Annex 3:
Summary of Reported Adverse Experiences

Product	Marlboro Amber *HeatSticks*
	Marlboro Green Menthol *HeatSticks*
	Marlboro Blue Menthol *HeatSticks*
	IQOS System Holder and Charger
	IQOS 3 System Holder and Charger
FDA STN	PM0000424-PM0000426, PM0000479 and PM0000634
Reporting Period	PM0000424-PM0000426 and PM0000479: March 1, 2020 to February 28, 2021
	PM0000634: December 7, 2020 to February 28, 2021

On the following pages Safety Update Report (SUR) for period between January 1, 2020 and December 31, 2020 is provided.

Safety Update Report

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

Report Number:	PMI_SURV_2020_SUR01
International Birth Date:	04-Nov-2014
Period Covered:	01-Jan-2020 to 31-Dec-2020
Product Name:	Electrically Heated Tobacco Product (EHTP) and Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS)
Sponsor:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	Final
Date:	20 Apr 2021
Author:	Kamila Kowa Scientist Product Surveillance Philip Morris Products S.A.
Reviewed by:	Nicolas Blanc. MD Manager Medical Operations Philip Morris Products S.A.
Approved by:	Stephen Malcolm. MD Director Safety Surveillance, New Capabilities Philip Morris Products S.A.
	Annie Heremans, MD Chief Medical Officer Philip Morris Products S.A.

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-2020 to 31-Dec-2020 (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 to be used exclusively with any authorized version of the THD, commercialized under the brand name IQOS™.

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-2020), the THS had been marketed in 64 markets worldwide: Albania, Andorra, Armenia, Austria, Belarus, Bosnia & Herzegovina, Bulgaria, Canada, Canary Islands, Colombia, Costa Rica, Croatia, Curacao, Cyprus, Czech Republic, Denmark, Dominican Republic, Estonia, France, Georgia, Germany, Greece, Guatemala, Hungary, Indonesia, Israel, Italy, Japan, Jordan, Kazakhstan, Kuwait, Latvia, Lebanon, Lithuania, Macedonia, Malaysia, Maldives, Mexico, Moldova, Monaco, Montenegro, Netherlands, New Zealand, Palestine, Philippines, Poland, Portugal, Reunion, Romania, Russia, Saudi Arabia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Turkish Cyprus, Ukraine, United Arab Emirates, United Kingdom, and United States.

No actions were taken due to safety reasons by the competent authorities or by 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 5.0 for THS (dated 02-Dec-2019).

The estimated cumulative subject exposure in clinical studies from the DIBD (30-Apr-2013) until the DLP of this SUR was 2,300 subjects. Cumulatively, 6,298 subjects were exposed to EHTP variants in PMI-sponsored Pre-Market studies up to the DLP of this SUR. The Post-Marketing exposure presented in number of units sold showed 15,465,879 for the reporting period and 59,254,850 cumulatively for THD, and 76,308,678,080 for the reporting period and 208,997,543,686 cumulatively for EHTP.

During the reporting interval, one PMI-sponsored clinical study was ongoing (P1-AAA-02-JP) and two studies were closed (P1-OHS-01-JP and P1-EXC-01-EU).

During the 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, most of spontaneous reports received by PMI are not medically confirmed, i.e. they were received directly from consumers and not from health care professionals. The evaluation of new information as well as the cumulative analysis did not show any change in the safety profile of the THS. Nevertheless, PMI will continue to evaluate all new safety information.

Taken together, the data presented in this SUR did not lead to any safety-related actions.

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AAA	Abdominal Aortic Aneurysm
AE	Adverse Event
AEP	Acute Eosinophilic Pneumonia
AR	Allergic Rhinitis
BT	Blend Test
CC	Conventional Cigarette
COT	Commercial Offer Test
DIBD	Development International Birth Date
DLP	Data Lock Point
EC	Electronic Cigarette
EHTP	Electrically Heated Tobacco Product
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
PBA	Perception and Behaviour Assessment
PMI	Philip Morris International

PT	Preferred Term
RRP	Reduced-Risk Product
RSI	Reference Safety Information
SA	Smoking Abstinence
SAE	Serious Adverse Event
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPI	Summary of Product Information
SUR	Safety Update Report
THD	Tobacco Heating Device
THS	Tobacco Heating System
WOT	Whole Offer Test

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-2020 to 31-Dec-2020 (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 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 has three distinct components that perform different functions:[1] (i) the EHTPs, which are made up of a tobacco plug, a hollow acetate tube, a polymer-film filter, a mouth piece filter, and mouth-end papers; (ii) the holder into which the EHTPs are inserted and which heats the tobacco material by means of an electronically controlled heating blade; and (iii) the charger that is used to recharge the THD. Product technical specifications and constituents, as well as product user instructions, are described in the Summary of Product Information (SPI) version 5.0 (Appendix 1) dated 02-Dec-2019 for THS.

The EHTP is commercialized under the brand name Marlboro HeatSticks or HEETS depending on the market and is to be used exclusively with the THD, commercialized under the brand name IQOS. 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.

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-2020), the THS had been marketed in 64 markets worldwide: Albania, Andorra, Armenia, Austria, Belarus, Bosnia & Herzegovina, Bulgaria, Canada, Canary Islands, Colombia, Costa Rica, Croatia, Curacao, Cyprus, Czech Republic, Denmark, Dominican Republic, Estonia, France, Georgia, Germany, Greece, Guatemala, Hungary, Indonesia, Israel, Italy, Japan, Jordan, Kazakhstan, Kuwait, Latvia, Lebanon, Lithuania, Macedonia, Malaysia, Maldives, Mexico, Moldova, Monaco, Montenegro, Netherlands, New Zealand, Palestine, Philippines, Poland, Portugal, Reunion, Romania, Russia, Saudi Arabia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Turkish Cyprus, Ukraine, United Arab Emirates, United Kingdom, and United States (U.S.).

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

No actions were 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

From 01-Jan-2020 onward, the SPI version 5.0 for THS (dated 02-Dec-2019) (Appendix 1) 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

Up to the DLP of this SUR, a total of 12 PMI-sponsored open-label randomized controlled clinical studies had been completed, while one study remained 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-AAA-02-JP[2]	Ongoing	Up to 3-years	49	16	17	0	16	0
P1-EXC-01-EU	Closed	3 Months	94	40	26	0	27	1
Total Exposure	**NA**	**NA**	**2,300**	**1,197**	**964**	**72**	**201**	**114**

[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 already 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**
Sex	Male	1,318
	Female	933
	Total	**2,251**[1]
Race	Caucasian (White)	1,271[2]
	Asian (Japanese)	707[2]
	Black or African American	275
	Native Hawaiian or Other Pacific Islander	14
	American Indian or Alaska Native	7
	Other	26
	Total	**2,300**

[1]The total does not include ongoing studies.
[2]The subtotal includes the actual number of subjects enrolled in the ongoing studies at the DLP (31-Dec-2020).

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 a total of eight pre-market studies: seven Pre-Market studies, including Blend Tests (BT), Whole Offer Tests (WOT), Commercial Offer Test (COT), and one Perception and Behavior Assessment (PBA) study.

The estimated Pre-Marketing exposure to the THS in these studies is based on the safety population who was exposed to at least one 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-2020), 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	US	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 "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] (n)	Cumulative (n)
THD	15,465,879	59,254,850
EHTP	76,308,678,080	208,997,543,686

n=number of units sold

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 by using the MedDRA (Medical Dictionary for Regulatory Activities) versions effective at the time of AE processing (latest version used 23.1). MedDRA versions are updated every six months and all AEs in the PMI global safety database are re-coded accordingly.

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

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-2020) 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 62 SAEs reported in 43 ICSRs. A total of 28 SAEs were reported in the THS arms, 27 SAEs in the CC arm, and seven 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=6). All but one SAE were assessed by principal investigators and by PMI as having no causal relationship to THS use. The principal investigator was unable to assess whether one SAE was related to THS use. This SAE occurred in 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 SAE 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-2020) are presented in Appendix 2b. The summary tabulations are presented by MedDRA SOC for the THS.

The cumulative summary tabulations present 25 SAEs reported in a total of 11 ICSRs. None of the SAEs were assessed by the principal investigators or by PMI as causally related to THS and in case of one SAE the assessment was not provided. 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 23.1. 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 health care professional, or consumer to a competent authority, marketing authorization holder or other organization (e.g. Regional Pharmacovigilance Centre, Poison Control Centre) that describes one 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 health care professionals.

- Interval summary tabulations of non-serious AEs and SAEs from post-marketing experience show 77,328 AEs (1,355 serious and 75,973 non-serious) from 45,244 ICSRs. The most represented SOCs (>5%) were: Respiratory, thoracic and mediastinal disorders (29.58%, n=22,872, 185 serious and 22,687 non-serious), Gastrointestinal disorders (15.55%, n=12,024, 68 serious and 11,956 non-serious), Injury, poisoning and procedural complications (12.44%, n=9,623, 32 serious and 9,591 non-serious), Nervous system disorders (11.73%, n=9,071, 114 serious and 8,957 non-serious), General disorders and administration site conditions (11.01%, n=8,516, 62 serious and 8,454 non-serious), and Product issues (10.61%, n=8,206, all non-serious).

  The most frequently reported AEs (>5%) were: Cough (8.89%, n=6,878, 20 serious and 6,858 non-serious), Thermal burn (7.79%, n=6,025, four serious and 6,021 non-

serious), Headache (6.20%, n=4,797, 15 serious and 4,782 non-serious), and Oropharyngeal pain (5.25%, n=4,063, 13 serious and 4,050 non-serious).

Out of the total 1,355 SAEs, the most frequently reported (>5%) were: Hypersensitivity (25.24%, n=342) and Angina pectoris (17.12%, n=232).

As discussed in sections 15.3.1.1 and 15.4.1.1, Hypersensitivity is a known important identified risk for THS products. For cases of Angina pectoris, the reported verbatim were "heart pain", "cardiac pain", "stinging pain in the heart", "piercing pain in the heart", "stabbing or feeling/pain/sensation in the heart", corresponding to the MedDRA coding "Angina pectoris". None of these cases of Angina pectoris were medically confirmed. In most of these cases, the consumer's medical history was not provided. The mean age of the consumers was 33.3 years. The mean and the median period between the start of THS and the start of the event was 51.78 days and six days, respectively. Out of these 232 events, three events of Angina pectoris led to hospitalization. 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 very 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).

- Cumulative summary tabulations of non-serious AEs and SAEs from post-marketing experience show 177,376 AEs (3,041 serious and 174,335 non-serious) from 97,831 ICSRs. The most represented SOCs (>5%) were: Respiratory, thoracic and mediastinal disorders (26.32%, n=46,685, 500 serious and 46,185 non-serious), Gastrointestinal disorders (17.99%, n=31,914, 193 serious and 31,721 non-serious), Injury, poisoning and procedural complications (12.71%, n=22,541, 114 serious and 22,427 non-serious), General disorders and administration site conditions (11.95%, n=21,197, 145 serious and 21,052 non-serious), Nervous system disorders (11.03%, n=19,571, 260 serious and 19,311 non-serious), and Product issues (10.25%, n=18,189, all non-serious).

  The most frequently reported AEs (>5%) were: Cough (7.73%, n=13,704, 47 serious and 13,657 non-serious), Thermal burn (7.40%, n=13,126, 15 serious and 13,111 non-serious), Headache (5.58%, n=9,905, 32 serious and 9,873 non-serious), and Device physical property issue (5.03%, n=8,915, all non-serious).

  Of the total 3,041 SAEs reported, the most frequently reported (>5%) were: Hypersensitivity (21.70%, n=660) and Angina pectoris (15.03%, n=457).

  As discussed in sections 15.3.1.1 and 15.4.1.1, Hypersensitivity is a known important identified risk for THS products. For cases of Angina pectoris, the reported verbatim were "heart pain", "cardiac pain", "stinging pain in the heart", "piercing pain in the heart", "stabbing feeling/pain/sensation in the heart", corresponding to the MedDRA coding "Angina pectoris". None of these cases of Angina pectoris were medically

confirmed. In most of these cases, no consumer's medical history was provided. The mean age of the consumers was 34.0 years. The mean and the median period between the start of THS and the start of the event was 33.41 days and three days, respectively. Of these 457 events, eight events of Angina pectoris led to hospitalization. Considering the verbatim reported, the mean age of the consumers, the short median latency, and the fact that most of the cases did not lead to hospitalization, it is very 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

Two PMI-sponsored clinical studies (P1-OHS-01-JP and P1-EXC-01-EU) have been completed for THS products during the period covered by this SUR.

- Study P1-OHS-01-JP is a six-month randomized, controlled, open-label, 2-arm parallel group, multicenter study that evaluates the effect on oral health status of smokers who have generalized chronic periodontitis and their response to mechanical periodontal treatment after switching from cigarette smoking to the THS.

Safety results: In this study, the product use category for each subject was determined by calculating the average use of each product over the entire study duration and reported as a monthly average. Subjects who used less than 30 HeatSticks and more than 30 cigarettes per month were classified as cigarette users. Similarly, subjects who used more than 30 HeatSticks and less than 30 cigarettes per month were classified as THS users. For subjects who used more than 30 HeatSticks and smoked more than 30 cigarettes per month, they were classified as dual users. All other product used patterns were classified under the "other" category. The overall Safety Set contained 179 enrolled subjects (70 subjects in THS users, 91 subjects in cigarette users, 17 subjects in dual users, and one subject in "other" user). In this study, seven subjects who were enrolled but NR were considered to be in the cigarette users group.

A total of 121 AEs was reported in 79 of 179 subjects (44.1%). The AE incidents in the THS users (31 of 70 subjects, 44.3%) and the cigarette users (34 of 91 subjects, 37.4%) were comparable. The AE incidents in the dual users (13 of 17 subjects, 76.5%) was higher than those in THS and cigarette users. Overall, the most common AEs by SOC were Gastrointestinal disorders [reported by 14 of 70 subjects (20.0%) in THS users, 18 of 91 subjects (19.8%) in cigarette users, and four of 17 subjects (23.5%) in dual users] and Infections and infestations [reported by 15 of 70 subjects (21.4%) in THS users, 13 of 91 subjects (14.3%) in cigarette users, and six of 17 subjects (35.3%) in dual users]. All other AEs by SOC were reported in <10% subjects overall. The most common AEs by Preferred Terms (PT) were dental caries [reported by six of 70 subjects (8.6%) in THS users, 12 of 91 subjects (13.2%) in cigarette users, and three of 17 subjects (17.6%) in dual users] and viral upper respiratory tract infection [reported by eight of 70 subjects (11.4%) in THS users, five of 91 subjects (5.5%) in cigarette users, and two of 17 subjects (11.8%) in dual users]. All other AEs by PT were reported in <5% of subjects overall.

Two SAEs (back pain and jaw cyst) were reported in cigarette users, while no SAEs were reported in other groups (THS users, dual users, and "other" user).

The majority of AEs during the study were assessed as mild in severity[1]. A total of six subjects experienced moderate AEs: periodontitis (n=1 subject) in THS users; pyrexia (n=1 subject), influenza (n=2 subjects), back pain (n=1 subject) in cigarette users; periodontitis (n=1 subject) in dual users. There were no AEs assessed as severe and no AEs that led to subject discontinuation from the study. No deaths were reported in this study.

