Photophobia	0	4	0	0	0	4
Photopsia	0	1	0	0	0	1
Swelling of eyelid	3	10	0	0	3	10
Vision blurred	11	113	0	2	11	115
Visual acuity reduced	1	3	0	0	1	3
Visual field defect	0	1	0	0	0	1
Visual impairment	18	82	0	1	18	83
Vitreous floaters	1	1	0	0	1	1
Xerophthalmia	0	1	0	1	0	2
Gastrointestinal disorders	**8623**	**49967**	**55**	**280**	**8678**	**50247**
Abdominal discomfort	229	1586	2	8	231	1594

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Abdominal distension	61	394	0	3	61	397
Abdominal pain	161	469	0	2	161	471
Abdominal pain lower	4	22	0	0	4	22
Abdominal pain upper	615	3156	3	11	618	3167
Abdominal rigidity	1	5	0	0	1	5
Abnormal faeces	2	7	0	1	2	8
Aerophagia	1	2	0	0	1	2
Allergic stomatitis	0	2	0	0	0	2
Anaesthesia oral	1	10	0	0	1	10
Anal incontinence	0	2	0	0	0	2
Angular cheilitis	0	2	0	0	0	2
Anorectal discomfort	0	4	0	0	0	4
Aphthous ulcer	37	329	0	0	37	329
Aptyalism	2	26	0	0	2	26
Barrett's oesophagus	0	0	0	1	0	1
Bile acid malabsorption	1	1	0	0	1	1
Bowel movement irregularity	0	12	0	0	0	12
Breath odour	25	148	0	1	25	149
Burning mouth syndrome	4	7	0	0	4	7
Cardiospasm	2	5	0	0	2	5
Change of bowel habit	0	2	0	0	0	2
Chapped lips	38	237	0	0	38	237
Cheilitis	41	329	0	0	41	329
Chronic gastritis	0	2	0	0	0	2
Coating in mouth	3	35	0	0	3	35
Colitis	9	12	0	1	9	13
Colitis ulcerative	0	0	1	3	1	3
Constipation	8	95	0	0	8	95
Crohn's disease	0	0	0	1	0	1
Dental caries	7	29	0	1	7	30
Dental discomfort	18	65	0	0	18	65
Dental paraesthesia	7	21	0	0	7	21
Dental plaque	6	39	0	0	6	39
Diaphragmatic hernia	0	1	0	0	0	1
Diarrhoea	100	524	1	7	101	531
Discoloured vomit	0	2	0	0	0	2
Dry mouth	596	3073	0	3	596	3076
Duodenal ulcer	0	0	0	4	0	4
Duodenitis	0	3	0	0	0	3

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Dysbiosis	1	1	0	0	1	1
Dyschezia	1	2	0	0	1	2
Dyspepsia	489	2609	1	6	490	2615
Dysphagia	47	307	0	4	47	311
Enamel anomaly	0	1	0	0	0	1
Enlarged uvula	0	15	0	0	0	15
Enteritis	0	2	0	0	0	2
Enterocolitis	0	0	0	1	0	1
Epigastric discomfort	5	21	0	0	5	21
Erosive duodenitis	0	0	0	1	0	1
Eructation	14	66	0	0	14	66
Faeces discoloured	1	5	0	0	1	5
Faeces hard	0	2	0	0	0	2
Faeces soft	1	2	0	0	1	2
Flatulence	38	120	1	1	39	121
Food poisoning	1	6	0	0	1	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 disorder	8	61	0	1	8	62
Gastric perforation	0	1	0	1	0	2
Gastric ulcer	0	1	6	30	6	31
Gastric ulcer perforation	0	0	0	1	0	1
Gastritis	23	111	0	1	23	112
Gastritis erosive	0	0	1	1	1	1
Gastrointestinal disorder	33	197	0	5	33	202
Gastrointestinal hypermotility	0	1	0	0	0	1
Gastrointestinal inflammation	0	6	0	0	0	6
Gastrointestinal motility disorder	1	4	0	0	1	4
Gastrointestinal oedema	0	0	0	2	0	2
Gastrointestinal pain	7	29	1	1	8	30
Gastrointestinal sounds abnormal	1	6	0	0	1	6
Gastrointestinal tract irritation	1	5	0	0	1	5
Gastrointestinal ulcer	0	1	0	0	0	1
Gastrooesophageal reflux disease	43	214	0	2	43	216

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Gastrooesophageal sphincter insufficiency	1	1	0	0	1	1
Gingival bleeding	519	2246	2	9	521	2255
Gingival blister	1	27	0	0	1	27
Gingival discolouration	1	29	0	0	1	29
Gingival discomfort	55	213	0	1	55	214
Gingival disorder	32	218	0	2	32	220
Gingival erosion	0	6	0	0	0	6
Gingival erythema	5	33	0	0	5	33
Gingival pain	175	749	0	0	175	749
Gingival pruritus	9	24	0	0	9	24
Gingival recession	16	72	0	2	16	74
Gingival scar	1	1	0	0	1	1
Gingival swelling	84	569	0	2	84	571
Gingival ulceration	1	11	0	0	1	11
Glossitis	41	251	0	0	41	251
Glossodynia	93	839	0	0	93	839
Haematemesis	0	0	6	13	6	13
Haematochezia	0	0	0	4	0	4
Haemorrhoids	3	7	0	0	3	7
Hiatus hernia	0	1	0	0	0	1
Hyperaesthesia teeth	41	250	0	0	41	250
Hyperchlorhydria	3	27	0	1	3	28
Hypertrophy of tongue papillae	0	2	0	0	0	2
Hypoaesthesia oral	56	488	0	1	56	489
Hypoaesthesia teeth	2	9	0	0	2	9
Intestinal ulcer	0	0	1	1	1	1
Irritable bowel syndrome	1	11	0	0	1	11
Large intestinal ulcer	0	0	0	1	0	1
Large intestine perforation	0	0	0	1	0	1
Leukoplakia oral	0	0	0	1	0	1
Lip blister	62	794	0	0	62	794
Lip discolouration	8	114	0	0	8	114
Lip disorder	4	56	0	0	4	56
Lip dry	67	388	0	0	67	388
Lip erosion	0	2	0	0	0	2
Lip erythema	20	244	0	0	20	244
Lip exfoliation	19	286	0	0	19	286
Lip haematoma	1	1	0	0	1	1

(b) (4)

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Lip haemorrhage	7	63	0	0	7	63
Lip oedema	0	3	0	0	0	3
Lip pain	51	794	0	1	51	795
Lip pruritus	4	24	0	0	4	24
Lip scab	0	3	0	0	0	3
Lip swelling	50	506	0	3	50	509
Lip ulceration	4	46	0	0	4	46
Loose tooth	7	40	0	0	7	40
Malpositioned teeth	0	1	0	0	0	1
Mouth cyst	0	2	0	0	0	2
Mouth haemorrhage	20	163	1	1	21	164
Mouth swelling	13	138	0	1	13	139
Mouth ulceration	59	425	1	2	60	427
Nausea	1746	9521	2	29	1748	9550
Nicotinic stomatitis	1	2	0	0	1	2
Noninfective gingivitis	84	386	0	1	84	387
Noninfective sialoadenitis	0	2	0	0	0	2
Odynophagia	8	88	0	1	8	89
Oesophageal dilatation	0	1	0	0	0	1
Oesophageal discomfort	1	17	0	0	1	17
Oesophageal disorder	2	15	0	0	2	15
Oesophageal irritation	2	10	0	0	2	10
Oesophageal obstruction	0	0	0	1	0	1
Oesophageal oedema	0	0	0	1	0	1
Oesophageal pain	8	42	0	1	8	43
Oesophageal rupture	0	1	0	0	0	1
Oesophageal spasm	1	1	0	0	1	1
Oesophagitis	3	35	0	2	3	37
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	1070	5095	1	5	1071	5100
Oral disorder	7	131	0	0	7	131
Oral mucosa erosion	0	2	0	0	0	2
Oral mucosal blistering	30	322	0	0	30	322
Oral mucosal discolouration	2	43	0	0	2	43
Oral mucosal eruption	4	61	0	0	4	61
Oral mucosal erythema	8	48	0	0	8	48
Oral mucosal exfoliation	2	98	0	0	2	98

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Oral mucosal roughening	6	15	0	0	6	15
Oral pain	80	737	0	2	80	739
Oral papule	1	3	0	0	1	3
Oral pigmentation	0	7	0	0	0	7
Oral pruritus	11	49	0	0	11	49
Palatal disorder	8	24	0	0	8	24
Palatal oedema	0	2	0	0	0	2
Palatal swelling	9	51	0	1	9	52
Palatal ulcer	0	4	0	0	0	4
Pancreatic disorder	7	22	0	1	7	23
Pancreatitis	0	0	4	10	4	10
Pancreatitis acute	0	0	0	2	0	2
Paraesthesia oral	50	290	0	1	50	291
Peptic ulcer	0	1	0	0	0	1
Periodontal disease	7	15	0	0	7	15
Pigmentation lip	1	9	0	0	1	9
Plicated tongue	4	38	1	1	5	39
Proctalgia	0	1	0	0	0	1
Rectal discharge	1	1	0	0	1	1
Reflux gastritis	0	10	0	0	0	10
Regurgitation	1	7	0	0	1	7
Retching	58	389	0	0	58	389
Saliva altered	3	14	0	0	3	14
Saliva discolouration	6	25	0	1	6	26
Salivary duct stenosis	0	1	0	0	0	1
Salivary gland disorder	0	4	0	0	0	4
Salivary gland enlargement	2	7	0	0	2	7
Salivary gland pain	1	7	0	0	1	7
Salivary hypersecretion	9	120	0	0	9	120
Scalloped tongue	0	1	0	0	0	1
Small intestinal obstruction	0	0	0	1	0	1
Stiff tongue	1	5	0	0	1	5
Stomatitis	158	1921	0	7	158	1928
Stomatitis haemorrhagic	0	1	0	0	0	1
Swollen tongue	26	164	0	1	26	165
Teeth brittle	0	5	0	0	0	5
Teething	2	4	0	0	2	4
Tongue blistering	18	104	0	0	18	104
Tongue coated	7	135	0	1	7	136