One AE (cough) out of the 121 AEs was reported as related to investigational product in dual users, while no related AE were reported in other groups (THS users, cigarette users, and "other" user).

A total of 13 AEs related to study procedures were reported in 11 of 179 subjects (6.1%). Most of these AEs were considered related to dental examinations and/or treatments. Overall, the most common AEs related to study procedures by SOC were Gastrointestinal disorders [reported by four of 70 subjects (5.7%) in THS users, two of 91 subjects (2.2%) in cigarette users, and one of 17 subjects (5.9%) in dual users], all other AEs by SOC were reported in <2% subjects overall. The most common AEs related to study procedures by PT were gingival pain [three subjects; THS users, cigarette users, and dual users (one subject each)], sensitivity of teeth [two subjects; THS and cigarette users (one subject each)], toothache (two subjects; THS users), gingivitis [two subjects; THS and dual users (one subject each)], and hyperaesthesia [two subjects; cigarette and dual users (one subject each)]. All other AEs related to study procedures were reported by one subject in total.

Safety conclusions: THS was well tolerated by study participants. Two SAEs were reported in cigarette users, while no SAEs were reported in other groups (THS users, dual users, and "other" user). There were no severe AEs and no AEs that led to subject discontinuation from the study. Only one AE related to investigational product was reported in dual users. There were no significant difference in the incidence of AEs related to study procedures between THS users and cigarette users.

- Study P1-EXC-01-EU is a randomized, controlled, open-label, 4-arm parallel group study to evaluate the effect of switching from cigarette smoking to the use of THS in healthy adult current smokers on exercise capacity and trainability.

Safety results: The overall Safety Set contained 94 enrolled subjects (26 subjects to the Cigarette arm, 25 subjects to the THS-1 arm, 15 subjects to the THS-2 arm, 27 subjects to the SA arm and one subject who was enrolled but NR). Among the randomized subjects, nine subjects discontinued the study prematurely: two subjects each in the cigarette, THS-2, and SA arms, and three subjects in the THS-1 arm. Reasons for discontinuation were lost to follow-up (n=2 subjects), physician decision (n=3 subjects), withdrawal by subject (n=1 subject), non-compliance with study procedures (n=1 subject) and other (n=1 subject).

[1] The AE intensity is assessed by the investigator following the grades provided in the study protocol:
- Mild: The AE was easily tolerated and did not interfere with daily activity.
- Moderate: The AE interfered with daily activity, but the patient was still able to function.
- Severe: The AE was incapacitating and required medical intervention.

Overall, 116 AEs occurred in 60 of the 94 subjects (63.8%), i.e., in 15 subjects of the Cigarette product use group (68.2%), 14 subjects of the THS-1 product use group (63.6%), eight subjects of the THS-2 product use group (61.5%), 18 subjects of the SA group (75.0%), and five of the "other" product use group (41.7%). The most frequently reported AEs by SOC were Infections and Infestations, experienced by 27 (28.7%) subjects, followed by Musculoskeletal and Connective Tissue Disorders, experienced by 14 (14.9%) subjects, and Investigations and Nervous System Disorders, experienced by nine (9.6%) subjects, respectively. By PT, the most frequent AEs were nasopharyngitis [20 subjects (21.3%)], headache [seven subjects (7.4%)] and back pain [seven subjects (7.4%)]. Increased blood triglycerides, procedural pain and cough were observed in five subjects (5.3%) each.

Two subjects experienced SAEs. One subject in the SA group (4.2%) experienced adenocarcinoma of the colon that required hospitalization and was classified as other medically important serious event. The other subject in the THS-2 product use group (7.7%) experienced uterine leiomyoma and ovarian cyst that required hospitalization.

Overall, 47 (50%) subjects reported 67 AEs of mild intensity[2] and 30 (31.9%) subjects reported 49 AEs of moderate intensity. No severe AE was reported, and no AE led to study discontinuation. No deaths occurred during the study.

Most AEs resolved without action taken (e.g., discontinuation of the product, temporary interruption, change in dose or frequency, continuation without any changes, etc.) (36 AEs in 20 subjects, 21.3%) or no action was applicable (75 AEs in 41 subjects, 43.6%). Product use was stopped due to two AEs in one subject (1.1%) or reduced due to three AEs in one subject (1.1%). Five AEs in four subjects (4.3%) required procedures, and for four AEs in three subjects (3.2%), other action was taken.

The majority of AEs (n=107) were assessed as not related to the use of the investigational product (cigarette or THS) and nine AEs in seven subjects (7.5%) were assessed as related, including six events (diarrhea, nausea, vomiting, dry skin, gingival bleeding and acne) in six subjects of the THS-1 product use group (18.2%) and three events (headache and two events of gingival bleeding) in three subjects of the THS-2 product use group (23.1%). In the Cigarette product use group, no related AEs were observed.

Ten AEs in seven subjects (7.4%) were reported as related to study procedures: three AEs (extrasystoles, dizziness and dyspnea) in two subjects in the Cigarette product use group (9.1%), and five AEs (constipation, tooth disorder, coccydynia, sleep disorder and pruritus) in four subjects in the SA group (16.7%), and two AEs (2 events of constipation) in one subject (8.3%) in the "other" product use group.

[2] The AE intensity is assessed by the investigator following the grades provided in the study protocol:
- Mild: The AE was easily tolerated and did not interfere with daily activity.
- Moderate: The AE interfered with daily activity, but the patient was still able to function.
- Severe: The AE was incapacitating and required medical intervention.

Safety conclusions: Overall, THS was well tolerated. Three SAEs assessed as not related to investigational product were reported in this study. No severe AEs were observed, and no subject was discontinued from the study due to an AE. Adverse events were mild to moderate and mostly not related to the investigational product or study procedures.

There were few clinically significant findings in safety laboratory parameters reported as AEs, and no medically relevant changes in vital sign and electrocardiography parameters, physical examination, and spirometry measurements. Self-reported cough assessments showed a reduced need to cough, most pronounced in the THS product use groups and the SA group, at the end of study participation based on self-reporting.

7.2 Ongoing Clinical Studies

One PMI-sponsored clinical study (P1-AAA-02-JP) was ongoing for the THS 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, 13 SAEs have been reported in seven subjects up to 31-Dec-2020.

Five SAEs in two subjects have been reported in THS arm (Death, Cardio-respiratory arrest, Pulmonary oedema, Patella fracture and Atrial fibrillation). The events of Death, Cardio-respiratory arrest and Pulmonary oedema occurred in the same subject and were considered by the principal investigator as unable to be assessed as having a causal relationship to THS use, while the sponsor assessed them as not related to THS use. The events of Patella fracture (that occurred as well in the same subject mentioned above) and Atrial fibrillation were assessed as not related to THS use by both the principal investigator and the sponsor. The fatal case is further described below.

Two SAEs in two subjects have been reported in Cigarette arm (Inflammatory pseudotumour and Tarsal tunnel syndrome) and assessed as not related to Cigarette by both the principal investigator and the sponsor. Six SAEs in three subjects were reported in smoking cessation arm (two SAEs of Large intestine polyp, one SAE of Enteritis, Peripheral arterial occlusive disease, Inguinal Hernia and Appendicitis) where the assessment of causal relationship to the products is not applicable.

The SAEs "Death", "Cardio-respiratory arrest" and "Pulmonary oedema" were considered by the principal investigator as unable to be assessed as having a causal relationship to THS use. These SAEs concerned a 71-year-old male Japanese subject with relevant ongoing diseases of AAA (as per inclusion criteria in the study protocol) and arterial hypertension. Relevant concomitant medications included amlodipine and valsartan since 2016 for hypertension and ketoprofen since 2017 for lumbar pain. Information on smoking habits was not provided. On 30-Nov-2018, the subject was randomized to the THS arm of study P1-AAA-02-JP. On 09-Sep-2019, the subject fell and broke his patella, and on 19-Sep-2019 had

open reduction and internal fixation under lumbar anesthesia (SAE "Patella fracture"). On 28-Jan-2020, the subject underwent a planned electrocardiogram examination (in the context of the study) that was assessed within normal ranges by the principal investigator. On 19-May-2020, blood pressure and heart rate were measured in the context of the study and were considered within normal ranges. On 04-Nov-2020, the Clinical Research Coordinator called the subject and confirmed that he had no significant change in physical condition. On 08-Nov-2020, the subject went out of the house and later was found lying down. Further information revealed that the subject had experienced a cardiopulmonary arrest and was urgently transported to a nearby hospital. His death was confirmed at the hospital. The autopsy image showed a dominant oedema in the lungs. Rupture of the AAA was not confirmed based on autopsy image. The principal investigator could not assess the causal relationship with THS use.

Company comment: The findings from autopsy image showed a dominant oedema in the lungs. Taking into consideration that four days before his death, the study coordinator called the subject and no change in physical condition was reported during the call and that on the day of his death (08-Nov-2020), the subject left the house and later was found lying down, the sponsor considered that the subject experienced an acute pulmonary oedema. The most common type of acute pulmonary oedema is cardiogenic pulmonary oedema. The most common causes of cardiogenic pulmonary oedema are acute myocardial infarction/ acute coronary syndrome, hypertensive crisis, acute pulmonary embolism, obstructive valvular disease, and acute arrhythmia. Taking into consideration that no valvular disease was reported in the medical history, it is most unlikely that the subject experienced an obstructive valvular disease. Similarly, it is unlikely that THS would have been the cause of an acute arrhythmia, taking into consideration that the subject was randomized to the THS arm almost two years before his death and that the last electrocardiogram done in the context of the study (28-Jan-2020) was considered normal by the principal investigator. Finally, it is unlikely that THS would have been the cause of acute myocardial infarction/ acute coronary syndrome, hypertensive crisis, or acute pulmonary embolism, taking into consideration the subject's medical history of AAA and hypertension and the smoking history (as per inclusion criteria in this study). For acute myocardial infarction/ acute coronary syndrome, hypertensive crisis and acute pulmonary embolism, the sponsor considered that the subject's medical history and smoking history provide a reasonable explanation. For those reasons mentioned above, the sponsor considered that there was no reasonable causal relationship between SAEs ("Death", "Cardio-respiratory arrest", "Pulmonary oedema") and THS use. The SAE of "Patella fracture" was considered as having no reasonable causal relationship to THS use by both the principal investigator and the sponsor.

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.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

One non-PMI sponsored clinical trial was ongoing for the THS during the period covered by this SUR: 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.

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. A total of 43 SAEs in 23 subjects were reported in THS arm. Among these 43 SAEs, the seriousness criteria were fatal in three SAEs (Cardiac failure acute, Myocardial ischemia, Completed suicide), life-threatening in one SAE (Acute myocardial infarction), hospitalization in 37 SAEs, and two SAE were classified as important medical events. None of these SAEs were assessed as related to THS. The fatal SAEs Cardiac failure acute and Myocardial ischemia occurred in the same subjects: a 56-year-old male consumer with medical history of significant alcohol beverage consumption and 40-year smoking history consisting of 26 cigarettes per day. No concomitant medication was reported. Six months after enrollment in the study, the subject was found dead at a party, after having consumed a large amount of alcohol. An autopsy was performed, and the official result indicated that the cause of death was acute cardiovascular failure due to ischemic heart disease. These two fatal SAEs were considered not related to THS. The fatal SAE of Completed suicide occurred in a 51-year-old male with no reported medical history, seven months after enrollment in the study. The family was not cooperative in clarifying the situation and refused to provide the autopsy report. The principal investigator concluded that this SAE was considered not related to THS.

The life-threatening SAE (Acute myocardial infarction) occurred in a 49-year-old male subject with medical history of hypertension, obesity, and 40-year smoking history consisting of 20 cigarettes per day. The SAE started 11 months after enrollment in the study and was reported to have resolved with sequelae. This SAE was considered not related to THS.

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

The PubMed and Embase databases were screened for publications containing new safety information associated with the THS products published during the reporting interval from 01-Jan-2020 to 31-Dec-2020 inclusive. The literature research was performed on 08-Jan-2021 using the following search strings:

- ✓ PubMed: "iqos[All Fields] OR (Morris, Philip[Full Author Name] AND "electronic"[All Fields] AND ("nicotine"[MeSH Terms] OR "nicotine"[All Fields]) AND "delivery"[All Fields] AND (system[All Fields] OR "device"[All Fields]) OR "heat-not-burn"[All Fields] OR "heated"[All Fields] AND ("tobacco"[MeSH Terms] OR "tobacco"[All Fields] OR "tobacco products"[MeSH Terms] OR ("tobacco"[All Fields] AND "products"[All Fields]) OR "tobacco products"[All Fields]))"
- ✓ Embase: iqos, AND 'heat not burn,' AND heated AND tobacco, AND philip AND morris, AND [1-1-2020]/sd NOT [1-1-2021]/sd

A total of 150 publications were retrieved and analyzed. Out of them, three articles include safety related information and are presented below.

The first article by Tajiri et al. [4] reported a case of acute eosinophilic pneumonia (AEP) in a 47-year-old female patient in Japan. Acute eosinophilic pneumonia is an acute respiratory illness characterized by diffuse pulmonary infiltrates and pulmonary eosinophilia. The pathogenesis and ethology of AEP remain poorly understood, but there may be some correlation between the AEP onset and prior inhalational exposure, such as to cigarette smoke. In this case, the patient has been diagnosed with asthma eight months ago and treated with inhaled corticosteroid and a long-acting β2-agonist. Four months later, the patient, who had been a smoker for 27 years, had switched from CCs to heated tobacco products (HTPs). The patient developed a non-productive cough shortly after starting to use HTP. Nevertheless, the patient continued using HTPs. The cough worsened despite further asthma treatment. The patient then developed a fever and general malaise. Two months later, the patient was found to have an abnormal chest X-ray shadow at a medical check-up. A chest computed tomography performed one and a half months later revealed lung abnormalities. Two weeks later, the patient was hospitalized and diagnosed with AEP. The patient improved after treatment with oral prednisolone. No relapse was observed after the cessation of HTP smoking and the initiation of oral corticosteroid treatment. The authors state that AEP was potentially induced by switching from CC smoking to using HTP as the cough, low-grade fever, and chest radiographic abnormalities developed soon after the change in smoking habits; however, no specific single additive or substance in cigarette smoke has been determined to be responsible for causing AEP. This case has been captured in the PMI global safety database as ICSRs retrieved through the literature screening although it is unknown if the patient was using THS. Acute eosinophilic pneumonia was considered by PMI as a new signal in Jan-2019 and refuted in Dec-2019. Since any initiation or re-initiation in tobacco could pose a risk of developing AEP, a causal association between exposure to THS use and AEP cannot be excluded as THS contains tobacco. Given that THS is intended for current smokers who would otherwise continue smoking and that the occurrence of AEP is very rare,

the risk for individual IQOS users is considered negligible especially with current cigarette smokers who switch to THS use.

The second article by Chaaban[5] is a systematic review on AEP associated with non-cigarette smoking products. A search in PubMed database showed 12 cases with a median age of 20 (15–60). Exposures included marijuana smoking (n=5), waterpipe usage (n=2), heat-not-burn cigarettes (HNBCs) use (n=2), electronic cigarette (EC) use (n=2) and synthetic cannabinoid use (n=1). Cases associated with illicit drug use were excluded. A recent change in smoking habits was reported in 50% of patients. Presenting symptoms were dyspnea (91.6%), cough (66.6%), fever (66.6%) and chest pain (25%). Among all patients, 90% had leukocytosis on presentation, but only 16.6% had peripheral eosinophilia. Concerning treatment and outcome, two patients (16.6%) did not require respiratory support, two patients (16.6%) required supplemental oxygen therapy, one patient (8.3%) was treated with non-invasive positive pressure ventilation, five patients (41.6%) required invasive mechanical ventilation, and two patients required extracorporeal membrane oxygenation. All patients received corticosteroids with varying regimens with five of them (41.6%) receiving oral corticosteroids. All patients responded to steroid therapy with no relapses reported. The authors concluded that AEP is reported not only with use of traditional cigarettes but also with use of waterpipe, marijuana and HNBCs. The disease has a similar presentation and clinical course to AEP associated with cigarette smoking and other exposures. This review is limited by the number of patients and quality of data available that comes mainly from case reports. Clinical, radiological, and laboratory details might have been omitted. Also, reporting bias cannot be excluded as the exposure is sometimes not disclosed by patients. Two cases concerning use of heat-not-burn, both reported in Japan, presented a 20-year-old male patient[6] and a 16-year-old male patient.[7] These cases were identified in articles published before the reporting period of this SUR and discussed in SUR covering period of 01-Jan-2018 to 31-Dec-2018. Acute eosinophilic pneumonia was considered by PMI as a new signal in Jan-2019 and refuted in Dec-2019. Since any initiation or re-initiation in tobacco could pose a risk of developing AEP, a causal association between exposure to THS use and AEP cannot be excluded as THS contains tobacco. Given that THS is intended for current smokers who would otherwise continue smoking and that the occurrence of AEP is very rare, the risk for individual IQOS users is considered negligible especially with current cigarette smokers who switch to THS use.

The last article by Chung et al.[8] aims to evaluate the health effect of novel tobacco products on asthma and allergic rhinitis (AR). The results were obtained from a large survey data on Korean middle and high school students (60,040 participants). In order to compare the combined effects of CC, ECs, and HTP use on current allergic diseases, the participants were classified into 18 groups based on the product used and smoking status (current, former, and never). Of all participants, 6.7%, 2.7%, and 2.9% were current CC, current ECs, and ever HTP users, respectively. Current CC and ever HTP use were significantly associated with current asthma and AR in adjusted models. Current ECs showed association with current AR but the association with asthma disappeared in the adjusted model. Among 18 groups, the groups including current CC use showed higher risk of current AR and asthma than never HTP, never EC, and never CC group. The odds ratio of current asthma especially increased

more in those who used ECs and/or HTP with CC concurrently than those in the never HTP-never EC-current CC user group. The authors conclude that using ECs and/or HTP in adolescents might enhance the adverse effect of CC on AR and asthma. As remarked by the authors, various environmental factors such as air pollution, tobacco smoke, and chemicals can cause upper and lower airway inflammation. Moreover, even though studies on HTP and chronic airway diseases are less common than EC, several studies have reported airway toxicity associated with HTP. Therefore, both EC and HTP have the potential to cause and aggravate AR and asthma through airway inflammation or toxicity as shown in this study. Additionally, as discussed by the authors, EC and HTP increased the risk of asthma only when combined with CC in this study suggesting that certain chemical compounds in EC or HTP could act as the adjuvant that strengthens the adverse effects of CC on allergic diseases. On the other hand, HTP showed the stronger additive effect combined with CC on asthma but not on AR in this study. Although this study had a large representative sample, the authors themselves reported several limitations including the status of tobacco product use that was only identified by "ever" or "never" use. The authors could not know whether the participant used HTP currently. Similarly, the definition of former users in CC and EC included everything from participants who used CC or EC once in a life time to previous heavy smoker who quit a month ago and the former users of CC and EC could be very heterogeneous. Finally, the results of a cross-sectional survey cannot confirm causality due to the limitations of such a design, i.e., the study design is missing the longitudinal aspect. These study limitations render inadequate the conclusion that the authors draw from this study.

The review of the recently published articles 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-2020) 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 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 and global websites, and AEs reported by PMI employees.
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-2020 to 31-Dec-2020) 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)	2,486 AEs retrieved: Most reported AEs (>1%): - Hypersensitivity, n=849 - Rash, n=592 - Rash macular, n=215 - Pharyngeal swelling, n=205 - Lip swelling, n=118 - Gingival swelling, n=87 - Urticaria, n=76 - Swollen tongue, n=37 - Swelling face, n=28 - Bronchospasm, n=27 - Mouth swelling, n=27
	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	884 AEs retrieved: - Accidental exposure to product by child, n=884 Co-reported AEs representing at least 1% of the total: - Vomiting, n=119 - Cough, n=19 - Irritability, n=19 - Pallor, n=15 - Nausea, n=11 - Retching, n=9 - Asthenia, n=8 - Somnolence, n=7 - Malaise, n=5 - Mood altered, n=5 - Hiccups, n=5

	Risk	Search criteria for Risk Assessment	Interval Retrieved AEs within Safety Database
			- Listless, n=4 - Salivary hypersecretion, n=3 - Pyrexia, n=3 - Fatigue, n=3 - Crying, n=3
	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)*	1,742 AEs retrieved: - Burning sensation, n=508 - Burning sensation mucosal, n=17 - Skin burning sensation, n=3 - Oral discomfort*, n=1,214 (only the following selected *LLTs* under the PT Oral discomfort are included in the risk assessment: - *Lip burning sensation of, n=783* - *Burning lips, n=171* - *Burning mouth, n=137* - *Burning oral sensation, n=63* - *Oral mucosal burning sensation, n=35* - *Oral hot feeling, n=25)* * note that the total number of AEs under the PT Oral discomfort is 1,357 out of which 1,214 were included in the risk assessment. The following *LLTs* have been excluded from the risk assessment: - *Oral discomfort (n=60)* - *Lip discomfort (n=51)* - *Discomfort in mouth (n=27)* - *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	7,819 AEs retrieved: - Thermal burn, n=6,027 - Burn oral cavity, n=1,726 - Burns second degree, n=46 - Airway burns, n=16 - Burns first degree, n=4

	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)" - "Fœtal disorders" - "Functional lactation disorders" - "Neonatal disorders" - "Normal pregnancy conditions and outcomes" -"Termination of pregnancy and risk of abortion"	<u>15 AEs retrieved:</u> - Exposure during pregnancy, n=9 - Maternal exposure during pregnancy, n=4 - Maternal exposure during breast feeding, n=1 - Morning sickness, n=1 <u>Co-reported AEs:</u> - Nausea, n=4 - Cough, n=2 - Thermal burn, n=2 - Dyspepsia, n=2 - Malaise, n=2 - Oral discomfort, n=1 - Product physical issue, n=1 - Oropharyngeal pain, n=1 - Hypertension, n=1 - Gastrointestinal disorder, n=1 - Accidental exposure to product, n=1 - Oropharyngeal discomfort, n=1 - Product complaint, n=1 - Device difficult to use, n=1 - Dizziness, n=1 - Dysphonia, n=1

15.2 Signal Evaluation

No signal was closed during the reporting period.

15.3 Evaluation of Risks and New Information

15.3.1 New information on Important Identified Risks

15.3.1.1 Hypersensitivity

A search covering the period from 01-Jan-2020 up to the DLP of this SUR was performed in the global safety database to retrieve all the hypersensitivity-related events with THS use. The electronic search included non-serious AEs and SAEs from solicited and unsolicited

sources and was carried out using the MedDRA SMQ Hypersensitivity (narrow scope). The latest MedDRA version used was 23.1.

A total of 2,486 AEs of hypersensitivity-related events with THS use (395 serious and 2,091 non-serious) were received in 2,097 ICSRs. The most reported AEs (>1%) were: Hypersensitivity (34.15%, n=849, 342 serious and 507 non-serious), Rash (23.81%, n=592, eight serious and 584 non-serious), Rash macular (8.65%, n=215, two serious and 213 non-serious), Pharyngeal swelling (8.25%, n=205, one serious and 204 non-serious), Lip swelling (4.75%, n=118, one serious and 117 non-serious), Gingival swelling (3.50%, n=87, one serious and 86 non-serious), Urticaria (3.06%, n=76, one serious and 75 non-serious), Swollen tongue (1.49%, n=37, all non-serious), Swelling face (1.13%, n=28, all non-serious), Bronchospasm (1.09%, n=27, two serious and 25 non-serious), and Mouth swelling (1.09%, n=27, all non-serious).

The most reported SAEs (>1%) were: Hypersensitivity (86.58%, n=342, 198 resolved or resolving, 100 with unknown outcome, and 44 not resolved), Angioedema (4.05%, n=16, eight resolved or resolving, seven with unknown outcome, one not resolved), Oropharyngeal blistering (2.28%, n=9, four with unknown outcome, three not resolved and two resolved), Rash (2.03%, n=8, seven resolved or resolving, and one not resolved), and Laryngeal oedema (1.01%, n=4, two not resolved, and two with unknown outcome).

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

The AEs belonging to the MedDRA SMQ Hypersensitivity represented 3.21% (2,486 /77,328) 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 one million users was estimated to be 150.86. 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=2,097). The calculation also includes the number of users during this period, which is estimated to be 13.9 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 0.15 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 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 884 events of Accidental exposure to product by child (five serious and 879 non-serious) were received in 884 ICSRs. A total of 290 AEs were co-reported, out of which four were assessed as serious including Choking (n=2), Unresponsive to stimuli (n=1) and Altered state of consciousness (n=1). Two events of Choking were reported in two ICSRs concerning neonates. Co-reported events in these two cases included Respiratory disorder, Vomiting and Cough. In both cases, the children ingested a part of EHTP. No medical intervention was deemed necessary. At the time of reporting, the outcome of the events was unknown. The event of Unresponsive to stimuli concerned a one-year-old child who accidentally ingested EHTP. Following the accidental exposure, the child experienced an additional event of Vomiting. No medical intervention was deemed necessary. The outcome of the events was unknown. The last serious event of Altered state of consciousness concerned a one-year-old child who ingested three EHTPs. The child experienced additional events of Vomiting and Hiccups, and was transported to the hospital where she exhibited signs of Mydriasis and Pallor. The patient underwent stomach pump and was treated with activator IV. The outcome of the events was unknown.

In 77.83% of ICSRs reporting Accidental exposure to product by children, no health-related events were co-reported (No adverse event, n=688). In the remaining cases, there were co-reported events with all non-serious AEs being the most frequent (>1%): Vomiting (41.03%, n=119), Cough (6.55%, n=19), Irritability (6.55%, n=19), Pallor (5.17%, n=15), Nausea (3.79%, n=11), Retching (3.10%, n=9), Asthenia (2.76%, n=8), Somnolence (2.41%, n=7), Malaise (1.72%, n=5), Mood altered (1.72%, n=5), Hiccups (1.72%, n=5), Listless (1.38%, n=4), Salivary hypersecretion (1.03%, n=3), Pyrexia (1.03%, n=3), Fatigue (1.03%, n=3), and Crying (1.03%, n=3). Vomiting, Pallor, and Nausea may be signs and symptoms of mild nicotine intoxication, which may potentially occur upon the accidental ingestion of EHTP.

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-2020 up to the DLP of this SUR was performed in the global safety database to retrieve data related to this risk. The electronic search included all SAEs and non-serious events from solicited and unsolicited sources.

The following selected MedDRA PTs were part of the search criteria: Burning sensation, Burning sensation mucosal, Skin burning sensation, and Oral discomfort. Only a selected list of *LLTs* under the PT Oral discomfort were included in the analysis, namely: *Burning corner of mouth, Burning lips, Burning mouth, Burning oral sensation, Lip burning sensation of, Oral hot feeling, and 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 1,742 AEs (two serious and 1,740 non-serious) were received in 1,710 ICSRs. The retrieved AEs among the selected PT list were: Burning sensation (n=508, one serious and 507 non-serious), Burning sensation mucosal (n=17, all non-serious), and Skin burning sensation (n=3, all non-serious). The AEs retrieved among the selected *LLTs* under the PT Oral discomfort were: *Lip burning sensation of* (n=783, one serious and 782 non-serious), *Burning lips* (n=171, all non-serious), *Burning mouth* (n=137, all non-serious), *Burning oral sensation* (n=63, all non-serious), *Oral mucosal burning sensation* (n=35, all non-serious), and *Oral hot feeling* (n=25, all non-serious). Of note, the total number of AEs under the PT Oral discomfort was 1,357, out of which 1,214 were included in the risk assessment. The *LLTs* excluded from the risk assessment were: *Oral discomfort* (n=60), *Lip discomfort* (n=51), *Discomfort in mouth* (n=27), and *Oral cavity discomfort* (n=5).

Two serious cases were identified. The first one concerned a 30-year-old consumer that experienced events of Burning sensation along with Chest discomfort. Both events were assessed as serious as they led to hospitalization. The details concerning the burning sensation including the location of the burning sensation was not provided. Both events were not resolved. The second case concerned an 83-year-old consumer that experienced events of Oral discomfort (*LLT Lip burning sensation of*) along with Product physical issue. The consumer reported that the "cigarette makes his lips boiling hot". The event of Oral discomfort was considered as serious as it led to hospitalization. No treatment was administered due to the event. The use of the products was not stopped. The event of Oral discomfort was reported as not resolved.

Information regarding these cases is scarce for at least two main reasons: i) because PMI is not able to contact consumers that do not provide affirmative consent to be contacted by the Company; ii) due to data privacy restrictions in several countries. Consequently, a thorough root cause analysis could not be performed.

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-2020 up to the DLP of this SUR was performed in the global safety database to retrieve data related to thermal burns while using the THS. The electronic search included all non-serious AEs and SAEs 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 7,819 AEs (five serious and 7,814 non-serious) were received in 7,567 ICSRs: Thermal burn (n=6,027, four serious and 6,023 non-serious), Burn oral cavity (n=1,726, one serious and 1,725 non-serious), Burns second degree (n=46, all non-serious), Airway burns (n=16, all non-serious), and Burns first degree (n=4, all non-serious).

There were five serious cases identified, four reporting a serious event of Thermal burn and one concerning an event of Burn oral cavity. All events were assessed as serious as they involved hospitalization. The reported events concerned laryngeal mucosa, lips, throat, tongue and throat, and the burnt area was not specified in one case. In four out of five cases, the patient underwent a treatment. The event outcome was reported as resolved for two events, resolving for two events and was unknown for the remaining event.

In about 74.38% of cases, the consumer reported the oral cavity (including mouth, lips, and tongue) as the body site affected. In about 5.69% of the cases, the reported body site were fingers and/or hands.

Information regarding these cases is scarce for at least two main reasons: i) because PMI is not able to contact consumers that do not provide affirmative consent to be contacted by the Company; ii) due to data privacy restrictions in several countries. Consequently, a thorough root cause analysis could not be performed.

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-202 to the DLP of this SUR was performed in the global safety database to retrieve data related to pregnancy and lactation. The electronic search for pregnancy reports included all non-serious AEs and SAEs from solicited and unsolicited sources and was carried out under the MedDRA SOC “Pregnancy, puerperium and perinatal conditions" and the following MedDRA SMQs (Narrow): "Neonatal exposures via breast milk", "Pregnancy, labour and delivery complications and risk factors (excl.

abortions and stillbirth)", "Fœtal disorders", "Functional lactation disorders", "Neonatal disorders", "Normal pregnancy conditions and outcomes", "Termination of pregnancy and risk of abortion".