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Tongue discolouration	16	89	0	0	16	89
Tongue discomfort	109	528	0	0	109	528
Tongue disorder	5	103	0	0	5	103
Tongue dry	10	72	0	0	10	72
Tongue eruption	8	63	0	1	8	64
Tongue erythema	7	68	0	0	7	68
Tongue exfoliation	1	13	0	0	1	13
Tongue haemorrhage	3	23	0	1	3	24
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 pruritus	7	23	0	0	7	23
Tongue rough	3	24	0	0	3	24
Tongue spasm	0	1	0	0	0	1
Tongue thrust	1	1	0	0	1	1
Tongue ulceration	9	85	0	0	9	85
Tooth deposit	7	31	0	0	7	31
Tooth discolouration	17	80	0	1	17	81
Tooth disorder	13	120	1	1	14	121
Tooth erosion	3	7	0	0	3	7
Tooth loss	2	20	0	1	2	21
Tooth pulp haemorrhage	2	4	0	0	2	4
Tooth socket haemorrhage	2	4	0	0	2	4
Toothache	153	782	0	4	153	786
Trichoglossia	0	19	0	0	0	19
Varicose veins sublingual	0	1	0	0	0	1
Vomiting	559	3029	18	48	577	3077
General disorders and administration site conditions	**4596**	**32472**	**22**	**196**	**4618**	**32668**
Administration site dryness	1	1	0	0	1	1
Administration site irritation	2	3	0	0	2	3
Adverse drug reaction	1	15	0	0	1	15
Adverse event	20	215	2	7	22	222
Adverse reaction	2	43	0	0	2	43
Alcohol interaction	0	9	0	0	0	9
Application site acne	6	7	0	0	6	7
Application site alopecia	2	3	0	0	2	3
Application site burn	0	1	0	0	0	1
Application site coldness	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Application site discolouration	1	1	0	0	1	1
Application site discomfort	1	3	0	0	1	3
Application site dryness	1	5	0	0	1	5
Application site erythema	1	3	0	0	1	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	4	9	0	0	4	9
Application site paraesthesia	4	8	0	0	4	8
Application site pruritus	1	1	0	0	1	1
Application site rash	1	4	0	0	1	4
Application site reaction	1	3	0	0	1	3
Application site swelling	1	3	0	0	1	3
Application site ulcer	1	1	0	0	1	1
Application site warmth	0	1	0	0	0	1
Asthenia	146	807	1	11	147	818
Axillary pain	1	1	0	0	1	1
Chest discomfort	591	3624	1	17	592	3641
Chest pain	785	3964	2	17	787	3981
Chills	15	89	0	0	15	89
Condition aggravated	17	172	1	6	18	178
Crepitations	1	4	0	0	1	4
Critical illness	0	0	1	1	1	1
Crying	19	67	0	1	19	68
Cyst	1	12	0	2	1	14
Death	0	0	2	11	2	11
Decreased activity	0	3	0	0	0	3
Device intolerance	0	8	0	0	0	8
Discharge	4	15	0	0	4	15
Discomfort	196	1259	0	2	196	1261
Disease complication	1	1	0	0	1	1
Disease susceptibility	0	1	0	0	0	1
Drug ineffective	5	8	0	0	5	8
Drug interaction	2	2	0	0	2	2
Drug intolerance	0	12	0	0	0	12
Drug-device interaction	1	1	0	0	1	1
Enanthema	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Energy increased	0	3	0	0	0	3
Exercise tolerance decreased	0	2	0	0	0	2
Face oedema	0	3	0	0	0	3
Facial discomfort	0	2	0	0	0	2
Facial pain	11	68	0	0	11	68
Fatigue	117	668	2	9	119	677
Feeling abnormal	178	1256	0	2	178	1258
Feeling cold	5	34	0	0	5	34
Feeling drunk	0	14	0	1	0	15
Feeling hot	65	1171	0	1	65	1172
Feeling jittery	0	6	0	0	0	6
Feeling of body temperature change	0	5	0	0	0	5
Feeling of relaxation	0	2	0	0	0	2
Foaming at mouth	0	2	0	0	0	2
Food interaction	0	4	0	0	0	4
Gait disturbance	8	29	0	0	8	29
Gait inability	0	13	0	0	0	13
General physical health deterioration	39	292	0	8	39	300
Generalised oedema	2	3	0	1	2	4
Glassy eyes	0	1	0	0	0	1
Hangover	2	16	0	0	2	16
Hernia	0	1	0	0	0	1
Hunger	5	35	0	0	5	35
Hyperplasia	0	1	0	0	0	1
Hyperthermia	1	2	0	0	1	2
Hypothermia	0	0	0	1	0	1
Idiopathic environmental intolerance	0	2	0	1	0	3
Ill-defined disorder	25	152	0	6	25	158
Illness	193	1225	0	12	193	1237
Impaired healing	0	3	0	0	0	3
Induration	0	1	0	0	0	1
Inflammation	26	147	0	3	26	150
Influenza like illness	0	11	0	2	0	13
Injection site discomfort	0	1	0	0	0	1
Injection site hypersensitivity	0	1	0	0	0	1
Injection site mass	1	1	0	0	1	1
Injection site pain	1	1	0	0	1	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Injection site urticaria	0	1	0	0	0	1
Injection site vesicles	1	2	0	0	1	2
Injury associated with device	0	3	0	1	0	4
Localised oedema	1	2	0	0	1	2
Malaise	757	7867	0	21	757	7888
Mass	0	5	0	0	0	5
Mucosa vesicle	0	1	0	0	0	1
Mucosal atrophy	0	1	0	0	0	1
Mucosal discolouration	0	2	0	0	0	2
Mucosal disorder	8	48	0	0	8	48
Mucosal dryness	34	182	0	0	34	182
Mucosal erosion	0	7	0	0	0	7
Mucosal haemorrhage	1	2	0	0	1	2
Mucosal hypertrophy	0	1	0	0	0	1
Mucosal induration	0	1	0	0	0	1
Mucosal inflammation	3	40	0	1	3	41
Mucosal membrane hyperplasia	0	1	0	0	0	1
Mucosal pain	2	6	0	0	2	6
Mucosal pigmentation	0	1	0	0	0	1
Mucosal ulceration	0	1	0	0	0	1
No adverse event	682	4765	2	2	684	4767
Nodule	1	5	0	1	1	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	8	17	1	1	9	18
Oedema mucosal	2	12	0	2	2	14
Oedema peripheral	0	5	0	0	0	5
Organ failure	0	0	0	1	0	1
Pain	184	966	0	5	184	971
Performance status decreased	0	1	0	0	0	1
Peripheral swelling	18	94	0	0	18	94
Physical deconditioning	0	1	0	0	0	1
Polyp	3	9	0	0	3	9
Pre-existing condition improved	0	1	0	0	0	1
Product intolerance	14	323	0	0	14	323
Pyrexia	61	291	3	23	64	314
Rebound effect	1	1	0	0	1	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Screaming	0	2	0	0	0	2
Secretion discharge	36	116	0	1	36	117
Sensation of blood flow	0	1	0	0	0	1
Sensation of foreign body	118	1031	0	4	118	1035
Sense of oppression	0	5	0	0	0	5
Sensitivity to weather change	0	1	0	0	0	1
Sluggishness	2	28	0	0	2	28
Swelling	46	199	1	5	47	204
Swelling face	22	126	0	0	22	126
Temperature intolerance	0	18	0	0	0	18
Temperature regulation disorder	0	3	0	0	0	3
Tenderness	2	5	0	0	2	5
Therapeutic product effect delayed	0	1	0	0	0	1
Therapeutic response increased	0	1	0	0	0	1
Therapeutic response unexpected	2	23	0	0	2	23
Thirst	44	395	0	1	44	396
Thirst decreased	0	2	0	0	0	2
Tobacco interaction	0	3	0	0	0	3
Ulcer	18	52	2	2	20	54
Ulcer haemorrhage	0	0	1	1	1	1
Unevaluable event	4	190	0	1	4	191
Visceral pain	1	1	0	0	1	1
Withdrawal syndrome	5	17	0	1	5	18
Xerosis	0	2	0	0	0	2
Hepatobiliary disorders	**24**	**80**	**2**	**10**	**26**	**90**
Biliary colic	1	7	0	1	1	8
Cholelithiasis	1	3	0	0	1	3
Gallbladder disorder	2	7	0	0	2	7
Hepatic failure	0	0	0	2	0	2
Hepatic pain	12	38	0	0	12	38
Hepatitis	0	0	0	2	0	2
Hepatitis toxic	0	0	1	1	1	1
Hepatomegaly	0	2	0	0	0	2
Hepatotoxicity	0	0	1	1	1	1
Liver disorder	7	22	0	1	7	23
Liver injury	0	0	0	2	0	2
Ocular icterus	1	1	0	0	1	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Immune system disorders	**757**	**2679**	**5**	**898**	**762**	**3577**
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	4	34	0	1	4	35
Allergy to metals	3	15	1	1	4	16
Allergy to plants	0	1	0	0	0	1
Anaphylactic reaction	0	0	0	1	0	1
Anaphylactic shock	0	0	1	10	1	10
Anaphylactoid reaction	0	0	0	1	0	1
Atopy	1	7	0	0	1	7
Autoimmune disorder	0	0	1	4	1	4
Decreased immune responsiveness	3	4	0	0	3	4
Device allergy	1	4	0	0	1	4
Drug hypersensitivity	2	4	0	0	2	4
Dust allergy	0	2	0	0	0	2
Food allergy	1	1	0	0	1	1
Hypersensitivity	738	2548	2	874	740	3422
Immune system disorder	1	9	0	2	1	11
Immunosuppression	0	1	0	2	0	3
Milk allergy	0	1	0	0	0	1
Mycotic allergy	0	1	0	0	0	1
Reaction to excipient	0	5	0	0	0	5
Sarcoidosis	0	0	0	2	0	2
Seasonal allergy	1	7	0	0	1	7
Sensitisation	2	7	0	0	2	7
Smoke sensitivity	0	3	0	0	0	3
Infections and infestations	**392**	**2266**	**67**	**325**	**459**	**2591**
Abscess	0	6	1	2	1	8
Abscess oral	0	5	0	0	0	5
Acarodermatitis	1	5	0	0	1	5
Acne pustular	0	8	0	0	0	8
Acute sinusitis	0	1	0	1	0	2
Adenoiditis	1	1	0	0	1	1
Appendicitis	0	0	0	1	0	1
Appendicitis perforated	0	0	0	1	0	1
Bacterial allergy	0	1	0	0	0	1
Bacterial infection	1	2	0	0	1	2
Bacterial rhinitis	0	0	0	1	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Blister infected	2	7	0	0	2	7
Bronchiolitis	0	1	0	0	0	1
Bronchitis	40	198	0	14	40	212
Burn infection	0	1	0	1	0	2
Candida infection	2	29	0	0	2	29
Cholecystitis infective	0	0	0	1	0	1
Chorioretinitis	0	0	0	1	0	1
Chronic sinusitis	0	1	0	0	0	1
Chronic tonsillitis	0	2	3	11	3	13
Complicated appendicitis	0	0	0	1	0	1
Conjunctivitis	1	10	0	1	1	11
Coronavirus infection	1	7	0	2	1	9
COVID-19	0	9	0	6	0	15
COVID-19 pneumonia	0	0	4	13	4	13
Creutzfeldt-Jakob disease	0	0	0	1	0	1
Cystitis	1	3	0	1	1	4
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	0	1	0	1
Ear infection	0	3	0	1	0	4
Empyema	0	0	0	1	0	1
Endocarditis	0	0	0	1	0	1
Epididymitis	0	0	0	2	0	2
Epiglottitis	0	0	0	1	0	1
Erythema induratum	0	1	0	0	0	1
Eye infection	0	1	0	0	0	1
Folliculitis	0	9	0	0	0	9
Fungal infection	2	9	0	0	2	9
Fungal pharyngitis	0	0	0	2	0	2
Furuncle	5	42	0	1	5	43
Gangrene	0	0	1	2	1	2
Gastroenteritis	1	10	0	0	1	10
Gastroenteritis viral	1	5	0	0	1	5
Gastrointestinal infection	0	1	0	0	0	1
Gingival abscess	2	3	0	5	2	8
Gingivitis	27	123	0	1	27	124
Helicobacter infection	1	1	0	0	1	1
Herpes dermatitis	0	2	0	0	0	2