A total of 15 pregnancy related non-serious AEs were received in 15 ICSRs: Exposure during pregnancy (n=9), Maternal exposure during pregnancy (n=4), Maternal exposure during breast feeding (n=1), and Morning sickness (n=1).

The co-reported AEs included Nausea (n=4), Cough (n=2), Thermal burn (n=2), Dyspepsia (n=2), Malaise (n=2), Oral discomfort (n=1), Product physical issue (n=1), Oropharyngeal pain (n=1), Hypertension (n=1), Gastrointestinal disorder (n=1), Accidental exposure to product (n=1), Oropharyngeal discomfort (n=1), Product complaint (n=1), Device difficult to use (n=1), Dizziness (n=1), and Dysphonia (n=1), all non-serious events.

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 AR through airway inflammation or toxicity.[8]

The SPI version 5.0 dated 02-Dec-2019, mentions that Hypersensitivity events may occur in users of the THS, in particular those with a past medical history of an allergic condition, such

as food, pet, or dust allergies. In case of signs and symptoms that may indicate a serious allergic event, users should stop using the THS and contact their physician immediately.

To characterize this risk, a cumulative search from the IBD (04-Nov-2014) to the DLP of this SUR was performed in the global safety database to retrieve hypersensitivity-related events with THS product use. The electronic search for Hypersensitivity included all non-serious AEs and SAEs from all sources and was carried out under the MedDRA SMQ Hypersensitivity (narrow). The solicited and unsolicited MedDRA version used was 23.1.

Cumulatively, 6,234 hypersensitivity-related AEs with THS use (801 serious and 5,433 non-serious) were received in 5,359 ICSRs. The most reported AEs (>1%) were: Hypersensitivity (28.33%, n=1,766, 661 serious and 1,105 non-serious), Rash (24.90%, n=1,552, 25 serious and 1,527 non-serious), Pharyngeal swelling (9.62%, n=600, three serious and 597 non-serious), Gingival swelling (6.58%, n=410, one serious and 409 non-serious), Lip swelling (5.79%, n=361, two serious and 359 non-serious), Rash macular (4.75%, n=296, three serious and 293 non-serious), Urticaria (4.54%, n=283, two serious and 281 non-serious), Swollen tongue (1.75%, n=109, one serious and 108 non-serious), Mouth swelling (1.65%, n=103, all non-serious), Rash pruritic (1.49%, n=93, two serious and 91 non-serious), Rash erythematous (1.19%, n=74, one serious and 73 non-serious), and Swelling face (1.12%, n=70, all non-serious).

The most reported SAEs (>1%) were: Hypersensitivity (82.52%, n=661, 372 resolved or resolving, 181 with unknown outcome, and 108 not resolved), Angioedema (4.12%, n=33, 21 resolved or resolving, eight with unknown outcome, and four not resolved), Oropharyngeal blistering (3.12%, n=25, 12 with unknown outcome, eight not resolved, and five resolved or resolving), Rash (3.12%, n=25, 18 resolved or resolving, six not resolved, and one with unknown outcome), and Laryngeal oedema (2.50%, n=20, nine not resolved, six resolved or resolving, and five with unknown outcome).

As mentioned in section 15.3.1.1, the reporting frequency rate of cases of Hypersensitivity is estimated to be 0.15 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 toxic exposures worldwide. A European retrospective study published the outcomes of e-liquid exposure incidents reported to 10 Poison Centers[21] 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% $p < 0.001$).[21] 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 six years old conducted in the U.S.[22,23] Chewing tobacco (67.3%) and snuff (25.0%) accounted for most of the other tobacco product exposures.[22] Most children were exposed through ingestion (95.5%) or multiple routes including ingestion (2.8%), and only 1.7% through non-ingestion routes.[22] A recent study aiming to analyse cases of acute exposure to ECs, e-liquids, and HNBC products containing nicotine based on toxicological consultations at the Czech Republic poisons control centre during a seven-year period (2012–2018) showed similar results.[24] 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 nine (6%) cases, ocular in six (4%) cases, and intravenous administration in three (2%) cases. The sources of exposure were: the cartridge with e-liquid (107 cases; 72%), refillable tank (29 cases; 20%), and HNBC refill (nine cases, 6%).[24]

Infants are susceptible to accidental tobacco ingestion because of a natural curiosity and a tendency for oral exploration.[25,26] Ingestion of as little as 1mg of nicotine by a small child can produce symptoms such as nausea and vomiting.[27] Severe toxic effects of nicotine ingestion may include weakness, convulsions, unresponsiveness, and impaired respiration, and ultimately, may lead to respiratory arrest and death.[27]

As described in SPI version 5.0 for THS (dated 02-Dec-2019), toxic effects of nicotine develop rapidly following acute overdose. The current data indicates that more than 500mg (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 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, 4,220 events of Accidental exposure to product by child (49 serious and 4,171 non-serious) were received in 4,220 ICSRs. In 79.34% of ICSRs reporting Accidental exposure to product by children, no health-related events were co-reported (No adverse

event, n=3,348). In the remaining part of cases there were a total of 1,256 co-reported events (53 serious and 1,203 non-serious).

The most frequently (>1%) co-reported AEs were: Vomiting (45.14%, n=567, 16 serious and 551 non-serious), Pallor (5.89%, n=74, eight serious and 66 non-serious), Cough (5.10%, n=64, all non-serious), Nausea (4.70%, n=59, one serious and 58 non-serious), Irritability (3.42%, n=43, all non-serious), Mood altered (3.26%, n=41, all non-serious), Malaise (2.31%, n=29, one serious and 28 non-serious), Crying (2.07%, n=26, one serious and 25 non-serious), Asthenia (2.07%, n=26, one serious and 25 non-serious), Hiccups (1.67%, n=21, all non-serious), Fatigue (1.43%, n=18, all non-serious), Somnolence (1.19%, n=15, all non-serious), Pyrexia (1.11%, n=14, one serious and 13 non-serious), Salivary hypersecretion (1.04%, n=13, all non-serious), Respiratory tract irritation (1.04%, n=13, all non-serious), and Choking (1.04%, n=13, nine serious and four non-serious). Of the 53 co-reported SAEs the most frequent (n>1) were: Vomiting (n=16), Choking (n=9), Pallor (n=8), and Drooling (n=2).

Vomiting and Pallor may be signs and symptoms of mild nicotine intoxication, which may potentially occur upon the accidental ingestion of EHTP.

Thirteen events of Choking (nine serious and four non-serious) were received in 13 ICSRs. All the children (age range 7 to 14 months, age was unknown in one case) introduced EHTPs or parts of them into their mouths. The co-reported events from 10 ICSRs included Cough (n=7), Vomiting (n=5), Respiratory tract irritation (n=3), Pyrexia (n=2), Respiratory disorder (n=1), Nasopharyngitis (n=1), Initial insomnia (n=1), and Pain (n=1), all non-serious AEs. The remaining three cases did not present any co-reported events. No medical intervention was deemed necessary in all 13 ICSRs. The event outcome of Choking was reported as resolving or resolved for three events (one serious and two non-serious) and was unknown for the remaining 10 events. Taking into consideration that none of these cases led to hospitalization and that no medical intervention was necessary, it is very unlikely that these refer to cases of airway obstruction.

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

A higher water content in the EHTPs may lead to production of aerosol which some users perceive as warm. To avoid exposure of EHTPs to high humidity, PMI has communicated through various channels and updated the user guide to instruct consumers to store the products in a dry and cool place.

To characterize this risk, a cumulative search from the IBD (04-Nov-2014) until the DLP of this SUR was performed in the global safety database. A list of selected MedDRA PTs has been used in the search strategy: Burning sensation, Burning sensation mucosal, Skin burning sensation, and Oral discomfort. Only a selected list of *LLTs* under the PT Oral discomfort

coding events of burning sensation at the level of the oral cavity were included in the analysis, such as: *Burning corner of mouth, Burning lips, Burning mouth, Burning oral sensation, Lip burning sensation of, Oral hot feeling, and Oral mucosal burning sensation*. The other *LLTs* (*Discomfort in mouth, Lip discomfort, Oral cavity discomfort, Oral discomfort*) were 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, 3,648 AEs (six serious and 3,642 non-serious) were received in 3,585 ICSRs. The retrieved AEs among the selected PT list were: Burning sensation (n=969, three serious and 966 non-serious), Burning sensation mucosal (n=23, all non-serious), and Skin burning sensation (n=9, all non-serious). The AEs retrieved among the selected *LLTs* under the PT Oral discomfort were: *Lip burning sensation of* (n=1,656, two serious and 1,654 non-serious), *Burning lips* (n=384, one serious and 383 non-serious), *Burning mouth* (n=288, all non-serious), *Burning oral sensation* (n=115, all non-serious), *Oral hot feeling* (n=106 all non-serious), and *Oral mucosal burning sensation* (n=98, all non-serious). Of note, the total number of AEs under the PT Oral discomfort was 3,013, out of which 2,647 AEs were included in the risk assessment. The *LLTs* excluded from the risk assessment were: *Oral discomfort* (n=154), *Lip discomfort* (n=120), *Discomfort in mouth* (n=76), and *Oral cavity discomfort* (n=16).

Among the three serious events of Burning sensation, two 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 three serious events of Oral discomfort, all of them concerned burning/ burning sensation of lips and were assessed as serious as they involved hospitalization.

Information regarding these cases is scarce for at least two main reasons: i) because PMI is not able to contact consumers that do not provide affirmative consent to be contacted by the Company; ii) due to data privacy restrictions in several countries. Consequently, a thorough root cause analysis could not be performed.

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.[28] 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.[29] 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.[30] The failure rate of lithium batteries established during the manufacturing is one in 10 million.[31]

The study by Corey et al. 2018[32] 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.[33] 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, five cases in 2015, and one 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.[34], 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 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. The last MedDRA version used was 23.1.

Cumulatively, 16,475 AEs (23 serious and 16,452 non-serious) were received in 15,879 ICSRs: Thermal burn (n=13,129, 16 serious and 13,113 non-serious), Burn oral cavity (n=3,145, three serious and 3,142 non-serious), Burns second degree (n=142, all non-serious), Airway burns (n=39, all non-serious), Burns first degree (n=15, all non-serious), Burns third degree (n=4, all serious), and Thermal burns of eye (n=1, non-serious).

In about 76.25% of cases, the consumer reported the oral cavity (including mouth, lips, and tongue) as the body site affected. In about 5.71% of the cases, the reported body site were fingers and/or hands.

Among the 16 serious events of Thermal burn, 15 events were assessed as serious as they led to hospitalization. In the remaining case, the charger caught on fire, and possibly exploded, which led to hand burn. 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, 13 cases reported a burn of lips or

hand, in the remaining two cases, the burn site was provided as laryngeal mucosa, throat, and in one case the site was unspecified.

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

Among the three serious events of Burn oral cavity, two were assessed as serious as they 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.

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[35] as it is clear that maternal smoking affects fetal wellbeing and growth.[36,37] Indeed, nicotine is able to cross the placenta, and therefore, may affect foetal development.[38] 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 5.0 for THS (dated 02-Dec-2019), pregnant women, women who think they may be pregnant, and breastfeeding women are advised against the use of the THS.

To characterize the risk associated with the use of the THS during Pregnancy and lactation, a cumulative search from the IBD (04-Nov-2014) until the DLP of this SUR was performed in the global safety database. The electronic search for pregnancy reports included all non-serious AEs and SAEs from solicited and unsolicited sources and was carried out under the MedDRA SOC "Pregnancy, puerperium and perinatal conditions" and the following MedDRA SMQs (Narrow): "Neonatal exposures via breast milk" "Pregnancy, labour and 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, 32 AEs (one serious and 31 non-serious) were received in 32 ICSRs including Exposure during pregnancy (n=20, all non-serious), Maternal exposure during pregnancy

(n=7, all non-serious), Morning sickness (n=1, non-serious), Maternal exposure during breast feeding (n=1, non-serious), Maternal exposure timing unspecified (n=1, non-serious), Pregnancy (n=1, non-serious), and Mastitis (n=1, serious).

The 36 co-reported AEs were all assessed as non-serious and included Nausea (n=7), Cough (n=3), Malaise (n=3), Oropharyngeal pain (n=2), Dyspepsia (n=2), Thermal burn (n=2), Dizziness (n=2), Abdominal pain upper (n=2) and the remaining events were reported once: Dysphonia, Hypertension, Product physical issue, Laryngitis, Oropharyngeal discomfort, Throat irritation, Product complaint, Tooth discolouration, Gastrointestinal disorder, Occupational exposure to product, Oral discomfort, Device difficult to use, and Accidental exposure to product.

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.

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-2020 to 31-Dec-2020.

Of note, most of the spontaneous reports received by PMI are not medically confirmed, i.e. they were received from consumers directly and not from health care professionals. 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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18 APPENDICES

18.1 Appendix 1: Reference Safety Information

THS Safety Product Information version 5.0 dated 02-Dec-2019

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:	5.0
Release Date:	02 December 2019
Replaces Previous Version:	Version 4.0
Previous Release Date:	18 December 2018

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ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
Alu	Aluminium
BoExp	Biomarker(s) of exposure
CI	Confidence Interval
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
LED	Light Emitting Diode
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Analyzed
NAB	N-nitrosoanabasine
NAT	N-nitrosoanatabine
NFDPM	Nicotine-free dry particulate matter
NNK	4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
NRT	Nicotine Replacement Therapy
PAHs	Polycyclic Aromatic Hydrocarbons
PLA	Polylactic acid
PMI	Philip Morris International
PT	Preferred Term
SPI	Summary of Product Information
THD	Tobacco Heating Device
THS	Tobacco Heating System
TPM	Total Particulate Matter

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 (currently marketed as IQOS with HeatSticks/HEETS) that heats tobacco without producing combustion. In comparison with cigarette smoke, the formation of harmful and potentially harmful constituents (HPHCs) is greatly reduced.

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

In addition, the results of the Exposure Response Study, measuring the biological response of participants who switch to the THS for six months compared with participants who continued to smoke, demonstrated favorable changes in clinical risk endpoints pointing in the direction of risk reduction in those who switched to the THS (2).

The purpose of this Summary of Product Information (SPI) is to be the reference for professionals (e.g. researchers, health care providers) on how to use the product safely and effectively, once it is commercially available in the market. In this way, the SPI will be the reference document for safety and efficacy for the conduct of clinical studies after commercialization (e.g. for Investigator-Initiated Studies). The SPI is also the document used to determine the expectedness of AEs associated with the use of THS once commercially available. This document does not replace the User Guide for the THS.

2 PRODUCT DESCRIPTION

2.1 Product Name

Electrically Heated Tobacco Products (EHTP) are marketed worldwide as HeatSticks and/or HEETS. The EHTP is to be used exclusively with the Tobacco Heating Device (THD). The EHTP and the THD are components of the Tobacco Heating System (THS).

2.2 THS components

As previously mentioned, the THS is made up of two main components (see Figure 1): The EHTP, which is a Tobacco Stick and the THD, which consists of either two elements (charger and holder) or one single element (holder only).