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Herpes virus infection	8	20	0	0	8	20
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	11	49	1	4	12	53
Infection susceptibility increased	0	0	0	1	0	1
Infective glossitis	1	10	0	1	1	11
Influenza	6	54	0	1	6	55
Injection site infection	0	1	0	0	0	1
Labyrinthitis	0	1	0	0	0	1
Laryngitis	21	90	1	3	22	93
Laryngopharyngitis	0	9	0	0	0	9
Lip infection	1	10	0	0	1	10
Localised infection	1	1	0	0	1	1
Lower respiratory tract infection	2	2	3	15	5	17
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	1	1	1	1
Mumps	1	6	0	0	1	6
Myringitis	0	0	0	1	0	1
Nasopharyngitis	38	308	0	1	38	309
Oral bacterial infection	0	0	0	1	0	1
Oral candidiasis	3	28	0	0	3	28
Oral fungal infection	2	14	0	0	2	14
Oral herpes	10	162	0	0	10	162
Oral infection	6	102	0	1	6	103
Oral pustule	0	7	0	1	0	8
Osteomyelitis	0	0	1	4	1	4
Otitis externa	0	2	0	0	0	2
Otitis media	0	2	0	0	0	2
Periodontitis	12	54	0	1	12	55
Periorbital infection	0	0	0	1	0	1
Peritonitis	0	0	0	2	0	2
Peritonsillar abscess	0	0	2	7	2	7
Pertussis	0	0	0	2	0	2
Pharyngeal abscess	0	0	0	1	0	1
Pharyngitis	61	263	1	4	62	267

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Pharyngitis bacterial	0	0	0	5	0	5
Pharyngitis streptococcal	0	3	0	0	0	3
Pharyngotonsillitis	0	0	0	1	0	1
Pneumonia	0	0	42	143	42	143
Pneumonia bacterial	0	0	1	1	1	1
Pneumonia chlamydial	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	1	1	1	1
Pulpitis dental	4	5	0	0	4	5
Purulence	0	2	0	0	0	2
Purulent discharge	0	13	0	0	0	13
Pustule	0	17	0	1	0	18
Pyoderma	0	0	0	1	0	1
Rash pustular	2	14	0	0	2	14
Respiratory tract infection	1	2	0	7	1	9
Respiratory tract infection viral	0	1	0	2	0	3
Rhinitis	13	84	0	0	13	84
Sepsis	0	0	0	1	0	1
Sialoadenitis	0	0	0	1	0	1
Sinusitis	20	70	1	3	21	73
Skin infection	0	8	0	0	0	8
Sputum purulent	0	3	0	1	0	4
Streptococcal infection	0	1	0	0	0	1
Subcutaneous abscess	0	3	0	0	0	3
Suspected COVID-19	1	1	0	0	1	1
Tetanus	0	0	0	1	0	1
Tinea infection	1	3	0	0	1	3
Tongue abscess	0	1	0	0	0	1
Tongue fungal infection	1	4	0	0	1	4
Tonsillitis	69	271	0	3	69	274
Tonsillitis bacterial	0	0	1	6	1	6
Tooth abscess	1	3	0	0	1	3
Tooth infection	0	4	0	0	0	4
Tracheitis	2	13	0	0	2	13
Tracheobronchitis	0	1	0	0	0	1
Tuberculosis	0	0	2	3	2	3

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Upper respiratory fungal infection	0	0	0	1	0	1
Upper respiratory tract infection	3	7	0	0	3	7
Urinary tract infection	0	2	0	0	0	2
Vestibular neuronitis	0	1	0	0	0	1
Viral infection	1	10	0	1	1	11
Viral pharyngitis	0	2	0	0	0	2
Injury, poisoning and procedural complications	**5052**	**33872**	**44**	**209**	**5096**	**34081**
Accident	0	1	0	1	0	2
Accidental exposure to product	83	509	0	4	83	513
Accidental exposure to product by child	886	5764	27	81	913	5845
Accidental overdose	0	2	0	0	0	2
Airway burns	12	69	0	1	12	70
Alcohol poisoning	0	2	0	0	0	2
Ankle fracture	0	0	1	1	1	1
Arthropod sting	1	2	0	0	1	2
Back injury	0	2	0	0	0	2
Bite	3	4	0	0	3	4
Blast injury	0	4	0	1	0	5
Burn oesophageal	5	38	0	0	5	38
Burn of internal organs	0	2	0	0	0	2
Burn oral cavity	644	4615	0	3	644	4618
Burns first degree	0	17	0	0	0	17
Burns second degree	6	183	0	0	6	183
Burns third degree	0	0	0	5	0	5
Carbon monoxide poisoning	0	1	0	0	0	1
Carcinogenicity	1	1	0	0	1	1
Chemical burn	3	11	0	0	3	11
Chemical burn of oral cavity	1	2	0	0	1	2
Chemical burn of respiratory tract	0	0	0	3	0	3
Chemical poisoning	0	0	1	4	1	4
Chillblains	0	2	0	0	0	2
Clavicle fracture	0	0	0	1	0	1
Cold burn	6	10	0	0	6	10
Colon injury	1	1	0	0	1	1
Comminuted fracture	0	0	0	1	0	1
Concussion	0	1	0	1	0	2

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Contusion	3	18	0	1	3	19
Dental restoration failure	0	3	0	0	0	3
Device difficult to use	27	944	0	0	27	944
Device maintenance issue	0	2	0	0	0	2
Device use error	0	9	0	0	0	9
Device use issue	0	21	0	0	0	21
Ear injury	0	1	0	0	0	1
Electric shock	20	73	0	0	20	73
Electrical burn	0	2	0	0	0	2
Expired product administered	0	2	0	0	0	2
Exposure during pregnancy	77	233	3	3	80	236
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	1	2	0	0	1	2
Exposure via eye contact	0	2	0	0	0	2
Exposure via inhalation	1	5	0	0	1	5
Eye contusion	0	2	0	0	0	2
Eye injury	0	3	0	0	0	3
Face injury	1	7	0	0	1	7
Fall	10	42	0	5	10	47
Femoral nerve injury	0	0	0	1	0	1
Foreign body	1	2	0	0	1	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	2	2	2	7
Fracture	1	1	0	0	1	1
Fracture displacement	0	0	0	1	0	1
Gas poisoning	0	1	0	0	0	1
Gingival injury	4	14	0	0	4	14
Hair injury	0	1	0	0	0	1
Head injury	0	3	0	1	0	4
Heat stroke	0	1	0	0	0	1
Incorrect route of product administration	0	2	0	0	0	2
Inflammation of wound	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Injury	5	25	0	0	5	25
Injury corneal	0	0	1	1	1	1
Intentional device misuse	0	5	0	0	0	5
Intentional overdose	0	2	0	1	0	3
Intentional product misuse	1074	1912	0	3	1074	1915
Intentional product misuse to child	1	1	0	0	1	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	6	0	6
Joint dislocation	0	1	1	2	1	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	0	1	1	1	1	2
Limb injury	5	32	0	1	5	33
Limb traumatic amputation	0	0	0	1	0	1
Lip injury	3	65	0	1	3	66
Lower limb fracture	0	0	0	1	0	1
Maternal exposure before pregnancy	1	1	0	0	1	1
Maternal exposure during breast feeding	1	3	0	0	1	3
Maternal exposure during pregnancy	84	122	0	0	84	122
Maternal exposure timing unspecified	0	2	0	0	0	2
Metal poisoning	0	0	0	3	0	3
Mouth injury	11	46	0	0	11	46
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	13	0	1	3	14
Nail injury	1	6	0	0	1	6
Nasal injury	2	6	0	0	2	6
Nerve injury	0	4	0	1	0	5
Nervous system injury	0	1	0	0	0	1
Occupational exposure to product	0	6	0	0	0	6
Oesophageal injury	0	1	0	0	0	1
Oesophagitis chemical	0	0	0	1	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Off label use	0	1	0	0	0	1
Oral contusion	2	11	0	0	2	11
Overdose	2	12	0	0	2	12
Palate injury	1	15	0	0	1	15
Pancreatic duct rupture	0	0	1	1	1	1
Pharyngeal injury	0	3	0	2	0	5
Plaque shift	1	2	0	0	1	2
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
Product administration error	1	2	0	0	1	2
Product preparation error	0	1	0	0	0	1
Product storage error	0	0	0	1	0	1
Product use complaint	5	34	0	0	5	34
Product use issue	1	16	0	0	1	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	40	0	0	3	40
Scratch	39	69	0	0	39	69
Silicosis	0	1	0	0	0	1
Skeletal injury	0	0	0	1	0	1
Skin abrasion	0	4	0	2	0	6
Skin injury	0	7	0	0	0	7
Skin laceration	2	13	0	0	2	13
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
Sunburn	0	1	0	0	0	1
Thermal burn	1930	18227	3	21	1933	18248
Thermal burns of eye	0	1	0	1	0	2
Tibia fracture	0	0	1	2	1	2
Tissue injury	1	1	0	0	1	1
Tobacco poisoning	43	219	1	4	44	223
Tongue injury	3	20	0	0	3	20