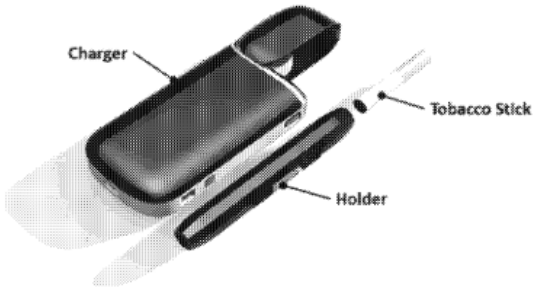

Figure 1 Picture of the THS components (THD with two elements)

2.2.1 The EHTP

The EHTP is designed to function with the Holder. It 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, an alu-wrapper is included in some versions of the EHTP (see Figure 2).

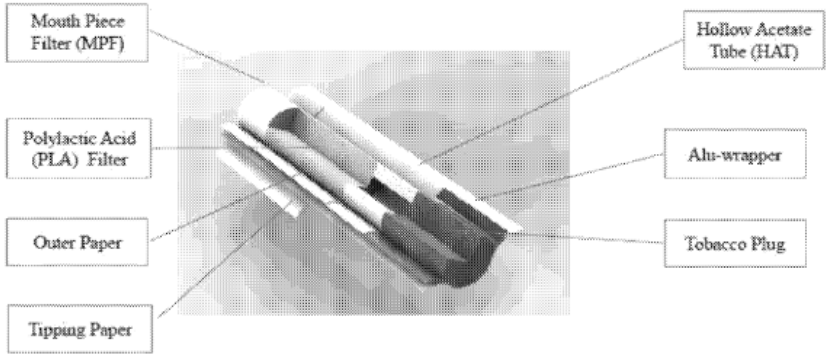

Figure 2 Schematic cross-sectional view of the EHTP

All the ingredients have been evaluated with regards to their toxicological potential and have been approved for use. The EHTP delivers nicotine, which is naturally present in tobacco. Each tobacco stick contains 5-6mg nicotine.

Table 1 shows, per product variant, the ingredients contained in the EHTP, in addition to blended tobacco.

Table 1 Ingredients contained in the EHTP, in addition to blended tobacco (3)

Category	Ingredient Name	Regular Variant	Menthol Variant
Tobacco Ingredient	Glycerol	x	x
Tobacco Ingredient	Water	x	x
Tobacco Ingredient	Guar Gum	x	x
Tobacco Ingredient	Cellulose	x	x
Tobacco Ingredient	(b) (4)		
Tobacco Ingredient	Propylene Glycol	x	x
Tobacco Ingredient	(b) (4)		
Tobacco Ingredient	Natural & Artificial Flavorings	x	x
Tobacco Plug Wrap Paper	Cellulose	x	x
Tobacco Plug Wrap Paper	Calcium Carbonate	x	x
Tobacco Plug Wrap Paper	Carboxymethylcellulose and its Sodium Salt	x	x
Tobacco Plug Adhesive	Ethylene-Vinyl Acetate Copolymer	x	x
Tobacco Plug Adhesive	Starch and/or Modified Starches	x	x
Tobacco Plug Adhesive	Propylene Glycol	x	x
Outer Paper	Cellulose	x	x
Outer Paper	Calcium Carbonate	x	x
Outer Paper	Epichlorhydrin Resin	x	
Outer Paper	Carboxymethylcellulose	x	x
Outer Paper	Guar Gum	x	
Outer Paper Adhesive	Ethylene-Vinyl Acetate Copolymer	x	x
Hollow Acetate Tube	Cellulose Acetate	x	x
Hollow Acetate Tube	Triacetin	x	x
Hollow Acetate Tube	Titanium Dioxide	x	x
Hollow Acetate Tube - Plugwrap Paper	Cellulose	x	x
Hollow Acetate Tube - Plugwrap Paper	Calcium Carbonate	x	x
Hollow Acetate Tube - Plugwrap Paper	Carboxymethylcellulose and its Sodium Salt	x	x
Hollow Acetate Tube - Adhesive	Polyvinyl Acetate	x	x
Hollow Acetate Tube - Adhesive	Hydroxyethylene - Vinyl Acetate Copolymer	x	x
Polylactic Acid Filter	Poly Lactic Resin	x	x
Polylactic Acid Filter	(b) (4)		
Polylactic Acid Filter			
Polylactic Acid Filter	Calcium Carbonate	x	x
Polylactic Acid Filter - Plug Wrap Paper	Cellulose	x	x
Polylactic Acid Filter - Plug Wrap Paper	Kaolin	x	x
Polylactic Acid Filter - Plug Wrap Paper	Rosin	x	x
Polylactic Acid Filter - Plug Wrap Paper	Optical Brightener	x	x
Polylactic Acid Filter - Adhesive	Polyvinyl Acetate	x	x
Polylactic Acid Filter - Adhesive	Ethylene-Vinyl Acetate Copolymer	x	x

Category	Ingredient Name	Regular Variant	Menthol Variant
Tobacco Ingredient	Glycerol	x	x
Polylactic Acid Filter - Adhesive	Hydrocarbon Resin	x	x
Polylactic Acid Filter - Adhesive	Paraffin	x	x
Polylactic Acid Filter - Adhesive	Hydroxyethylene - Vinyl Acetate Copolymer	x	x
Polylactic Acid Filter - Adhesive	Polyisobutylene	x	x
Mouth Piece Filter	(b)(4)		
Mouth Piece Filter	Triacetin	x	x
Mouth Piece Filter	Titanium Dioxide	x	x
Mouth Piece Filter - Plug Wrap Paper	Cellulose	x	x
Mouth Piece Filter - Plug Wrap Paper	Rosin	x	x
Mouth Piece Filter - Plug Wrap Paper	Optical Brightener	x	x
Mouth Piece Filter - Plug Wrap Paper	Kaolin	x	x
Mouth Piece Filter - Adhesive	Polyvinyl Acetate	x	x
Mouth Piece Filter - Adhesive	Ethylene-Vinyl Acetate Copolymer	x	x
Mouth Piece Filter - Adhesive	Hydrocarbon Resin	x	x
Mouth Piece Filter - Adhesive	Paraffin	x	x
Mouth Piece Filter - Adhesive	Polyisobutylene	x	x
Mouth Piece Filter - Adhesive	Hydroxyethylene - Vinyl Acetate Copolymer	x	x
Tipping Paper	Cellulose	x	x
Tipping Paper	Calcium Carbonate	x	x
Tipping Paper	Kaolin	x	x
Tipping Paper	Titanium Dioxide	x	x
Tipping Paper	Starch and/or Modified Starches	x	x
Tipping Paper	Alkylketene Dimer	x	x
Tipping Paper	Epichlorhydrin Resin	x	x
Tipping Paper	Pigments	x	x
Tipping Paper - Adhesive	Ethylene-Vinyl Acetate Copolymer	x	x
Tipping Paper - Adhesive	Hydroxyethylene - Vinyl Acetate Copolymer	x	x
Alu Wrapper*	Aluminium	x	x

* Only in some versions

2.2.2 THD with two elements (holder and charger)

2.2.2.1 The Holder

The Holder is a slim electrical heating unit that heats the EHTP in a controlled manner by using a heater blade.

Depending on the version, the Holder stores enough energy for one single inhalation experience or two consecutive inhalation experiences, delivering puffs over a period of about 6 minutes or 14 puffs (whichever comes first) for each experience. A Light Emitting Diode (LED) indicates when the experience can start and when the experience ends.

Once this cycle is complete, the Holder must be recharged before a new EHTP can be used.

2.2.2.2 The Charger

The power supply for the Holder is the Charger. It holds enough energy for approximately 20 uses of the Holder and can be recharged from household power.

The Charger stores the Holder when not in use, and provides a secure environment for the cleaning process of the heater blade.

2.2.3 THD with one single element (holder only)

The THD with one single element consists of a holder heating the EHTP in a controlled manner by using a heater blade.

The holder of the THD with one single element stores enough energy for approximatively 10 inhalation experiences, delivering puffs over a period of about 6 minutes or 14 puffs (whichever comes first) for each inhalation experience. A LED indicates when the experience can start and when the experience ends.

The Holder of the THD with one single element can be recharged from household power.

Figure 3 Picture of the THD with one single element

2.3 Product Variants

Different EHTP product variants are available on the market. EHTPs are available in different tobacco blends/flavors options, including the Regular (non-Menthol variant) and the Menthol variants.

2.4 THS Aerosol

Table 2 shows the levels of a selected list of compounds and HPHCs found, under the Health Canada Intense (HCI) machine-smoking conditions[1], in the aerosol of the Regular and Menthol variants of the THS in comparison with the levels found in a 3R4F reference cigarette. These data show that levels of the majority of HPHCs are reduced in the THS by more than 90% compared to the reference cigarette (4, 5).

[1] Puffing regime, first described by Health Canada, when taking one puff of 55 ml volume and 2 seconds duration every 30 s with 100 % of the ventilation zone on the cigarette filter blocked

Table 2 Analytes yields from the THS (Regular and Menthol variants) and a cigarette (3R4F standard) obtained under HCI machine-smoking conditions

Parameter (Unit)	THS (Regular)	THS (Menthol)	Reference cigarette (3R4F)
	mean ± $CI_{95\%}$ /stick	mean ± $CI_{95\%}$ /stick	mean ± $CI_{95\%}$ /cigarette
TPM[2] (mg/stick)	54.1 ± 2.4	53.8 ± 3.6	46.3 ± 2.9
Water (mg/stick)	39.4 ± 4.6	39.1 ± 3.6	13.3 ± 1.6
Nicotine (mg/stick)	1.26 ± 0.24	1.32 ± 0.11	2.09 ± 0.14
NFDPM[3] (mg/stick)	13.4 ± 2.8	13.4 ± 0.6	30.9 ± 1.9
Carbon monoxide (mg/stick)	0.598 ± 0.072	0.620 ± 0	30.7 ± 3.0
Benzo[a]pyrene (ng/stick)	1.19 ± 0.08	1.08 ± 0.09	13.7 ± 0.8
Menthol (mg/stick)	n.a.	2.98 ± 0.21	n.a.
Glycerol (mg/stick)	4.1 ± 1.07	4.59 ± 0.47	2.39 ± 0.15
1-aminonaphthalene (ng/stick)	0.063 ± 0.006	<0.061	19.7 ± 1.6
2-aminonaphthalene (ng/stick)	<0.035	<0.035	14.8 ± 1.9
3-aminobiphenyl (ng/stick)	<0.013	<0.013	3.90 ± 0.42
4-aminobiphenyl (ng/stick)	<0.021	n.a.	3.13 ± 0.60
o-toluidine (ng/stick)	1.204 ± 0.149	0.868 ± 0.087	90.5 ± 3.1
Acetaldehyde (µg/stick)	213 ± 19	220 ± 22	1589 ± 76
Acetone (µg/stick)	33.8 ± 6.4	42.6 ± 8.1	729 ± 36
Acrolein (µg/stick)	9.44 ± 0.87	10.91 ± 2.98	193 ± 21
Butyraldehyde (µg/stick)	25.3 ± 2.7	26.4 ± 0.9	103.9 ± 8.3
Crotonaldehyde (µg/stick)	3.75 ± 0.34	4.15 ± 0.64	92.1 ± 13.2
Formaldehyde (µg/stick)	5.22 ± 0.24	6.19 ± 2.00	68.7 ± 7.8
Methyl ethyl ketone (µg/stick)	7.94 ± 0.75	10.19 ± 2.23	241 ± 16

[2] Total particulate matter

[3] Nicotine-free dry particulate matter

Parameter (Unit)	THS (Regular)	THS (Menthol)	Reference cigarette (3R4F)
	mean ± $CI_{95\%}$ /stick	mean ± $CI_{95\%}$ /stick	mean ± $CI_{95\%}$ /cigarette
Propionaldehyde (µg/stick)	13.6 ± 1.5	15.9 ± 2.2	147 ± 8
Acrylonitrile (µg/stick)	0.186 ± 0.028	0.196 ± 0.016	31.6 ± 2.3
1,3-butadiene (µg/stick)	0.319 ± 0.073	0.411 ± 0.093	91.8 ± 11.0
Benzene (µg/stick)	0.575 ± 0.072	0.628 ± 0.073	100.4 ± 2.8
Isoprene (µg/stick)	2.44 ± 0.50	2.63 ± 0.60	869 ± 50
Pyridine (µg/stick)	9.38 ± 0.95	10.08 ± 0.46	51.8 ± 7.5
Quinoline (µg/stick)	0.014 ± 0.002	0.010 ± 0.003	0.390 ± 0.101
Styrene (µg/stick)	0.672 ± 0.063	0.632 ± 0.079	28.9 ± 2.2
Toluene (µg/stick)	1.61 ± 0.17	1.67 ± 0.37	198.8 ± 10.9
Catechol (µg/stick)	16.4 ± 0.6	12.8 ± 1.3	88.7 ± 2.6
o-cresol (µg/stick)	0.105 ± 0.017	0.059 ± 0.007	4.86 ± 0.50
m-cresol (µg/stick)	0.042 ± 0.006	0.032 ± 0.005	3.71 ± 0.34
p-cresol (µg/stick)	0.073 ± 0.009	0.042 ± 0.007	8.50 ± 0.78
Hydroquinone (µg/stick)	7.86 ± 0.63	6.21 ± 0.86	84.1 ± 3.3
Phenol (µg/stick)	1.51 ± 0.23	1.00 ± 0.17	13.2 ± 0.9
Resorcinol (µg/stick)	0.055 ± 0.013	0.036 ± 0.005	1.95 ± 0.55
Acetamide (µg/stick)	4.13 ± 0.21	3.43 ± 0.17	13.7 ± 0.7
Acrylamide (µg/stick)	2.27 ± 0.28	1.90 ± 0.12	5.3 ± 0.4
NAB (ng/stick)	3.52 ± 0.48	3.27 ± 0.15	34.1 ± 3.0
NAT (ng/stick)	22.3 ± 1.6	18.6 ± 2.9	300 ± 53
NNK (ng/stick)	10.1 ± 0.4	7.9 ± 1.1	257 ± 39
NNN (ng/stick)	10.3 ± 0.4	7.7 ± 1.0	268 ± 50
Ammonia (µg/stick)	15.6 ± 1.1	13.9 ± 1.1	39.2 ± 4.1
Hydrogen cyanide (µg/stick)	3.78 ± 0.44	5.57 ± 0.35	451 ± 47
Nitric oxide (µg/stick)	21.0 ± 8.1	18.4 ± 3.6	501 ± 33

Parameter (Unit)	THS (Regular)	THS (Menthol)	Reference cigarette (3R4F)
	mean ± $CI_{95\%}$ /stick	mean ± $CI_{95\%}$ /stick	mean ± $CI_{95\%}$ /cigarette
Nitrogen oxides (µg/stick)	22.6 ± 8.8	19.4 ± 4.0	541 ± 74
Arsenic (ng/stick)	<1.13	<1.13	6.56 ± 0.46
Cadmium (ng/stick)	<0.350	<0.350	122 ± 12
Chromium (ng/stick	<0.17	0.44	2.70[a]
Lead (ng/stick)	<3.35	<3.35	25.1 ± 2.1
Mercury (ng/stick)	1.02 ± 0.05	1.12 ± 0.19	4.17 ± 0.74
Nickel (ng/stick)	<0.55	0.88	1.30[a]
Selenium (ng/stick)	<0.550	<0.550	1.43 ± 0.15
Ethylene oxide (µg/stick)	0.314 ± 0.011	0.273 ± 0.036	34.2 ± 3.6
Nitrobenzene (ng/stick)	0.092 ± 0.008	0.155 ± 0.004	0.55 ± 0.04
Propylene oxide (µg/stick)	0.175 ± 0.03	0.14 ± 0.019	1.72 ± 0.16
Vinyl chloride (ng/stick)	<3.47	<3.47	95.3 ± 12.3
Benz[*a*]anthracene (ng/stick)	2.58 ± 0.17	2.50 ± 0.06	26.6 ± 1.7
Dibenz[*a*,*h*]anthracene (ng/stick)	<0.100	<0.100	1.79 ± 0.14
Pyrene (ng/stick)	7.93 ± 0.78	7.71 ± 0.63	87.3 ± 4.1

CI is the confidence interval of the mean,
n.a.: not analyzed.
<: median lower than the limit of quantitation, in this case LOQ is given.
If at least one value is below the LOQ, the median is given and the CI is not mentioned.
[a] CI not calculated.

3 PRODUCT PARTICULARS

3.1 Target Population

The intended population for the THS is legal age adult smokers who would otherwise continue to smoke.

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, has been exposed to excessive heat or moisture or if its batteries appear to be leaking.

The Holder may warm up slightly when in use.

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

3.3 Warnings and Precautions

To reduce the risk of injury, the THS shall always be used in accordance with the manufacturer's instructions (see THS User Guide).

Pregnant or breastfeeding women should be advised against the use of the THS.

3.3.1 Specific Risks that Lead to a Precaution for Use

3.3.1.1 Hypersensitivity

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

3.3.1.2 Risk of Accidental Exposure to product by Children

The THS shall be kept away from children at all times and it must be ensured they do not play with this product. The accidental exposure (ingestion) of EHTPs may potentially cause signs and symptoms of nicotine intoxication (see Section 3.7). In case of accidental exposure to product by children, users of the THS should be instructed to contact a physician immediately.

3.3.1.3 Burning sensation during Hot and Humid Weather Conditions

The water in the aerosol increases heat transfer properties and, under hot and humid weather conditions, may intensify the feeling of higher temperatures of the aerosol. THS users are encouraged to keep the THS in a dry environment and prevent them from exposure to high humidity to help avoid the perceived burning sensation when using the THS. If users continue to experience discomfort, they should be advised against further usage of the THS in hot conditions during periods of high humidity and should be advised to contact a physician.

3.3.2 Risks Associated with Starting Using the Product

The THS contains nicotine, which is addictive.

Due to the stimulation 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. Users who experience those signs/symptoms should be instructed to reduce product use by increasing the interval between single inhalation experiences, and/or by decreasing the number of puffs and/or the intensity of puffing.

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 a few hours 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 tobacco exposure/use 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 exposure to EHTPs by children may potentially cause signs and symptoms of nicotine intoxication (see specific warnings and precautions in section 3.3.1.2).

When using the THS during hot and humid weather conditions, consumers may feel a burning sensation (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 a few hours 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 3 and Table 4 are to be considered expected with the THS use.

3.5.2.1 Identified Risks

Table 3 provides the list of identified risks associated with the use of THS based on clinical studies and post-market experience.

Table 3 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 4 provides the list of nicotine class effect risks with the 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) and nicotine inhalator/inhaler (14, 15) were selected as references for nicotine class effect risks. Additionally, the SPC for the nicotine mouth spray was added in the selected references for class effect risks, after identification of this product in the list of NRTs from McNeil Products (16).

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 4 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 - Dysgeusia - Burning sensation - Paraesthesia - Seizure
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 - 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. Smoking causes periodontitis, which is characterized by an inflammation of the gingiva (17). A review of the literature found that smokers experience a decreased vascular response and therefore gum bleeding may be suppressed in smokers despite the periodontitis due to a decrease in blood flow in gum tissues (18). This effect is due to the impact on the cellular response including inflammatory and regenerative functions, which impairs periodontal healing in smokers (19-21). Smoking also reduces the angiogenic response to plaque and in consequence leads to reduced bleeding in smokers (22).

Quitting smoking has been associated with an increased risk of gum bleeding due to an increase in blood flow in gum tissues (23). This effect is transient and seen particularly during the first months after quitting (24).

Switching to THS reduces the exposure to toxicants / harmful and potentially harmful constituents (associated with cigarette smoking) by over 90% compared to continued smoking (1). 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 (i.e., an increase in blood flow in gum tissues). This effect of switching to THS is transient and similar to what is seen after 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 ingested (e.g. accidentally by children).

Toxic effects of nicotine develop rapidly following acute overdose. The current data indicate that more than 500 mg (6 to 7mg/kg) of oral nicotine is an accurate estimate of the acute lethal oral dose in adults (25). One EHTP contains, in average, 5 – 6mg 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 (26) 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 these cases (27, 28), 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 6 minutes and that the terminal half-life of nicotine was around 2 to 4 hours (29).

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 that can take several weeks.

Product acceptability as measured by nicotine uptake and reduction of urge-to-smoke was comparable to cigarette smoking; thus, the THS offers an experience close to what smokers expect when smoking cigarettes (30, 31).

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 THS generated aerosol 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 (4). In vivo 90-day inhalation study performed with the THS demonstrated a lower toxicity compared to the exposure to cigarette smoke (32-34).

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

04-Nov-2014 (Japan)

6 DATE OF REVISION OF THE TEXT

02-December-2019

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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 System Organ Class	MedDRA Preferred Term	CC	THS unspecified	THS Menthol	THS Regular	SA	Total
Blood and lymphatic system disorders	Anaemia	0	0	0	1	0	**1**
Cardiac disorders	Acute myocardial infarction	1	0	0	0	0	**3**
	Atrial fibrillation	0	1	0	0	0	
	Cardio-respiratory arrest	0	1	0	0	0	
Gastrointestinal disorders	Enteritis	0	0	0	0	1	**5**
	Inguinal hernia	0	0	0	0	1	
	Large intestine polyp	0	0	0	0	2	
	Pancreatitis chronic	1	0	0	0	0	
General disorders and administration site conditions	Death	1	1	0	0	0	**2**
Infections and infestations	Appendicitis	0	0	0	1	1	**13**
	Cellulitis	1	0	0	0	0	
	Cellulitis staphylococcal	1	0	0	0	0	
	Epiglottitis	0	0	0	1	0	
	Influenza	0	0	0	1	0	
	Peritonitis	0	0	0	1	0	
	Pneumonia mycoplasmal	0	0	0	1	0	
	Pyelonephritis acute	1	0	0	1	0	
	Sinusitis	0	0	1	0	0	
	Tooth infection	1	0	0	0	0	
	Urosepsis	1	0	0	0	0	
Injury, poisoning and procedural complications	Clavicle fracture	1	0	0	0	0	**10**
	Foot fracture	0	0	0	1	0	
	Head injury	0	0	0	1	0	
	Hip fracture	0	0	0	1	0	
	Multiple fractures	0	0	0	1	0	

MedDRA System Organ Class	MedDRA Preferred Term	CC	THS unspecified	THS Menthol	THS Regular	SA	Total
	Patella fracture	0	1	0	0	0	
	Pulmonary contusion	1	0	0	0	0	
	Rib fracture	1	0	0	0	0	
	Skin laceration	0	0	0	1	0	
	Traumatic haemothorax	1	0	0	0	0	
Metabolism and nutrition disorders	Diabetic ketoacidosis	0	0	1	0	0	**1**
Musculoskeletal and connective tissue disorders	Back pain	1	0	0	0	0	**4**
	Costochondritis	0	0	0	1	0	
	Jaw cyst	1	0	0	0	0	
	Vertebral osteophyte	1	0	0	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of colon	0	0	0	0	1	**6**
	Breast cancer	1	0	0	0	0	
	Inflammatory pseudotumour	1	0	0	0	0	
	Intestinal metastasis	0	0	0	1	0	
	Papillary thyroid cancer	1	0	0	0	0	
	Uterine leiomyoma	0	1	0	0	0	
Nervous system disorders	Myelopathy	1	0	0	0	0	**4**
	Seizure	0	0	0	1	0	
	Tarsal tunnel syndrome	1	0	0	0	0	
	Transient ischaemic attack	1	0	0	0	0	
Psychiatric disorders	Adjustment disorder with depressed mood	1	0	0	0	0	**4**
	Alcohol abuse	0	0	0	1	0	
	Completed suicide	0	0	0	1	0	
	Suicidal ideation	1	0	0	0	0	
Renal and urinary disorders	Nephrolithiasis	1	0	0	0	0	**1**

MedDRA System Organ Class	MedDRA Preferred Term	CC	THS unspecified	THS Menthol	THS Regular	SA	Total
Reproductive system and breast disorders	Menorrhagia	0	0	0	1	0	**2**
	Ovarian cyst	0	1	0	0	0	
Respiratory, thoracic and mediastinal disorders	Pleural effusion	1	0	0	0	0	**3**
	Pneumonia aspiration	0	0	0	1	0	
	Pulmonary oedema	0	1	0	0	0	
Social circumstances	Bereavement	1	0	0	0	0	**1**
Vascular disorders	Peripheral arterial occlusive disease	0	0	0	0	1	**2**
	Peripheral ischaemia	1	0	0	0	0	
Total		**27**	**7**	**2**	**19**	**7**	**62**

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

MedDRA System Organ Class	MedDRA Preferred Term	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	**44**	**109**	**0**	**2**	**44**	**111**
Anaemia	3	6	0	1	3	7
Blood disorder	0	1	0	0	0	1
Coagulopathy	0	1	0	0	0	1
Lymph node pain	6	13	0	0	6	13
Lymphadenitis	4	9	0	0	4	9
Lymphadenopathy	31	79	0	1	31	80
Cardiac disorders	**492**	**1174**	**310**	**639**	**802**	**1813**
Acute myocardial infarction	0	0	0	1	0	1
Angina pectoris	2	2	232	457	234	459
Arrhythmia	0	0	50	102	50	102
Arteriospasm coronary	0	0	2	2	2	2
Atrial fibrillation	0	0	1	1	1	1
Atrioventricular block	0	1	0	0	0	1
Bradycardia	0	0	0	2	0	2
Cardiac arrest	0	0	0	2	0	2
Cardiac discomfort	18	53	1	1	19	54
Cardiac disorder	53	110	3	6	56	116
Cardiac failure	0	0	1	2	1	2
Cardiac fibrillation	0	0	0	2	0	2
Cardiopulmonary failure	0	0	1	1	1	1
Cardiovascular disorder	13	27	0	1	13	28
Dressler's syndrome	1	1	0	0	1	1
Extrasystoles	1	5	0	0	1	5
Gastrocardiac syndrome	0	1	0	0	0	1
Myocardial infarction	0	1	15	36	15	37
Myocardial ischaemia	0	0	1	2	1	2
Palpitations	223	604	2	11	225	615
Pericardial effusion	0	0	0	1	0	1
Pericarditis	0	0	0	2	0	2
Sinus arrhythmia	1	1	0	0	1	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Sinus tachycardia	0	0	0	1	0	1
Tachyarrhythmia	1	1	0	1	1	2
Tachycardia	179	367	1	5	180	372
Congenital, familial and genetic disorders	**0**	**1**	**0**	**0**	**0**	**1**
Albinism	0	1	0	0	0	1
Ear and labyrinth disorders	**160**	**389**	**4**	**5**	**164**	**394**
Deafness	0	0	2	3	2	3
Deafness transitory	0	1	0	0	0	1
Ear congestion	3	19	0	0	3	19
Ear discomfort	16	36	0	0	16	36
Ear disorder	3	6	0	0	3	6
Ear pain	12	28	0	0	12	28
Ear pruritus	0	3	0	0	0	3
Ear swelling	3	5	0	0	3	5
Excessive cerumen production	0	1	0	0	0	1
Hypoacusis	1	14	1	1	2	15
Inner ear inflammation	1	2	0	0	1	2
Motion sickness	7	21	0	0	7	21
Tinnitus	24	59	0	0	24	59
Vertigo	90	193	1	1	91	194
Vertigo positional	0	1	0	0	0	1
Endocrine disorders	**16**	**37**	**0**	**2**	**16**	**39**
Autoimmune thyroid disorder	0	0	0	1	0	1
Goitre	2	5	0	0	2	5
Hyperthyroidism	0	0	0	1	0	1
Hypothyroidism	0	1	0	0	0	1
Thyroid cyst	1	1	0	0	1	1
Thyroid disorder	9	18	0	0	9	18
Thyroid mass	2	3	0	0	2	3
Thyroid pain	1	5	0	0	1	5
Thyroiditis	1	4	0	0	1	4
Eye disorders	**229**	**648**	**12**	**20**	**241**	**668**
Accommodation disorder	0	1	0	0	0	1
Asthenopia	3	9	0	0	3	9
Blepharospasm	2	4	0	0	2	4
Blindness	0	0	4	4	4	4

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Blindness transient	0	0	1	2	1	2
Chromatopsia	0	1	0	0	0	1
Conjunctival haemorrhage	0	0	1	1	1	1
Conjunctival irritation	0	1	0	0	0	1
Conjunctivitis allergic	1	3	0	0	1	3
Dark circles under eyes	2	5	0	0	2	5
Diplopia	2	4	0	0	2	4
Dry eye	13	76	0	0	13	76
Eczema eyelids	0	1	0	0	0	1
Erythema of eyelid	1	2	0	0	1	2
Excessive eye blinking	0	2	0	0	0	2
Exophthalmos	0	0	1	1	1	1
Eye allergy	1	2	0	0	1	2
Eye colour change	0	1	0	0	0	1
Eye discharge	1	7	0	0	1	7
Eye disorder	2	10	0	0	2	10
Eye haemorrhage	0	1	0	0	0	1
Eye inflammation	1	2	0	1	1	3
Eye irritation	12	27	0	1	12	28
Eye movement disorder	3	4	0	0	3	4
Eye oedema	1	1	0	0	1	1
Eye pain	20	67	0	0	20	67
Eye paraesthesia	0	1	0	0	0	1
Eye pruritus	20	42	0	1	20	43
Eye swelling	17	45	1	2	18	47
Eyelid irritation	0	2	0	0	0	2
Eyelid oedema	2	3	0	0	2	3
Eyelid ptosis	1	1	0	0	1	1
Eyelid rash	1	2	0	0	1	2
Eyelids pruritus	1	3	0	0	1	3
Lacrimation increased	39	97	1	2	40	99
Maculopathy	0	1	0	0	0	1
Metamorphopsia	0	2	0	0	0	2
Mydriasis	2	3	0	0	2	3
Ocular discomfort	8	14	0	0	8	14

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Ocular hyperaemia	13	48	0	0	13	48
Ocular hypertension	0	0	1	1	1	1
Periorbital pain	0	1	0	0	0	1
Periorbital swelling	2	6	0	0	2	6
Photophobia	2	4	0	0	2	4
Photopsia	1	1	0	0	1	1
Swelling of eyelid	3	6	0	0	3	6
Vision blurred	30	83	1	2	31	85
Visual acuity reduced	0	2	0	0	0	2
Visual impairment	22	49	0	1	22	50
Xerophthalmia	0	1	1	1	1	2
Gastrointestinal disorders	**11956**	**31721**	**68**	**193**	**12024**	**31914**
Abdominal discomfort	486	1016	3	5	489	1021
Abdominal distension	90	246	2	2	92	248
Abdominal pain	97	199	2	2	99	201
Abdominal pain lower	3	16	0	0	3	16
Abdominal pain upper	873	1742	2	6	875	1748
Abdominal rigidity	0	4	0	0	0	4
Abnormal faeces	1	4	1	1	2	5
Aerophagia	0	1	0	0	0	1
Ageusia	1	1	0	0	1	1
Allergic stomatitis	1	2	0	0	1	2
Anaesthesia oral	3	7	0	0	3	7
Anal incontinence	0	1	0	0	0	1
Angular cheilitis	0	1	0	0	0	1
Anorectal discomfort	0	4	0	0	0	4
Aphthous ulcer	93	261	0	0	93	261
Aptyalism	8	18	0	0	8	18
Bowel movement irregularity	2	8	0	0	2	8
Breath odour	22	81	1	1	23	82
Burning mouth syndrome	1	1	0	0	1	1
Cardiospasm	0	2	0	0	0	2
Change of bowel habit	0	2	0	0	0	2