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Tooth fracture	1	4	0	1	1	5
Tooth injury	11	44	0	1	11	45
Toxicity to various agents	4	11	0	0	4	11
Tracheal injury	1	2	0	0	1	2
Traumatic haematoma	0	1	0	0	0	1
Traumatic lung injury	1	10	0	0	1	10
Upper limb fracture	0	1	0	0	0	1
Vascular injury	0	1	0	0	0	1
Wound	8	97	1	1	9	98
Wound complication	0	3	0	0	0	3
Wound haemorrhage	0	14	0	0	0	14
Wound secretion	1	5	0	0	1	5
Wrong technique in device usage process	0	7	0	0	0	7
Wrong technique in product usage process	1	10	0	0	1	10
Investigations	**645**	**3431**	**9**	**51**	**654**	**3482**
Alanine aminotransferase increased	1	5	0	0	1	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	1	3	0	0	1	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	1	1	0	0	1	1
Blood carbon monoxide increased	0	1	0	0	0	1
Blood cholesterol increased	2	10	0	0	2	10
Blood creatinine increased	0	1	0	0	0	1
Blood glucose	2	3	0	0	2	3
Blood glucose abnormal	0	2	0	0	0	2
Blood glucose decreased	0	5	0	0	0	5
Blood glucose increased	11	46	0	0	11	46
Blood growth hormone	1	1	0	0	1	1
Blood immunoglobulin E increased	0	1	0	0	0	1
Blood magnesium increased	1	1	0	0	1	1
Blood mercury abnormal	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Blood pressure abnormal	47	104	0	0	47	104
Blood pressure decreased	38	191	0	2	38	193
Blood pressure immeasurable	0	1	0	0	0	1
Blood pressure increased	225	1032	2	14	227	1046
Blood pressure systolic decreased	0	1	0	0	0	1
Blood pressure systolic increased	1	2	0	0	1	2
Blood test abnormal	1	3	0	0	1	3
Blood triglycerides increased	0	1	0	0	0	1
Blood uric acid abnormal	1	1	0	0	1	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 abnormal	2	4	0	0	2	4
Body temperature decreased	1	6	0	0	1	6
Body temperature fluctuation	1	6	0	0	1	6
Body temperature increased	12	91	0	5	12	96
Breath sounds	2	6	0	0	2	6
Breath sounds abnormal	3	23	0	2	3	25
Breath sounds absent	0	1	0	0	0	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	0	0	0	1	0	1
Drug level	1	1	0	0	1	1
Electrocardiogram abnormal	0	1	0	0	0	1
Endoscopy upper gastrointestinal tract	1	2	0	0	1	2
Epinephrine increased	0	3	0	0	0	3
Fractional flow reserve	0	1	0	0	0	1
Full blood count abnormal	0	1	0	0	0	1
Gamma-glutamyltransferase increased	0	1	0	0	0	1
Gastric pH decreased	4	24	0	1	4	25
General physical condition abnormal	0	12	2	4	2	16
Haemoglobin increased	0	2	0	0	0	2
Heart rate	8	14	0	0	8	14
Heart rate abnormal	5	21	0	0	5	21

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Heart rate decreased	3	19	1	2	4	21
Heart rate increased	187	961	1	10	188	971
Heart rate irregular	19	48	1	1	20	49
Hepatic enzyme increased	0	3	0	0	0	3
Histamine level increased	0	1	0	0	0	1
Hormone level abnormal	1	5	0	0	1	5
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
Intelligence test	0	1	0	0	0	1
Intraocular pressure increased	0	4	0	0	0	4
Intraocular pressure test	2	3	0	0	2	3
Investigation abnormal	0	2	0	0	0	2
Laboratory test abnormal	0	1	0	0	0	1
Laryngoscopy	1	1	0	0	1	1
Liver function test abnormal	2	3	0	0	2	3
Liver function test increased	0	1	0	0	0	1
Lumbar puncture	1	1	0	0	1	1
Lymph node palpable	0	3	0	0	0	3
Magnetic resonance imaging abnormal	0	1	0	0	0	1
Nicotine test	0	1	0	0	0	1
Occult blood negative	0	1	0	0	0	1
Oxygen consumption decreased	5	14	0	0	5	14
Oxygen consumption increased	0	1	0	0	0	1
Oxygen saturation decreased	2	8	1	2	3	10
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	1	5	0	0	1	5
Pulmonary arterial pressure	1	1	0	0	1	1
Pulmonary function test decreased	0	4	0	0	0	4
Pulse abnormal	1	7	0	0	1	7
Pulse pressure increased	0	2	0	0	0	2
Quality of life decreased	0	1	0	0	0	1
Respiratory rate decreased	3	3	0	1	3	4
Respiratory rate increased	3	19	0	0	3	19

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Rheumatoid factor	1	1	0	0	1	1
SARS-CoV-2 test negative	0	1	0	0	0	1
SARS-CoV-2 test positive	1	1	0	0	1	1
Sputum abnormal	1	5	0	0	1	5
Thyroid function test abnormal	0	1	0	0	0	1
Thyroid hormones increased	0	1	0	0	0	1
Total lung capacity decreased	8	20	0	0	8	20
Transaminases increased	0	1	0	0	0	1
Urine viscosity increased	0	1	0	0	0	1
Vital capacity decreased	1	1	0	0	1	1
Weight	0	1	0	0	0	1
Weight abnormal	0	3	0	0	0	3
Weight decreased	5	37	0	1	5	38
Weight increased	23	568	0	1	23	569
White blood cell count decreased	0	2	0	2	0	4
White blood cell count increased	0	1	1	1	1	2
X-ray abnormal	0	1	0	0	0	1
Metabolism and nutrition disorders	**54**	**415**	**5**	**44**	**59**	**459**
Acidosis	1	2	0	0	1	2
Appetite disorder	1	8	0	0	1	8
Dairy intolerance	1	1	0	0	1	1
Decreased appetite	25	175	0	2	25	177
Dehydration	19	94	0	0	19	94
Diabetes mellitus	0	0	5	25	5	25
Diabetes mellitus inadequate control	0	0	0	13	0	13
Diabetic complication	0	1	0	0	0	1
Diet refusal	1	1	0	0	1	1
Eating disorder symptom	0	1	0	0	0	1
Feeding disorder	0	16	0	0	0	16
Fluid intake reduced	0	1	0	0	0	1
Fluid retention	1	11	0	0	1	11
Food craving	0	1	0	0	0	1
Food intolerance	1	1	0	0	1	1
Glucose tolerance impaired	0	1	0	0	0	1
Histamine intolerance	0	0	0	1	0	1
Hyperglycaemia	1	2	0	0	1	2

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Hyperinsulinaemia	0	1	0	0	0	1
Hyperlipidaemia	0	1	0	0	0	1
Hyperphagia	0	3	0	0	0	3
Hypervolaemia	0	1	0	0	0	1
Hypoglycaemia	0	3	0	0	0	3
Hypovitaminosis	0	1	0	0	0	1
Increased appetite	3	56	0	0	3	56
Ketoacidosis	0	0	0	1	0	1
Lactose intolerance	0	2	0	0	0	2
Metabolic disorder	0	2	0	0	0	2
Obesity	0	1	0	1	0	2
Polydipsia	0	13	0	0	0	13
Poor feeding infant	0	1	0	0	0	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
Musculoskeletal and connective tissue disorders	**217**	**1133**	**3**	**22**	**220**	**1155**
Antisynthetase syndrome	0	1	0	0	0	1
Arthralgia	24	80	1	2	25	82
Arthritis	0	4	0	0	0	4
Arthropathy	0	3	0	0	0	3
Back disorder	0	1	0	0	0	1
Back pain	29	111	0	1	29	112
Bone disorder	0	1	0	1	0	2
Bone loss	1	1	0	0	1	1
Bone pain	5	19	0	0	5	19
Costochondritis	0	1	0	0	0	1
Fibromyalgia	0	1	0	0	0	1
Flank pain	1	23	0	0	1	23
Fracture pain	0	1	0	0	0	1
Groin pain	0	1	0	0	0	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	1	3	0	1	1	4
Joint swelling	1	4	0	0	1	4

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Knee deformity	1	1	0	0	1	1
Ligament disorder	1	1	0	0	1	1
Limb discomfort	5	24	0	1	5	25
Mastication disorder	5	14	0	1	5	15
Mobility decreased	0	1	0	0	0	1
Muscle contracture	0	2	0	0	0	2
Muscle discomfort	1	3	0	0	1	3
Muscle disorder	0	2	0	0	0	2
Muscle spasms	35	125	0	0	35	125
Muscle tightness	3	6	0	1	3	7
Muscle twitching	2	15	0	1	2	16
Muscular weakness	2	38	0	0	2	38
Musculoskeletal chest pain	1	33	0	0	1	33
Musculoskeletal discomfort	5	36	0	1	5	37
Musculoskeletal disorder	0	1	0	0	0	1
Musculoskeletal pain	0	9	0	0	0	9
Musculoskeletal stiffness	5	45	0	0	5	45
Myalgia	6	49	0	0	6	49
Myokymia	0	1	0	0	0	1
Myositis	0	2	0	0	0	2
Neck mass	0	1	0	0	0	1
Neck pain	27	135	0	3	27	138
Osteitis	1	2	0	0	1	2
Osteoarthritis	0	1	0	0	0	1
Osteochondrosis	0	0	2	4	2	4
Pain in extremity	27	157	0	0	27	157
Pain in jaw	24	152	0	2	24	154
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	2	3	0	1	2	4
Tendon pain	0	2	0	0	0	2
Tendonitis	0	1	0	0	0	1
Trismus	2	4	0	0	2	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**39**	**43**	**119**	**46**	**158**
Adenoma benign	0	1	0	0	0	1
Benign neoplasm	1	2	0	0	1	2

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Brain neoplasm	0	0	1	2	1	2
Brain neoplasm malignant	0	0	0	1	0	1
Cancer in remission	0	1	0	0	0	1
Cancer pain	0	0	0	1	0	1
Fibroma	1	1	0	0	1	1
Hepatic neoplasm	0	0	0	1	0	1
Laryngeal cancer	0	0	1	1	1	1
Laryngeal papilloma	0	1	0	0	0	1
Leukaemia	0	0	0	1	0	1
Lip and/or oral cavity cancer	0	0	1	1	1	1
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	0	1	0	5
Lung neoplasm malignant	0	1	15	39	15	40
Lymphoma	0	0	1	2	1	2
Melanocytic naevus	0	2	0	0	0	2
Metastases to bladder	0	0	1	1	1	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	1	1	1	1
Neoplasm	0	4	0	0	0	4
Neoplasm malignant	0	0	19	45	19	45
Neoplasm skin	0	1	0	0	0	1
Oral neoplasm	0	0	1	1	1	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
Skin papilloma	0	2	0	0	0	2
Small intestine carcinoma	0	0	1	1	1	1
Testis cancer	0	0	1	1	1	1
Throat cancer	0	0	0	3	0	3
Thyroid cancer	0	0	0	2	0	2

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Tongue neoplasm	1	2	0	1	1	3
Tongue neoplasm malignant stage unspecified	0	0	0	1	0	1
Nervous system disorders	**5843**	**32329**	**76**	**430**	**5919**	**32759**
Ageusia	23	103	0	1	23	104
Akathisia	0	1	0	0	0	1
Altered state of consciousness	0	1	0	2	0	3
Amnesia	3	9	0	0	3	9
Anosmia	5	46	0	0	5	46
Aphasia	3	13	0	0	3	13
Ataxia	0	1	0	0	0	1
Autonomic nervous system imbalance	2	7	0	3	2	10
Balance disorder	3	31	0	1	3	32
Bradykinesia	0	2	0	0	0	2
Brain stem infarction	0	0	0	1	0	1
Burning sensation	267	1661	0	3	267	1664
Burning sensation mucosal	2	31	0	0	2	31
Carotid artery stenosis	0	0	0	1	0	1
Cerebral disorder	2	7	0	0	2	7
Cerebral haemorrhage	0	0	0	3	0	3
Cerebral hypoperfusion	0	0	0	1	0	1
Cerebral infarction	0	0	0	5	0	5
Cerebral microinfarction	0	0	0	1	0	1
Cerebral vasoconstriction	0	0	0	2	0	2
Cerebrovascular accident	0	0	5	25	5	25
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	0	4	0	0	0	4
Cognitive disorder	0	2	0	0	0	2
Cold-stimulus headache	1	1	0	0	1	1
Coma	0	0	0	2	0	2
Coordination abnormal	2	9	0	0	2	9
Depressed level of consciousness	0	1	5	11	5	12
Disturbance in attention	2	40	0	0	2	40
Dizziness	1423	8871	5	41	1428	8912
Dizziness exertional	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Dizziness postural	0	16	0	0	0	16
Dreamy state	0	2	0	0	0	2
Drooling	5	19	0	2	5	21
Dysarthria	2	12	0	1	2	13
Dysgeusia	145	1280	0	0	145	1280
Dysgraphia	0	1	0	0	0	1
Dyskinesia	0	3	0	0	0	3
Dysstasia	2	20	0	1	2	21
Dystonia	0	0	0	1	0	1
Electric shock sensation	2	42	0	1	2	43
Epilepsy	0	1	2	14	2	15
Exaggerated startle response	0	1	0	0	0	1
Facial paralysis	0	0	0	4	0	4
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	1	1	0	0	1	1
Glossopharyngeal neuralgia	1	1	0	0	1	1
Haemorrhage intracranial	0	0	0	1	0	1
Hand-eye coordination impaired	0	1	0	0	0	1
Head discomfort	50	333	0	2	50	335
Head titubation	0	2	0	0	0	2
Headache	3507	17297	8	43	3515	17340
Hemihypoaesthesia	0	0	0	1	0	1
Hemiplegia	0	0	0	2	0	2
Hyperaesthesia	1	6	0	0	1	6
Hypersomnia	0	5	0	0	0	5
Hypertonia	0	1	0	0	0	1
Hypoaesthesia	49	314	1	7	50	321
Hypogeusia	2	13	0	0	2	13
Hypokinesia	0	6	0	0	0	6
Hyporeflexia	0	1	0	0	0	1
Hyposmia	0	13	0	0	0	13
Hypotonia	1	3	0	0	1	3
Infant irritability	0	1	0	0	0	1
Intracranial pressure increased	0	0	3	10	3	10
Judgement impaired	1	1	0	0	1	1
Lethargy	17	62	1	2	18	64

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Loss of consciousness	0	3	13	96	13	99
Memory impairment	0	18	0	1	0	19
Meningeal disorder	0	1	0	0	0	1
Mental impairment	0	2	1	6	1	8
Migraine	75	356	2	4	77	360
Migraine with aura	0	1	0	0	0	1
Monoplegia	0	0	1	2	1	2
Motor dysfunction	0	3	0	0	0	3
Movement disorder	3	7	0	0	3	7
Myoclonus	0	1	0	0	0	1
Nervous system disorder	5	17	0	0	5	17
Neuralgia	0	10	0	1	0	11
Neurological symptom	0	1	0	0	0	1
Neurotoxicity	0	0	0	1	0	1
Nystagmus	0	1	0	0	0	1
Occipital neuralgia	1	1	0	0	1	1
Paraesthesia	48	214	0	2	48	216
Paraesthesia mucosal	0	1	0	0	0	1
Paraparesis	0	0	0	5	0	5
Parosmia	8	103	0	0	8	103
Patient elopement	1	2	0	1	1	3
Post-traumatic epilepsy	0	1	0	0	0	1
Presyncope	17	98	0	0	17	98
Psychomotor hyperactivity	0	2	0	0	0	2
Reflexes abnormal	1	3	0	0	1	3
Sedation	0	2	0	0	0	2
Seizure	1	2	3	12	4	14
Sensory disturbance	1	19	0	0	1	19
Sensory loss	1	8	0	0	1	8
Sensory processing disorder	0	1	0	0	0	1
Sinus headache	0	4	0	0	0	4
Sleep deficit	1	5	0	0	1	5
Slow speech	0	1	0	0	0	1
Somnolence	29	193	1	1	30	194
Speech disorder	3	47	1	2	4	49
Speech disorder developmental	1	1	0	0	1	1
Stupor	0	1	0	0	0	1
Syncope	0	22	22	89	22	111
Taste disorder	67	566	0	0	67	566

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Tension headache	7	28	0	0	7	28
Thermohypoaesthesia	0	2	0	0	0	2
Tongue paralysis	0	0	1	4	1	4
Transient ischaemic attack	0	0	1	4	1	4
Tremor	49	260	0	2	49	262
Unresponsive to stimuli	0	0	0	1	0	1
Uvular spasm	0	1	0	0	0	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
Pregnancy, puerperium and perinatal conditions	**11**	**22**	**1**	**7**	**12**	**29**
Abortion of ectopic pregnancy	0	0	0	1	0	1
Abortion spontaneous	0	0	1	3	1	3
Ectopic pregnancy	0	0	0	2	0	2
Imminent abortion	0	0	0	1	0	1
Large for dates baby	0	1	0	0	0	1
Live birth	1	1	0	0	1	1
Morning sickness	5	12	0	0	5	12
Normal newborn	0	1	0	0	0	1
Pre-eclampsia	1	1	0	0	1	1
Pregnancy	2	3	0	0	2	3
Somatic symptom disorder of pregnancy	1	1	0	0	1	1
Umbilical cord around neck	1	1	0	0	1	1
Unintended pregnancy	0	1	0	0	0	1
Product issues	**1358**	**24201**	**5**	**5**	**1363**	**24206**
Device battery explosion	0	2	0	0	0	2
Device breakage	29	173	2	2	31	175
Device catching fire	8	41	0	0	8	41
Device colour issue	1	8	0	0	1	8
Device connection issue	0	1	0	0	0	1
Device defective	1	29	0	0	1	29
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

(b) (4)

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Device ineffective	1	1	0	0	1	1
Device issue	41	1177	0	0	41	1177
Device leakage	8	66	0	0	8	66
Device malfunction	21	1296	2	2	23	1298
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	661	11636	1	1	662	11637
Device power source issue	2	17	0	0	2	17
Device temperature issue	19	28	0	0	19	28
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
Physical product label issue	1	2	0	0	1	2
Product adhesion issue	0	1	0	0	0	1
Product after taste	4	5	0	0	4	5
Product availability issue	0	1	0	0	0	1
Product caught fire	1	27	0	0	1	27
Product coating issue	0	1	0	0	0	1
Product colour issue	1	10	0	0	1	10
Product complaint	91	2521	0	0	91	2521
Product contamination	0	1	0	0	0	1
Product deposit	1	3	0	0	1	3
Product distribution issue	0	1	0	0	0	1
Product label issue	0	1	0	0	0	1
Product leakage	0	2	0	0	0	2
Product odour abnormal	121	1004	0	0	121	1004
Product physical consistency issue	0	15	0	0	0	15
Product physical issue	125	4050	0	0	125	4050
Product quality issue	62	728	0	0	62	728
Product size issue	1	2	0	0	1	2
Product substitution issue	0	3	0	0	0	3
Product supply issue	0	1	0	0	0	1
Product taste abnormal	158	1310	0	0	158	1310
Suspected counterfeit product	0	1	0	0	0	1
Suspected product quality issue	0	5	0	0	0	5

(b) (4)

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Undersensing	0	2	0	0	0	2
Psychiatric disorders	**450**	**2152**	**4**	**34**	**454**	**2186**
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	2	0	0	1	2
Affective disorder	2	8	0	0	2	8
Aggression	1	6	0	0	1	6
Agitation	5	53	0	1	5	54
Anger	2	8	0	1	2	9
Anhedonia	0	2	0	0	0	2
Anxiety	94	305	0	1	94	306
Anxiety disorder	0	3	0	0	0	3
Apathy	5	16	0	0	5	16
Attention deficit hyperactivity disorder	0	1	0	0	0	1
Aversion	2	8	0	0	2	8
Behavioural addiction	0	1	0	0	0	1
Bipolar disorder	0	0	0	1	0	1
Bradyphrenia	0	2	0	0	0	2
Breath holding	1	1	0	0	1	1
Breathing-related sleep disorder	0	1	0	0	0	1
Bruxism	3	5	0	0	3	5
Completed suicide	0	0	0	1	0	1
Confusional state	6	40	1	1	7	41
Daydreaming	2	8	0	0	2	8
Decreased eye contact	0	1	0	1	0	2
Decreased interest	1	3	0	0	1	3
Dependence	0	12	0	2	0	14
Depressed mood	5	42	0	0	5	42
Depression	7	31	0	0	7	31
Depressive symptom	0	1	0	0	0	1
Disinhibition	0	1	0	0	0	1
Disorientation	3	26	0	0	3	26
Distractibility	0	3	0	0	0	3
Drug dependence	0	1	0	0	0	1
Dysphemia	0	2	0	0	0	2
Dysphoria	0	10	0	0	0	10
Eating disorder	0	21	0	0	0	21

(b) (4)