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Chapped lips	45	155	0	0	45	155
Cheilitis	72	244	0	0	72	244
Chronic gastritis	1	2	0	0	1	2
Coating in mouth	11	24	0	0	11	24
Colitis	1	3	0	0	1	3
Colitis ulcerative	0	0	1	1	1	1
Constipation	19	66	0	0	19	66
Dental caries	8	14	1	1	9	15
Dental discomfort	14	27	0	0	14	27
Dental paraesthesia	5	8	0	0	5	8
Dental plaque	6	14	0	0	6	14
Diaphragmatic hernia	1	1	0	0	1	1
Diarrhoea	145	322	3	5	148	327
Discoloured vomit	0	2	0	0	0	2
Diverticulitis	0	0	1	1	1	1
Dry mouth	787	1801	0	3	787	1804
Duodenal ulcer	0	0	2	4	2	4
Duodenitis	2	2	0	0	2	2
Dyschezia	1	1	0	0	1	1
Dysgeusia	2	2	0	0	2	2
Dyspepsia	716	1546	3	5	719	1551
Dysphagia	75	194	1	4	76	198
Enamel anomaly	1	1	0	0	1	1
Enlarged uvula	4	13	0	0	4	13
Enteritis	0	2	0	0	0	2
Enterocolitis	0	0	0	1	0	1
Epigastric discomfort	10	14	0	0	10	14
Erosive duodenitis	0	0	0	1	0	1
Eructation	19	39	0	0	19	39
Faeces discoloured	2	4	0	0	2	4
Faeces hard	0	1	0	0	0	1
Faeces soft	0	1	0	0	0	1
Flatulence	30	66	0	0	30	66
Food poisoning	1	3	0	0	1	3
Frequent bowel movements	3	12	0	0	3	12
Functional gastrointestinal disorder	1	2	0	0	1	2

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Gastric cyst	0	1	0	0	0	1
Gastric dilatation	1	3	0	0	1	3
Gastric disorder	20	43	0	0	20	43
Gastric perforation	1	1	1	1	2	2
Gastric ulcer	0	0	8	21	8	21
Gastric ulcer perforation	0	0	0	1	0	1
Gastritis	26	65	0	1	26	66
Gastrointestinal disorder	64	130	3	4	67	134
Gastrointestinal hypermotility	1	1	0	0	1	1
Gastrointestinal inflammation	1	3	0	0	1	3
Gastrointestinal motility disorder	1	3	0	0	1	3
Gastrointestinal oedema	0	0	1	1	1	1
Gastrointestinal pain	12	17	0	0	12	17
Gastrointestinal sounds abnormal	0	3	0	0	0	3
Gastrointestinal tract irritation	0	1	0	0	0	1
Gastrointestinal ulcer	1	1	0	0	1	1
Gastrooesophageal reflux disease	60	128	1	2	61	130
Gingival bleeding	433	1295	2	6	435	1301
Gingival blister	7	24	0	0	7	24
Gingival discolouration	3	24	0	0	3	24
Gingival discomfort	60	118	0	1	60	119
Gingival disorder	36	157	0	2	36	159
Gingival erosion	1	5	0	0	1	5
Gingival erythema	9	24	0	0	9	24
Gingival pain	145	431	0	0	145	431
Gingival pruritus	6	10	0	0	6	10
Gingival recession	18	38	2	2	20	40
Gingival swelling	84	407	1	1	85	408
Gingival ulceration	4	9	0	0	4	9
Glossitis	48	176	0	0	48	176
Glossodynia	180	621	0	0	180	621
Haematemesis	0	0	1	6	1	6

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Haematochezia	0	0	2	3	2	3
Haemorrhoids	2	3	0	0	2	3
Hiatus hernia	0	1	0	0	0	1
Hyperaesthesia teeth	67	157	0	0	67	157
Hyperchlorhydria	11	16	1	1	12	17
Hypertrophy of tongue papillae	1	1	0	0	1	1
Hypoaesthesia oral	96	342	1	1	97	343
Hypoaesthesia teeth	0	6	0	0	0	6
Irritable bowel syndrome	7	8	0	0	7	8
Large intestinal ulcer	0	0	1	1	1	1
Large intestine perforation	0	0	1	1	1	1
Lip blister	174	641	0	0	174	641
Lip discolouration	29	77	0	0	29	77
Lip disorder	10	41	0	0	10	41
Lip dry	97	248	0	0	97	248
Lip erosion	0	2	0	0	0	2
Lip erythema	57	204	0	0	57	204
Lip exfoliation	49	233	0	0	49	233
Lip haemorrhage	9	48	0	0	9	48
Lip injury	1	1	0	0	1	1
Lip oedema	1	2	0	0	1	2
Lip pain	183	645	0	1	183	646
Lip pruritus	8	15	0	0	8	15
Lip scab	2	2	0	0	2	2
Lip swelling	117	359	1	2	118	361
Lip ulceration	12	36	0	0	12	36
Loose tooth	10	27	0	0	10	27
Malpositioned teeth	0	1	0	0	0	1
Mouth cyst	0	1	0	0	0	1
Mouth haemorrhage	19	128	0	0	19	128
Mouth swelling	27	103	0	0	27	103
Mouth ulceration	113	288	1	1	114	289
Nausea	2437	5853	6	24	2443	5877
Nicotinic stomatitis	0	1	0	0	0	1
Noninfective gingivitis	76	221	1	1	77	222
Noninfective sialoadenitis	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Odynophagia	19	79	0	1	19	80
Oesophageal dilatation	0	1	0	0	0	1
Oesophageal discomfort	6	13	0	0	6	13
Oesophageal disorder	4	9	0	0	4	9
Oesophageal irritation	3	6	0	0	3	6
Oesophageal pain	10	22	0	1	10	23
Oesophageal rupture	0	1	0	0	0	1
Oesophagitis	7	28	0	1	7	29
Oral cavity fistula	0	1	0	0	0	1
Oral discharge	0	2	0	0	0	2
Oral discomfort	1354	2996	1	4	1355	3000
Oral disorder	17	110	0	0	17	110
Oral mucosa erosion	0	2	0	0	0	2
Oral mucosal blistering	76	236	0	0	76	236
Oral mucosal discolouration	6	38	0	0	6	38
Oral mucosal eruption	23	44	0	0	23	44
Oral mucosal erythema	6	33	0	0	6	33
Oral mucosal exfoliation	8	88	0	0	8	88
Oral mucosal roughening	0	8	0	0	0	8
Oral pain	153	551	0	2	153	553
Oral papule	0	1	0	0	0	1
Oral pigmentation	1	6	0	0	1	6
Oral pruritus	9	29	0	0	9	29
Palatal disorder	6	15	0	0	6	15
Palatal oedema	0	2	0	0	0	2
Palatal swelling	12	34	0	1	12	35
Palatal ulcer	2	4	0	0	2	4
Pancreatic disorder	2	7	0	1	2	8
Pancreatitis	0	0	1	3	1	3
Pancreatitis acute	0	0	0	2	0	2
Paraesthesia oral	45	187	1	1	46	188
Periodontal disease	1	5	0	0	1	5
Pigmentation lip	5	6	0	0	5	6

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Plicated tongue	4	31	0	0	4	31
Reflux gastritis	2	7	0	0	2	7
Regurgitation	2	6	0	0	2	6
Retching	105	253	0	0	105	253
Saliva altered	4	7	0	0	4	7
Saliva discolouration	2	15	0	1	2	16
Salivary duct stenosis	1	1	0	0	1	1
Salivary gland disorder	1	3	0	0	1	3
Salivary gland enlargement	1	3	0	0	1	3
Salivary gland pain	0	5	0	0	0	5
Salivary hypersecretion	26	78	0	0	26	78
Scalloped tongue	0	1	0	0	0	1
Stiff tongue	1	4	0	0	1	4
Stomatitis	320	1555	1	7	321	1562
Stomatitis haemorrhagic	1	1	0	0	1	1
Swollen tongue	37	108	0	1	37	109
Teeth brittle	3	5	0	0	3	5
Throat irritation	1	1	0	0	1	1
Tongue blistering	22	71	0	0	22	71
Tongue coated	12	109	1	1	13	110
Tongue discolouration	15	55	0	0	15	55
Tongue discomfort	126	309	0	0	126	309
Tongue disorder	16	84	0	0	16	84
Tongue dry	15	42	0	0	15	42
Tongue eruption	17	45	0	1	17	46
Tongue erythema	17	54	0	0	17	54
Tongue exfoliation	6	12	0	0	6	12
Tongue haemorrhage	2	18	0	1	2	19
Tongue movement disturbance	1	2	0	0	1	2
Tongue necrosis	0	0	0	1	0	1
Tongue oedema	0	1	0	0	0	1
Tongue pruritus	5	11	0	0	5	11
Tongue rough	6	16	0	0	6	16
Tongue spasm	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Tongue ulceration	15	56	0	0	15	56
Tooth deposit	6	17	0	0	6	17
Tooth discolouration	14	35	1	1	15	36
Tooth disorder	25	82	0	0	25	82
Tooth erosion	1	1	0	0	1	1
Tooth loss	7	10	0	1	7	11
Tooth pulp haemorrhage	1	1	0	0	1	1
Tooth socket haemorrhage	2	2	0	0	2	2
Toothache	189	459	1	4	190	463
Trichoglossia	2	18	0	0	2	18
Varicose veins sublingual	1	1	0	0	1	1
Vomiting	647	1907	3	29	650	1936
General disorders and administration site conditions	**8454**	**21052**	**62**	**145**	**8516**	**21197**
Adverse drug reaction	2	10	0	0	2	10
Adverse event	59	151	1	4	60	155
Adverse reaction	4	40	0	0	4	40
Alcohol interaction	7	8	0	0	7	8
Asthenia	181	488	5	10	186	498
Burning sensation	2	2	0	0	2	2
Chest discomfort	877	2334	5	12	882	2346
Chest pain	808	2288	7	14	815	2302
Chills	23	53	0	0	23	53
Cold sweat	1	1	0	0	1	1
Condition aggravated	49	127	1	5	50	132
Crepitations	0	1	0	0	0	1
Crying	6	31	0	1	6	32
Cyst	1	9	1	2	2	11
Death	0	0	1	2	1	2
Decreased activity	3	3	0	0	3	3
Device intolerance	2	7	0	0	2	7
Discharge	1	7	0	0	1	7
Discomfort	359	720	0	2	359	722
Drug intolerance	10	12	0	0	10	12
Energy increased	1	1	0	0	1	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Exercise tolerance decreased	2	2	0	0	2	2
Face oedema	1	3	0	0	1	3
Facial pain	23	48	0	0	23	48
Fatigue	188	391	3	6	191	397
Feeling abnormal	337	768	0	2	337	770
Feeling cold	13	25	0	0	13	25
Feeling drunk	4	13	0	1	4	14
Feeling hot	308	836	0	1	308	837
Feeling jittery	3	6	0	0	3	6
Feeling of body temperature change	2	5	0	0	2	5
Feeling of relaxation	0	1	0	0	0	1
Foaming at mouth	0	1	0	0	0	1
Food interaction	1	4	0	0	1	4
Gait disturbance	4	15	0	0	4	15
Gait inability	6	8	0	0	6	8
General physical health deterioration	68	189	4	7	72	196
Generalised oedema	1	1	0	1	1	2
Glassy eyes	0	1	0	0	0	1
Hangover	7	10	0	0	7	10
Hernia	0	1	0	0	0	1
Hunger	11	22	0	0	11	22
Hyperhidrosis	1	1	0	0	1	1
Hyperplasia	1	1	0	0	1	1
Hyperthermia	1	1	0	0	1	1
Ill-defined disorder	33	98	3	4	36	102
Illness	353	830	3	9	356	839
Impaired healing	0	2	0	0	0	2
Induration	1	1	0	0	1	1
Inflammation	37	87	1	2	38	89
Influenza like illness	4	10	1	2	5	12
Injury associated with device	0	3	0	0	0	3
Localised oedema	1	1	0	0	1	1
Malaise	2808	5216	12	21	2820	5237
Mass	3	3	0	0	3	3
Mucosal atrophy	1	1	0	0	1	1
Mucosal discolouration	2	2	0	0	2	2

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Mucosal disorder	11	26	0	0	11	26
Mucosal dryness	78	112	0	0	78	112
Mucosal erosion	6	7	0	0	6	7
Mucosal haemorrhage	1	1	0	0	1	1
Mucosal hypertrophy	1	1	0	0	1	1
Mucosal induration	0	1	0	0	0	1
Mucosal inflammation	18	30	0	1	18	31
Mucosal membrane hyperplasia	0	1	0	0	0	1
Mucosal pain	0	3	0	0	0	3
Mucosal pigmentation	1	1	0	0	1	1
No adverse event	744	3589	0	0	744	3589
Nodule	1	3	0	1	1	4
Non-cardiac chest pain	0	3	0	0	0	3
Nonspecific reaction	1	1	0	0	1	1
Oedema	1	5	0	0	1	5
Oedema mucosal	4	8	0	1	4	9
Oedema peripheral	2	5	0	0	2	5
Pain	200	531	2	5	202	536
Performance status decreased	1	1	0	0	1	1
Peripheral swelling	30	62	0	0	30	62
Physical deconditioning	1	1	0	0	1	1
Polyp	2	5	0	0	2	5
Product intolerance	108	176	0	0	108	176
Pyrexia	54	178	7	17	61	195
Screaming	0	1	0	0	0	1
Secretion discharge	38	67	0	1	38	68
Sensation of blood flow	0	1	0	0	0	1
Sensation of foreign body	291	668	2	4	293	672
Sense of oppression	2	4	0	0	2	4
Sensitivity to weather change	0	1	0	0	0	1
Sluggishness	8	13	0	0	8	13
Swelling	43	108	2	4	45	112