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Emotional disorder	0	1	0	0	0	1
Emotional distress	0	9	0	0	0	9
Euphoric mood	1	19	0	0	1	19
Factitious disorder	0	1	0	0	0	1
Fear	7	39	0	0	7	39
Fear of death	2	6	0	1	2	7
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	4	0	0	1	4
Hallucination	0	2	0	6	0	8
Hallucination, auditory	0	1	0	1	0	2
Hallucination, visual	0	0	0	1	0	1
Illness anxiety disorder	0	1	0	0	0	1
Impatience	0	1	0	0	0	1
Inappropriate affect	0	2	0	0	0	2
Indifference	0	1	0	0	0	1
Initial insomnia	0	16	0	0	0	16
Insomnia	57	356	1	2	58	358
Intentional self-injury	0	0	0	1	0	1
Irritability	33	255	0	1	33	256
Laziness	3	7	0	0	3	7
Libido decreased	0	7	0	0	0	7
Listless	2	12	1	1	3	13
Loss of libido	1	1	0	0	1	1
Mental disorder	4	14	0	1	4	15
Mental fatigue	0	2	0	0	0	2
Mental status changes	0	5	0	0	0	5
Middle insomnia	2	7	0	0	2	7
Mood altered	21	90	1	1	22	91
Mood swings	3	5	0	0	3	5
Morbid thoughts	2	4	0	0	2	4
Morose	1	1	0	0	1	1
Nervousness	14	84	0	0	14	84
Neurosis	1	2	0	0	1	2
Nicotine dependence	62	198	0	0	62	198
Nightmare	1	7	0	0	1	7
Obsessive-compulsive disorder	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Panic attack	30	116	0	3	30	119
Panic disorder	2	9	0	1	2	10
Panic reaction	6	17	0	0	6	17
Paranoia	0	2	0	0	0	2
Personality change	0	1	0	0	0	1
Poor quality sleep	7	25	0	1	7	26
Premature ejaculation	1	1	0	0	1	1
Psychotic disorder	1	2	0	0	1	2
Restlessness	4	16	0	0	4	16
Self esteem decreased	0	1	0	0	0	1
Sleep disorder	10	55	0	1	10	56
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	15	55	0	0	15	55
Suicidal ideation	0	0	0	2	0	2
Suicide attempt	0	0	0	1	0	1
Tearfulness	2	2	0	0	2	2
Tension	11	26	0	0	11	26
Terminal insomnia	0	1	0	0	0	1
Thinking abnormal	1	5	0	0	1	5
Thought blocking	1	1	0	0	1	1
Tic	1	2	0	0	1	2
Tobacco abuse	0	14	0	0	0	14
Tobacco withdrawal symptoms	0	5	0	0	0	5
Renal and urinary disorders	**23**	**99**	**0**	**10**	**23**	**109**
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	1	8	0	0	1	8
Chronic kidney disease	0	0	0	1	0	1
Dysuria	5	9	0	0	5	9
Haematuria	1	1	0	0	1	1
Incontinence	0	1	0	0	0	1
Micturition disorder	1	3	0	0	1	3
Micturition urgency	1	1	0	1	1	2
Nephrolithiasis	0	0	0	1	0	1
Pollakiuria	0	7	0	0	0	7

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Polyuria	0	2	0	0	0	2
Renal disorder	3	8	0	0	3	8
Renal failure	0	0	0	1	0	1
Renal pain	9	40	0	1	9	41
Urinary incontinence	0	1	0	1	0	2
Urinary retention	0	0	0	2	0	2
Urinary tract discomfort	0	2	0	0	0	2
Urine odour abnormal	2	15	0	0	2	15
Reproductive system and breast disorders	**13**	**64**	**11**	**39**	**24**	**103**
Adnexa uteri pain	0	1	0	0	0	1
Breast discomfort	0	1	0	0	0	1
Breast enlargement	1	1	0	0	1	1
Breast inflammation	0	1	0	0	0	1
Breast pain	4	12	0	0	4	12
Breast tenderness	1	2	0	0	1	2
Cervical friability	0	1	0	0	0	1
Dysmenorrhoea	0	1	0	0	0	1
Erectile dysfunction	0	5	11	38	11	43
Erection increased	0	1	0	0	0	1
Genital discomfort	0	1	0	0	0	1
Genital disorder	1	1	0	0	1	1
Heavy menstrual bleeding	0	1	0	0	0	1
Menometrorrhagia	0	1	0	0	0	1
Menstrual disorder	1	4	0	0	1	4
Menstruation delayed	0	2	0	0	0	2
Menstruation irregular	1	2	0	0	1	2
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	1	2	0	0	1	2
Penile discharge	0	1	0	0	0	1
Prostatic disorder	0	1	0	0	0	1
Prostatitis	0	1	0	0	0	1
Sexual dysfunction	2	10	0	0	2	10
Spontaneous penile erection	0	1	0	0	0	1
Suppressed lactation	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

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Uterine polyp	1	1	0	0	1	1
Vaginal disorder	0	1	0	0	0	1
Vaginal flatulence	0	1	0	0	0	1
Respiratory, thoracic and mediastinal disorders	**18241**	**83960**	**81**	**669**	**18322**	**84629**
Adenoidal hypertrophy	0	1	0	0	0	1
Allergic bronchitis	0	1	0	0	0	1
Allergic cough	17	54	0	0	17	54
Allergic sinusitis	1	2	0	0	1	2
Alveolar proteinosis	0	0	0	1	0	1
Alveolitis	0	1	0	0	0	1
Anoxia	0	0	0	1	0	1
Aphonia	90	464	0	3	90	467
Apnoea	0	0	0	7	0	7
Apnoeic attack	0	0	0	1	0	1
Asphyxia	0	2	0	21	0	23
Aspiration	0	0	0	1	0	1
Asthma	123	571	7	25	130	596
Asthmatic crisis	0	0	0	2	0	2
Bronchial disorder	12	105	0	2	12	107
Bronchial hyperreactivity	0	3	0	0	0	3
Bronchial irritation	2	47	0	0	2	47
Bronchial obstruction	0	0	0	1	0	1
Bronchial oedema	0	1	0	3	0	4
Bronchial secretion retention	2	4	0	0	2	4
Bronchial varices	0	1	0	0	0	1
Bronchiectasis	0	0	0	1	0	1
Bronchitis chronic	3	14	0	1	3	15
Bronchospasm	9	64	0	4	9	68
Bronchostenosis	0	0	0	1	0	1
Catarrh	13	61	0	0	13	61
Childhood asthma	1	2	0	0	1	2
Choking	0	17	2	19	2	36
Choking sensation	756	2529	0	4	756	2533
Chronic obstructive pulmonary disease	2	20	0	2	2	22
Chronic respiratory disease	1	2	0	0	1	2
Cough	6416	26231	10	59	6426	26290
Cough decreased	0	7	0	0	0	7
Cough variant asthma	3	6	0	0	3	6

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Cystic lung disease	0	1	0	0	0	1
Decreased bronchial secretion	0	1	0	0	0	1
Diaphragmalgia	2	8	0	0	2	8
Diaphragmatic disorder	1	5	0	0	1	5
Dry throat	1102	4786	0	3	1102	4789
Dysphonia	197	1212	0	4	197	1216
Dyspnoea	1660	7793	11	91	1671	7884
Dyspnoea at rest	0	1	0	1	0	2
Dyspnoea exertional	0	36	0	0	0	36
Ear, nose and throat disorder	2	2	0	0	2	2
Emphysema	6	13	1	3	7	16
Eosinophilic pneumonia acute	0	0	1	4	1	4
Epiglottic cyst	0	1	0	0	0	1
Epistaxis	60	667	1	7	61	674
Haemoptysis	26	237	1	5	27	242
Hiccups	51	267	0	1	51	268
Hyperactive pharyngeal reflex	0	5	0	0	0	5
Hyperventilation	2	9	0	0	2	9
Hypopnoea	3	21	0	0	3	21
Hypoxia	0	0	2	7	2	7
Increased bronchial secretion	1	5	0	0	1	5
Increased upper airway secretion	8	48	0	0	8	48
Increased viscosity of bronchial secretion	1	8	0	0	1	8
Increased viscosity of upper respiratory secretion	1	7	0	0	1	7
Interstitial lung disease	0	0	1	1	1	1
Irregular breathing	1	6	0	0	1	6
Laryngeal discomfort	9	49	0	0	9	49
Laryngeal disorder	3	11	0	0	3	11
Laryngeal inflammation	1	11	0	0	1	11
Laryngeal obstruction	0	0	0	1	0	1
Laryngeal oedema	0	4	4	28	4	32
Laryngeal pain	14	66	0	0	14	66
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	2	20	0	1	2	21

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Lower respiratory tract congestion	5	15	0	0	5	15
Lower respiratory tract inflammation	1	1	0	0	1	1
Lung disorder	157	643	4	15	161	658
Lung hyperinflation	0	1	0	0	0	1
Lung infiltration	0	2	0	0	0	2
Mouth breathing	0	2	0	0	0	2
Nasal congestion	98	649	0	1	98	650
Nasal crusting	0	13	0	0	0	13
Nasal cyst	0	1	0	0	0	1
Nasal discharge discolouration	1	5	0	0	1	5
Nasal discomfort	18	97	0	0	18	97
Nasal disorder	1	12	0	0	1	12
Nasal dryness	36	241	0	0	36	241
Nasal inflammation	2	26	0	0	2	26
Nasal mucosal blistering	0	1	0	0	0	1
Nasal mucosal discolouration	0	2	0	0	0	2
Nasal mucosal disorder	2	9	0	0	2	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	4	18	0	0	4	18
Nasal polyps	0	4	0	0	0	4
Nasal pruritus	5	25	0	0	5	25
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	4	27	0	1	4	28
Oropharyngeal blistering	0	3	2	31	2	34
Oropharyngeal discolouration	1	6	0	0	1	6
Oropharyngeal discomfort	370	1982	0	2	370	1984
Oropharyngeal pain	2548	14291	3	29	2551	14320
Oropharyngeal plaque	4	11	0	0	4	11
Oropharyngeal scar	0	1	0	0	0	1
Oropharyngeal spasm	6	19	0	1	6	20
Oropharyngeal swelling	1	5	0	0	1	5
Painful respiration	3	39	0	0	3	39
Paranasal sinus discomfort	1	2	0	0	1	2

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	1	5	0	0	1	5
Pharyngeal cyst	1	2	0	0	1	2
Pharyngeal disorder	9	74	0	1	9	75
Pharyngeal enanthema	0	2	0	0	0	2
Pharyngeal erythema	21	72	0	1	21	73
Pharyngeal exudate	0	2	0	1	0	3
Pharyngeal haemorrhage	0	0	4	77	4	77
Pharyngeal hypoaesthesia	4	26	0	0	4	26
Pharyngeal inflammation	17	125	0	3	17	128
Pharyngeal lesion	0	1	0	0	0	1
Pharyngeal mass	0	14	0	0	0	14
Pharyngeal oedema	5	17	0	0	5	17
Pharyngeal paraesthesia	10	92	0	1	10	93
Pharyngeal swelling	114	840	0	5	114	845
Pharyngeal ulceration	2	12	0	0	2	12
Pleural effusion	1	6	0	1	1	7
Pleural thickening	0	1	0	0	0	1
Pleurisy	1	1	1	1	2	2
Pleuritic pain	0	3	0	0	0	3
Pneumonitis	2	15	1	4	3	19
Pneumothorax	0	0	2	9	2	9
Pneumothorax spontaneous	0	0	0	2	0	2
Productive cough	367	2257	1	4	368	2261
Pulmonary calcification	2	3	0	0	2	3
Pulmonary congestion	0	8	0	16	0	24
Pulmonary embolism	0	0	0	5	0	5
Pulmonary fibrosis	0	0	0	3	0	3
Pulmonary haemorrhage	0	0	1	3	1	3
Pulmonary infarction	0	0	0	1	0	1
Pulmonary mass	1	5	0	0	1	5
Pulmonary oedema	0	1	12	39	12	40
Pulmonary pain	325	1686	2	8	327	1694
Pulmonary sarcoidosis	0	0	0	2	0	2
Pulmonary toxicity	0	0	0	1	0	1
Rales	0	12	0	1	0	13
Reflux laryngitis	0	2	0	0	0	2
Respiration abnormal	1	32	0	1	1	33

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Respiratory arrest	0	0	0	2	0	2
Respiratory depression	0	0	0	1	0	1
Respiratory disorder	16	143	0	3	16	146
Respiratory disorder neonatal	0	1	0	0	0	1
Respiratory distress	0	1	0	4	0	5
Respiratory failure	0	0	4	13	4	13
Respiratory fatigue	0	2	0	0	0	2
Respiratory muscle weakness	0	1	0	0	0	1
Respiratory symptom	0	2	0	0	0	2
Respiratory tract congestion	30	143	0	1	30	144
Respiratory tract inflammation	0	12	0	0	0	12
Respiratory tract irritation	33	211	1	1	34	212
Respiratory tract oedema	0	1	0	6	0	7
Rhinalgia	12	90	0	0	12	90
Rhinitis allergic	5	24	0	0	5	24
Rhinitis atrophic	0	1	0	0	0	1
Rhinorrhoea	74	441	0	5	74	446
Rhonchi	2	4	0	0	2	4
Sinus congestion	0	15	0	0	0	15
Sinus disorder	2	26	0	0	2	26
Sinus pain	1	8	0	0	1	8
Sleep apnoea syndrome	0	2	0	0	0	2
Sneezing	53	271	0	2	53	273
Snoring	10	32	0	0	10	32
Sputum discoloured	14	128	0	0	14	128
Sputum increased	2	19	0	0	2	19
Sputum retention	0	14	0	0	0	14
Stridor	2	2	0	0	2	2
Suffocation feeling	325	1055	2	7	327	1062
Tachypnoea	0	2	0	0	0	2
Throat clearing	8	83	0	0	8	83
Throat irritation	2728	11065	0	20	2728	11085
Throat lesion	3	13	0	1	3	14
Throat tightness	51	377	0	1	51	378
Tonsillar cyst	2	2	0	1	2	3
Tonsillar disorder	0	45	0	0	0	45
Tonsillar erythema	1	5	0	0	1	5
Tonsillar exudate	0	4	0	0	0	4

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Tonsillar haemorrhage	0	1	0	1	0	2
Tonsillar hypertrophy	22	148	0	0	22	148
Tonsillar inflammation	6	53	0	1	6	54
Tonsillar ulcer	0	4	0	0	0	4
Tonsillolith	1	3	0	0	1	3
Tracheal disorder	0	9	0	0	0	9
Tracheal inflammation	2	8	0	0	2	8
Tracheal oedema	0	0	0	3	0	3
Tracheal pain	3	32	0	0	3	32
Upper airway obstruction	0	0	0	1	0	1
Upper respiratory tract congestion	9	85	0	0	9	85
Upper respiratory tract inflammation	1	11	0	2	1	13
Upper respiratory tract irritation	1	15	0	0	1	15
Upper-airway cough syndrome	1	3	0	0	1	3
Vasomotor rhinitis	0	1	0	0	0	1
Vocal cord atrophy	1	1	0	0	1	1
Vocal cord disorder	9	76	0	2	9	78
Vocal cord dysfunction	1	4	0	0	1	4
Vocal cord inflammation	2	16	0	0	2	16
Vocal cord polyp	1	2	0	0	1	2
Vocal cord thickening	1	5	0	1	1	6
Wheezing	48	208	0	4	48	212
Yawning	2	11	0	0	2	11
Skin and subcutaneous tissue disorders	**1171**	**8266**	**17**	**128**	**1188**	**8394**
Acne	114	626	1	4	115	630
Acne cystic	0	1	0	0	0	1
Acne varioliformis	0	1	0	0	0	1
Alopecia	11	48	0	1	11	49
Angioedema	0	0	11	51	11	51
Blister	98	608	0	3	98	611
Blister rupture	0	7	0	0	0	7
Blood blister	0	6	0	0	0	6
Circumoral oedema	0	1	0	0	0	1
Cold sweat	3	69	0	0	3	69
Cold urticaria	0	1	0	0	0	1
Dandruff	2	13	0	0	2	13
Decubitus ulcer	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Dermal cyst	0	2	0	0	0	2
Dermatitis	7	72	0	0	7	72
Dermatitis acneiform	0	8	0	0	0	8
Dermatitis allergic	14	65	0	0	14	65
Dermatitis atopic	3	27	0	0	3	27
Dermatitis bullous	0	0	0	1	0	1
Dermatitis contact	0	9	0	0	0	9
Dilated pores	0	1	0	0	0	1
Dry skin	23	132	0	1	23	133
Dyshidrotic eczema	2	6	0	0	2	6
Eczema	19	58	0	0	19	58
Erythema	91	533	0	1	91	534
Erythema nodosum	1	1	0	1	1	2
Fingerprint loss	1	1	0	0	1	1
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	0	1	0	0	0	1
Hidradenitis	0	1	0	0	0	1
Hyperhidrosis	39	220	0	1	39	221
Hyperkeratosis	2	6	0	0	2	6
Keratosis pilaris	0	1	0	0	0	1
Leukoplakia	2	3	0	0	2	3
Lichen planus	0	0	0	1	0	1
Lichenification	0	1	0	0	0	1
Livedo reticularis	0	1	0	0	0	1
Madarosis	0	3	0	0	0	3
Mechanical urticaria	0	1	0	0	0	1
Melanosis	1	1	0	0	1	1
Miliaria	0	2	0	0	0	2
Nail bed bleeding	0	1	0	0	0	1
Nail bed inflammation	0	1	0	0	0	1
Nail discolouration	0	3	0	0	0	3
Nail disorder	1	3	0	0	1	3
Nail hypertrophy	0	1	0	0	0	1
Neurodermatitis	0	1	0	0	0	1
Night sweats	0	1	0	0	0	1
Occupational dermatitis	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Oedema blister	0	1	0	0	0	1
Onychoclasis	3	5	0	0	3	5
Onycholysis	0	1	0	0	0	1
Pain of skin	3	18	0	0	3	18
Palmar erythema	1	3	0	0	1	3
Palmoplantar pustulosis	0	2	0	0	0	2
Papule	1	3	0	0	1	3
Perioral dermatitis	1	5	0	0	1	5
Petechiae	1	2	0	0	1	2
Photosensitivity reaction	0	2	0	0	0	2
Pigmentation disorder	2	14	0	1	2	15
Piloerection	0	2	0	0	0	2
Pityriasis rosea	0	1	0	0	0	1
Pruritus	177	1327	2	9	179	1336
Pruritus allergic	1	2	0	0	1	2
Psoriasis	6	25	0	1	6	26
Purpura	0	3	0	0	0	3
Rash	303	2210	1	28	304	2238
Rash erythematous	14	94	0	1	14	95
Rash follicular	0	1	0	0	0	1
Rash macular	56	540	1	6	57	546
Rash papular	2	21	0	1	2	22
Rash pruritic	9	114	0	2	9	116
Rash vesicular	1	7	0	0	1	7
Rosacea	0	1	0	0	0	1
Scab	2	53	0	0	2	53
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	1	11	0	0	1	11
Sensitive skin	0	5	0	0	0	5
Skin atrophy	1	2	0	0	1	2
Skin burning sensation	3	18	0	0	3	18
Skin depigmentation	0	6	0	0	0	6
Skin discolouration	4	69	0	1	4	70
Skin discomfort	0	5	0	0	0	5
Skin disorder	16	268	0	0	16	268
Skin exfoliation	36	173	0	1	36	174

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Skin fissures	1	6	0	0	1	6
Skin haemorrhage	0	9	0	0	0	9
Skin hypertrophy	0	3	0	0	0	3
Skin induration	1	2	0	0	1	2
Skin irritation	17	91	0	1	17	92
Skin lesion	0	9	0	0	0	9
Skin mass	0	0	0	1	0	1
Skin necrosis	0	0	0	2	0	2
Skin odour abnormal	4	22	0	0	4	22
Skin plaque	0	1	0	0	0	1
Skin reaction	1	17	0	0	1	17
Skin striae	0	2	0	0	0	2
Skin swelling	2	16	0	0	2	16
Skin tightness	0	3	0	0	0	3
Skin ulcer	0	3	0	0	0	3
Skin weeping	0	5	0	0	0	5
Skin wrinkling	3	14	0	1	3	15
Solar lentigo	1	3	0	0	1	3
Spider naevus	0	1	0	0	0	1
Sticky skin	0	1	0	0	0	1
Urticaria	61	463	1	5	62	468
Urticaria chronic	0	1	0	0	0	1
Urticaria pressure	1	1	0	0	1	1
Xeroderma	0	1	0	0	0	1
Yellow nail syndrome	1	1	0	0	1	1
Yellow skin	0	6	0	0	0	6
Social circumstances	**57**	**234**	**8**	**10**	**65**	**244**
Adoption	0	1	0	0	0	1
Alcohol use	0	1	2	2	2	3
Bedridden	0	1	0	0	0	1
Breast feeding	1	1	0	0	1	1
Crime	0	1	0	0	0	1
Divorced	0	0	2	2	2	2
Drug abuser	0	0	2	2	2	2
Ex-tobacco user	0	5	0	0	0	5
Impaired driving ability	0	4	0	0	0	4
Impaired work ability	2	2	0	0	2	2
Loss of personal independence in daily activities	1	6	0	1	1	7

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Military service	0	1	0	0	0	1
Multigravida	2	2	0	0	2	2
Non-tobacco user	1	5	0	0	1	5
Passive smoking	42	171	2	3	44	174
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
Physical disability	0	1	0	0	0	1
Pollution	0	1	0	0	0	1
Postmenopause	0	1	0	0	0	1
Primigravida	0	3	0	0	0	3
Tobacco user	8	22	0	0	8	22
Unhealthy diet	0	1	0	0	0	1
Wheelchair user	0	1	0	0	0	1
Surgical and medical procedures	**14**	**58**	**4**	**17**	**18**	**75**
Adenotonsillectomy	1	1	0	0	1	1
Cardiac operation	0	1	0	0	0	1
Cardioversion	0	2	0	0	0	2
Cholecystectomy	1	1	0	0	1	1
Dental disorder prophylaxis	0	1	0	0	0	1
Dental operation	0	1	0	0	0	1
Endodontic procedure	0	1	0	0	0	1
Fowler's position	0	1	0	0	0	1
Gallbladder operation	1	1	0	0	1	1
Gastric operation	1	1	0	0	1	1
Gingival operation	0	1	0	0	0	1
Hospitalisation	0	1	3	9	3	10
Infusion	0	1	0	0	0	1
Injection	0	1	0	0	0	1
Intestinal malrotation repair	0	1	0	0	0	1
Large intestine operation	0	0	1	1	1	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	1	1	0	0	1	1
Mechanical ventilation	0	1	0	0	0	1
Nasal cavity packing	1	1	0	0	1	1
Nerve block	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Oxygen therapy	0	1	0	0	0	1
Pancreatic operation	1	1	0	0	1	1
Routine health maintenance	1	3	0	0	1	3
Salivary gland resection	0	0	0	1	0	1
Skin graft	0	4	0	0	0	4
Surgery	3	11	0	1	3	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	2	11	0	0	2	11
Tooth restoration	1	1	0	0	1	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
Vascular disorders	**240**	**1186**	**22**	**89**	**262**	**1275**
Aneurysm	0	1	0	2	0	3
Angiopathy	4	26	0	0	4	26
Aortic aneurysm	1	1	0	0	1	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	0	1	0	0	0	1
Blood pressure fluctuation	6	67	0	2	6	69
Bloody discharge	2	5	0	0	2	5
Capillary disorder	1	2	0	0	1	2
Capillary fragility	2	3	0	0	2	3
Circulatory collapse	0	0	0	1	0	1
Cyanosis	2	12	0	0	2	12
Embolism	0	0	0	1	0	1
Flushing	6	46	0	2	6	48
Haematoma	1	3	0	0	1	3
Haemorrhage	0	2	6	22	6	24
Hot flush	6	30	0	0	6	30
Hyperaemia	0	2	0	0	0	2
Hypertension	134	591	4	14	138	605
Hypertensive crisis	0	0	1	5	1	5
Hypotension	22	77	0	1	22	78
Infarction	0	0	4	7	4	7
Internal haemorrhage	0	0	1	2	1	2

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Ischaemia	1	1	0	0	1	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	22	172	1	9	23	181
Peripheral artery occlusion	0	0	0	1	0	1
Peripheral coldness	2	22	0	0	2	22
Peripheral vascular disorder	3	17	0	1	3	18
Phlebitis	0	2	0	0	0	2
Poor peripheral circulation	0	3	0	0	0	3
Raynaud's phenomenon	1	2	0	0	1	2
Shock	0	1	1	1	1	2
Shock symptom	0	0	1	1	1	1
Superficial vein prominence	0	1	0	0	0	1
Thrombophlebitis	0	1	0	0	0	1
Thrombosis	0	0	2	12	2	12
Varicose vein	2	15	0	0	2	15
Vascular insufficiency	0	1	0	0	0	1
Vascular occlusion	3	8	0	1	3	9
Vascular pain	2	10	0	0	2	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	10	32	0	0	10	32
Vasodilatation	1	3	0	0	1	3
Vasospasm	3	8	0	0	3	8
Vein disorder	2	4	0	0	2	4
Vein rupture	0	1	1	1	1	2
Venous occlusion	0	2	0	0	0	2
Vessel perforation	1	1	0	0	1	1
Grand Total	**48645**	**283067**	**837**	**4993**	**49482**	**288060**

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 *IQOS* 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

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
					"heat-not-burn cigarettes" two weeks before admission to hospital.		

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

Study Protocol Number	Study title	Country	Study start	Status
P1-AAA-02-JP	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 *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.	Ongoing
P1-REXC-10	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 Tobacco Heating System (THS) compared to continuing CC smoking, for 5 days in confinement	United Kingdom	November 2022 The entire study duration per subject will be 12 to 39 days.	Ongoing
P1-COPD-04-INT	A 3-year, 3-group, preference, multi-center study to demonstrate the slowing of disease 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	Europe, U.S., and Asia	December 2022 The entire study duration per subject will be maximum 39 months.	Ongoing
ABOUT-HF-ND-PV-06-INT	A multi-country quantitative study to evaluate the psychometric	U.S., Germany, Italy, Russia, and Japan	August 2021	Closed

	properties of the ABOUT™–Health and Functioning questionnaire for adult users of tobacco and/or nicotine products			

18.5 Appendix 5: Market Specific Appendices

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*™ Tobacco Heating System 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-2022 to 31-Dec-2022 and cumulatively from 30-Apr-2019 to 31-Dec-2022. 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 34 non-serious AEs was received from 14 ICSRs in the U.S. during the reporting period. The most frequently reported AEs (>5%) were: *Cough* (n=4, 11.76%), *Headache* (n=3, 8.82%), *Oropharyngeal pain* (n=3, 8.82%), *Throat irritation* (n=2, 5.88%) *Product quality issue* (n=2, 5.88%), and *Abdominal discomfort* (n=2, 5.88%). No SAEs were received from the U.S. during the period covered by this SUR. As mentioned in the SPI version 7.0 for THS (dated 10-May-2022), *Cough, Throat irritation, Nausea, Oropharyngeal pain,* and *Headache* are already known class effect AEs associated with the use of nicotine-containing products.

The most represented SOCs (>5%) were: *Respiratory, thoracic and mediastinal disorders* (n=11, 32.35%), *Product issues* (n=7, 20.59%), *Gastrointestinal disorders* (n=7, 20.59%), *Nervous system disorders* (n=5, 14.71%), and *Injury, poisoning and procedural complications* (n=2, 5.88%).

Cumulatively, there were 231 non-serious AEs received from 92 ICSRs in the U.S. Cumulatively, no SAEs were received from the U.S.

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
Cardiac disorders	**0**	**2**	**0**	**0**	**0**	**2**
Palpitations	0	2	0	0	0	2
Ear and labyrinth disorders	**1**	**1**	**0**	**0**	**1**	**1**
Vertigo	1	1	0	0	1	1
Gastrointestinal disorders	**7**	**36**	**0**	**0**	**7**	**36**
Abdominal discomfort	2	4	0	0	2	4
Abdominal distension	0	1	0	0	0	1
Abdominal pain upper	0	1	0	0	0	1
Breath odour	1	1	0	0	1	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	1	2	0	0	1	2
Gingival bleeding	1	1	0	0	1	1
Glossitis	0	1	0	0	0	1
Nausea	0	10	0	0	0	10
Oral discomfort	0	3	0	0	0	3
Retching	1	1	0	0	1	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	1	1	0	0	1	1
General disorders and administration site conditions	**0**	**14**	**0**	**0**	**0**	**14**
Chest discomfort	0	1	0	0	0	1
Chest pain	0	3	0	0	0	3
Fatigue	0	1	0	0	0	1
Feeling abnormal	0	1	0	0	0	1
Illness	0	1	0	0	0	1
No adverse event	0	5	0	0	0	5
Pain	0	2	0	0	0	2
Hepatobiliary disorders	**0**	**1**	**0**	**0**	**0**	**1**
Hepatic pain	0	1	0	0	0	1
Immune system disorders	**1**	**2**	**0**	**0**	**1**	**2**
Device allergy	1	1	0	0	1	1
Hypersensitivity	0	1	0	0	0	1
Infections and infestations	**0**	**1**	**0**	**0**	**0**	**1**
Pharyngitis streptococcal	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Injury, poisoning and procedural complications	**2**	**29**	**0**	**0**	**2**	**29**
Accidental exposure to product by child	1	6	0	0	1	6
Burn oral cavity	0	2	0	0	0	2
Device difficult to use	0	4	0	0	0	4
Exposure during pregnancy	0	2	0	0	0	2
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
Investigations	**0**	**4**	**0**	**0**	**0**	**4**
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
Nervous system disorders	**5**	**28**	**0**	**0**	**5**	**28**
Anosmia	0	1	0	0	0	1
Burning sensation	0	1	0	0	0	1
Dizziness	1	4	0	0	1	4
Dysgeusia	0	2	0	0	0	2
Head discomfort	0	1	0	0	0	1
Headache	3	16	0	0	3	16
Somnolence	0	1	0	0	0	1
Taste disorder	1	2	0	0	1	2
Product issues	**7**	**57**	**0**	**0**	**7**	**57**
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	1	12	0	0	1	12
Product complaint	1	13	0	0	1	13
Product distribution issue	0	1	0	0	0	1
Product odour abnormal	1	5	0	0	1	5
Product physical issue	1	7	0	0	1	7
Product quality issue	2	4	0	0	2	4
Product taste abnormal	1	7	0	0	1	7
Psychiatric disorders	**0**	**8**	**0**	**0**	**0**	**8**
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	0	1	0	0	0	1
Panic attack	0	1	0	0	0	1
Sleep disorder	0	1	0	0	0	1
Respiratory, thoracic and mediastinal disorders	**11**	**47**	**0**	**0**	**11**	**47**

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Asthma	0	1	0	0	0	1
Cough	4	15	0	0	4	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	1	1	0	0	1	1
Oropharyngeal pain	3	12	0	0	3	12
Respiratory tract irritation	1	1	0	0	1	1
Sneezing	0	1	0	0	0	1
Snoring	0	1	0	0	0	1
Throat irritation	2	6	0	0	2	6
Throat tightness	0	1	0	0	0	1
Vascular disorders	**0**	**1**	**0**	**0**	**0**	**1**
Cyanosis	0	1	0	0	0	1
Grand Total	**34**	**231**	**0**	**0**	**34**	**231**

18.6 Appendix 6: Signatures

Safety Update Report

Period Covered: 01-Jan-2022 to 31-Dec-2022

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

IQOS™ with *Marlboro HeatSticks*™ or *HEETS*™

Justification	**Name/*Title***	**Signature**	**Date**
Author	(b) (6) ***Medical Writer***		
Review	(b) (6) / ***Senior Safety Lead***		
Review	(b) (6) / ***Manager Medical Operations***		
Approval	(b) (6) / ***Global Head Safety Surveillance***		
Approval	(b) (6) / ***Chief Medical Officer***		

Signature: (b) (6)
(b) (6) Apr 17, 2023 10:34 GMT+5.5)

Email: (b) (6) @labcorp.com

Signature: (b) (6)
(b) (6) (Apr 17, 2023 09:06 GMT+2)

Email: (b) (6) @pmi.com

Signature: (b) (6)
(b) (6) (Apr 17, 2023 09:07 GMT+2)

Email: (b) (6) @pmi.com

Signature: (b) (6)
(b) (6) pr 17, 2023 10:42 GMT+2)

Email: (b) (6) @pmi.com

Signature: (b) (6)
(b) (6) (Apr 17, 2023 11:31 GMT+2)

Email: (b) (6) @pmi.com

IQOS SUR2022_v1.0_14Apr2023_US

Final Audit Report 2023-04-17

Created:	2023-04-14
By:	(b) (6) @pmi.com
Status:	Signed
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"IQOS SUR2022_v1.0_14Apr2023_US" History

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2023-04-14 - 12:23:27 PM GMT

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2023-04-17 - 4:50:18 AM GMT

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2023-04-17 - 5:03:58 AM GMT

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Signature Date: 2023-04-17 - 5:04:00 AM GMT - Time Source: server

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2023-04-17 - 7:06:30 AM GMT

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Agreement completed.
2023-04-17 - 9:31:21 AM GMT