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Swelling face	27	69	0	0	27	69
Temperature intolerance	4	15	0	0	4	15
Temperature regulation disorder	0	3	0	0	0	3
Tenderness	0	1	0	0	0	1
Therapeutic response unexpected	1	2	0	0	1	2
Thirst	99	255	0	1	99	256
Thirst decreased	1	2	0	0	1	2
Tobacco interaction	0	2	0	0	0	2
Ulcer	11	23	0	0	11	23
Unevaluable event	41	156	0	1	41	157
Withdrawal syndrome	2	8	1	1	3	9
Xerosis	0	2	0	0	0	2
Hepatobiliary disorders	**10**	**41**	**3**	**5**	**13**	**46**
Biliary colic	1	5	1	1	2	6
Cholelithiasis	2	2	0	0	2	2
Gallbladder disorder	0	2	0	0	0	2
Hepatic failure	0	0	1	2	1	2
Hepatic pain	7	18	0	0	7	18
Hepatomegaly	0	2	0	0	0	2
Liver disorder	0	12	1	1	1	13
Liver injury	0	0	0	1	0	1
Immune system disorders	**541**	**1178**	**348**	**673**	**889**	**1851**
Allergic oedema	0	1	0	0	0	1
Allergic reaction to excipient	14	19	0	0	14	19
Allergy to animal	1	1	0	0	1	1
Allergy to chemicals	1	9	0	1	1	10
Allergy to metals	6	12	0	0	6	12
Allergy to plants	1	1	0	0	1	1
Anaphylactic reaction	0	0	1	1	1	1
Anaphylactic shock	0	0	3	5	3	5
Anaphylactoid reaction	0	0	0	1	0	1
Atopy	1	4	0	0	1	4
Autoimmune disorder	0	0	0	1	0	1

MedDRA SOC MedDRA PT	**Interval Non-serious**	**Cumulative Non-serious**	**Interval Serious**	**Cumulative Serious**	**Interval Total**	**Cumulative Total**
Decreased immune responsiveness	0	1	0	0	0	1
Device allergy	1	3	0	0	1	3
Dust allergy	1	1	0	0	1	1
Hypersensitivity	507	1104	342	660	849	1764
Immune system disorder	1	7	1	1	2	8
Immunosuppression	1	1	0	0	1	1
Multiple chemical sensitivity	0	0	0	1	0	1
Reaction to excipient	2	5	0	0	2	5
Reaction to food additive	1	1	0	0	1	1
Sarcoidosis	0	0	1	2	1	2
Seasonal allergy	1	4	0	0	1	4
Sensitisation	2	2	0	0	2	2
Smoke sensitivity	0	2	0	0	0	2
Infections and infestations	**420**	**1498**	**67**	**160**	**487**	**1658**
Abscess	4	6	0	1	4	7
Abscess oral	0	3	0	0	0	3
Acarodermatitis	2	3	0	0	2	3
Acne pustular	3	6	0	0	3	6
Acute sinusitis	0	1	0	1	0	2
Bacterial allergy	1	1	0	0	1	1
Bacterial rhinitis	0	0	0	1	0	1
Blister infected	0	4	0	0	0	4
Bronchiolitis	0	1	0	0	0	1
Bronchitis	45	126	4	12	49	138
Burn infection	0	1	0	1	0	2
Candida infection	16	17	0	0	16	17
Chorioretinitis	0	0	0	1	0	1
Chronic tonsillitis	0	2	4	6	4	8
Conjunctivitis	1	6	0	1	1	7
Coronavirus infection	1	1	0	0	1	1
COVID-19	2	2	0	0	2	2
Cystitis	1	1	1	1	2	2
Dermatitis infected	0	1	0	0	0	1
Dysentery	0	0	1	1	1	1
Ear infection	1	3	0	0	1	3

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Empyema	0	0	1	1	1	1
Erythema induratum	0	1	0	0	0	1
Folliculitis	3	8	0	0	3	8
Fungal infection	2	4	0	0	2	4
Furuncle	0	34	1	1	1	35
Gangrene	0	0	1	1	1	1
Gastroenteritis	3	7	0	0	3	7
Gastroenteritis viral	1	4	0	0	1	4
Gingival abscess	0	1	0	5	0	6
Gingivitis	16	77	0	1	16	78
Herpes dermatitis	0	1	0	0	0	1
Herpes virus infection	0	9	0	0	0	9
Herpes zoster	1	6	0	0	1	6
Hordeolum	0	5	0	0	0	5
Infected skin ulcer	0	0	1	1	1	1
Infection	2	28	1	3	3	31
Infection susceptibility increased	0	0	1	1	1	1
Infective glossitis	0	8	0	1	0	9
Influenza	12	36	1	1	13	37
Labyrinthitis	0	1	0	0	0	1
Laryngitis	19	55	0	1	19	56
Lip infection	1	9	0	0	1	9
Lower respiratory tract infection	0	0	2	4	2	4
Lower respiratory tract infection fungal	0	0	1	1	1	1
Mastitis	0	0	0	1	0	1
Mumps	3	3	0	0	3	3
Myringitis	0	0	1	1	1	1
Nasopharyngitis	53	225	1	1	54	226
Oral bacterial infection	0	0	0	1	0	1
Oral candidiasis	9	18	0	0	9	18
Oral fungal infection	5	9	0	0	5	9
Oral herpes	33	127	0	0	33	127
Oral infection	2	95	0	1	2	96
Oral pustule	3	4	1	1	4	5
Osteomyelitis	0	0	0	1	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Otitis externa	0	2	0	0	0	2
Otitis media	0	1	0	0	0	1
Periodontitis	18	31	0	1	18	32
Periorbital infection	0	0	0	1	0	1
Peritonsillar abscess	0	0	2	4	2	4
Pertussis	0	0	1	1	1	1
Pharyngeal abscess	0	0	0	1	0	1
Pharyngitis	52	177	0	3	52	180
Pharyngitis bacterial	0	0	2	2	2	2
Pharyngitis streptococcal	0	1	0	0	0	1
Pharyngotonsillitis	0	0	1	1	1	1
Pneumonia	0	0	25	67	25	67
Pneumonia klebsiella	0	0	1	1	1	1
Pneumonia viral	0	0	0	1	0	1
Pulpitis dental	0	1	0	0	0	1
Purulence	1	2	0	0	1	2
Purulent discharge	6	12	0	0	6	12
Pustule	8	11	1	1	9	12
Rash pustular	4	8	0	0	4	8
Respiratory tract infection	0	0	3	7	3	7
Respiratory tract infection viral	0	1	1	1	1	2
Rhinitis	19	61	0	0	19	61
Sinusitis	12	37	1	2	13	39
Skin infection	1	7	0	0	1	7
Sputum purulent	1	3	0	1	1	4
Subcutaneous abscess	0	1	0	0	0	1
Tinea infection	0	1	0	0	0	1
Tongue abscess	0	1	0	0	0	1
Tongue fungal infection	1	1	0	0	1	1
Tonsillitis	47	155	1	3	48	158
Tonsillitis bacterial	0	0	4	5	4	5
Tooth abscess	1	1	0	0	1	1
Tooth infection	0	3	0	0	0	3
Tracheitis	1	7	0	0	1	7
Tuberculosis	0	0	1	1	1	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Upper respiratory tract infection	0	3	0	0	0	3
Urinary tract infection	1	1	0	0	1	1
Viral infection	1	7	0	1	1	8
Viral pharyngitis	1	2	0	0	1	2
Injury, poisoning and procedural complications	**9591**	**22426**	**32**	**114**	**9623**	**22540**
Accident	3	3	0	0	3	3
Accidental exposure to product	76	359	0	4	76	363
Accidental exposure to product by child	879	4171	5	49	884	4220
Accidental overdose	1	1	0	0	1	1
Airway burns	16	39	0	0	16	39
Alcohol poisoning	0	2	0	0	0	2
Back injury	1	2	0	0	1	2
Blast injury	1	2	0	0	1	2
Burn oesophageal	7	31	0	0	7	31
Burn of internal organs	1	2	0	0	1	2
Burn oral cavity	1726	3143	1	3	1727	3146
Burns first degree	4	15	0	0	4	15
Burns second degree	46	141	0	0	46	141
Burns third degree	0	0	0	4	0	4
Chemical burn	3	6	0	0	3	6
Chemical burn of oral cavity	1	1	0	0	1	1
Chemical burn of respiratory tract	0	0	2	2	2	2
Chemical poisoning	0	0	1	1	1	1
Cold burn	2	2	0	0	2	2
Contusion	3	12	1	1	4	13
Dental restoration failure	2	2	0	0	2	2
Device difficult to use	516	683	0	0	516	683
Device maintenance issue	2	2	0	0	2	2
Device use error	3	8	0	0	3	8
Device use issue	3	15	0	0	3	15
Electric shock	25	41	0	0	25	41

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Electrical burn	0	2	0	0	0	2
Exposure during pregnancy	9	13	0	0	9	13
Exposure to toxic agent	0	2	0	0	0	2
Eye contusion	1	2	0	0	1	2
Eye injury	1	2	0	0	1	2
Face injury	3	5	0	0	3	5
Fall	9	20	1	4	10	24
Foreign body	1	1	0	0	1	1
Foreign body in eye	1	2	0	0	1	2
Foreign body in gastrointestinal tract	0	1	0	0	0	1
Foreign body in mouth	0	1	0	0	0	1
Foreign body in respiratory tract	1	7	0	1	1	8
Foreign body in throat	3	4	0	0	3	4
Gingival injury	4	9	0	0	4	9
Hair injury	1	1	0	0	1	1
Head injury	1	3	0	0	1	3
Heat stroke	1	1	0	0	1	1
Incorrect route of product administration	0	2	0	0	0	2
Inflammation of wound	1	1	0	0	1	1
Injury	4	15	0	0	4	15
Intentional device misuse	0	2	0	0	0	2
Intentional product misuse	20	22	0	1	20	23
Intentional product use issue	1	2	0	0	1	2
Joint dislocation	0	1	0	0	0	1
Joint injury	1	1	0	0	1	1
Laryngeal injury	0	0	0	1	0	1
Ligament sprain	1	1	0	0	1	1
Limb injury	6	20	0	0	6	20
Limb traumatic amputation	0	0	1	1	1	1
Lip injury	19	44	0	1	19	45
Lower limb fracture	0	0	1	1	1	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Maternal exposure during breast feeding	1	1	0	0	1	1
Maternal exposure during pregnancy	4	7	0	0	4	7
Metal poisoning	0	0	1	3	1	3
Mouth injury	8	30	0	0	8	30
Mucosal excoriation	1	1	0	0	1	1
Muscle injury	0	0	0	1	0	1
Muscle strain	1	5	0	0	1	5
Nail injury	1	5	0	0	1	5
Nasal injury	0	3	0	0	0	3
Nerve injury	2	3	0	0	2	3
Occupational exposure to product	0	6	0	0	0	6
Oesophagitis chemical	0	0	1	1	1	1
Off label use	0	1	0	0	0	1
Oral contusion	2	6	0	0	2	6
Overdose	5	8	0	0	5	8
Palate injury	1	13	0	0	1	13
Pharyngeal injury	1	2	1	1	2	3
Poisoning	4	10	9	12	13	22
Product administration error	1	1	0	0	1	1
Product use complaint	12	16	0	0	12	16
Product use issue	2	8	0	0	2	8
Respiratory fume inhalation disorder	2	2	0	0	2	2
Retinal injury	0	0	1	1	1	1
Rib fracture	0	0	0	1	0	1
Road traffic accident	1	2	0	1	1	3
Scar	11	30	0	0	11	30
Scratch	6	10	0	0	6	10
Skin abrasion	1	3	0	1	1	3
Skin injury	3	7	0	0	3	7
Skin laceration	2	4	0	0	2	4
Skin wound	0	2	0	0	0	2
Spinal column injury	0	1	0	0	0	1
Thermal burn	6020	13110	4	15	6024	13125

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Thermal burns of eye	0	1	0	0	0	1
Tobacco poisoning	48	115	0	1	48	116
Tongue injury	8	13	0	0	8	13
Tooth fracture	1	3	1	1	2	4
Tooth injury	4	14	1	1	5	15
Toxicity to various agents	3	5	0	0	3	5
Tracheal injury	0	1	0	0	0	1
Traumatic haematoma	0	1	0	0	0	1
Traumatic lung injury	0	2	0	0	0	2
Vascular injury	0	1	0	0	0	1
Wound	21	74	0	0	21	74
Wound complication	0	2	0	0	0	2
Wound haemorrhage	3	14	0	0	3	14
Wound secretion	0	4	0	0	0	4
Wrong technique in device usage process	0	6	0	0	0	6
Wrong technique in product usage process	1	4	0	0	1	4
Investigations	**1071**	**1914**	**16**	**36**	**1087**	**1950**
Alanine aminotransferase increased	0	1	0	0	0	1
Allergy test positive	1	1	0	0	1	1
Amino acid level increased	1	1	0	0	1	1
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	1	0	0	0	1
Blood carbon monoxide increased	1	1	0	0	1	1
Blood cholesterol increased	4	7	0	0	4	7
Blood count 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 glucose abnormal	0	2	0	0	0	2
Blood glucose decreased	1	5	0	0	1	5
Blood glucose increased	12	26	0	0	12	26
Blood pressure abnormal	15	26	0	0	15	26
Blood pressure decreased	51	98	1	1	52	99
Blood pressure increased	262	518	2	9	264	527
Blood pressure systolic decreased	0	1	0	0	0	1
Blood pressure systolic increased	0	1	0	0	0	1
Blood test abnormal	0	1	0	0	0	1
Blood triglycerides increased	0	1	0	0	0	1
Blood urine present	1	1	0	0	1	1
Body mass index increased	1	1	0	0	1	1
Body temperature abnormal	0	1	0	0	0	1
Body temperature decreased	1	4	0	0	1	4
Body temperature fluctuation	0	4	0	0	0	4
Body temperature increased	27	61	1	5	28	66
Breath sounds	4	4	0	0	4	4
Breath sounds abnormal	5	14	0	1	5	15
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
C-reactive protein increased	0	0	1	1	1	1
Electrocardiogram abnormal	1	1	0	0	1	1
Endoscopy upper gastrointestinal tract	0	1	0	0	0	1
Epinephrine increased	1	3	0	0	1	3
Gastric pH decreased	8	18	1	1	9	19

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
General physical condition abnormal	3	8	1	2	4	10
Haemoglobin increased	1	2	0	0	1	2
Heart rate abnormal	2	9	0	0	2	9
Heart rate decreased	7	13	1	1	8	14
Heart rate increased	226	503	2	8	228	511
Heart rate irregular	11	21	0	0	11	21
Hepatic enzyme increased	1	2	0	0	1	2
Histamine level increased	0	1	0	0	0	1
Hormone level abnormal	1	1	0	0	1	1
Immunoglobulins increased	1	1	0	0	1	1
Inspiratory capacity decreased	1	1	0	0	1	1
Intraocular pressure increased	1	4	0	0	1	4
Intraocular pressure test	0	1	0	0	0	1
Investigation abnormal	2	2	0	0	2	2
Laboratory test abnormal	1	1	0	0	1	1
Liver function test abnormal	1	1	0	0	1	1
Liver function test increased	1	1	0	0	1	1
Lymph node palpable	2	3	0	0	2	3
Magnetic resonance imaging abnormal	0	1	0	0	0	1
Oxygen consumption decreased	1	5	0	0	1	5
Oxygen consumption increased	1	1	0	0	1	1
Oxygen saturation decreased	1	5	1	1	2	6
Oxygen saturation increased	0	1	0	0	0	1
Physical examination abnormal	1	1	0	0	1	1
Platelet count decreased	0	0	1	1	1	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Product residue present	2	3	0	0	2	3
Pulmonary function test decreased	1	3	0	0	1	3
Pulse abnormal	0	1	0	0	0	1
Pulse pressure increased	0	1	0	0	0	1
Quality of life decreased	0	1	0	0	0	1
Respiratory rate decreased	0	0	0	1	0	1
Respiratory rate increased	2	9	0	0	2	9
Sputum abnormal	1	2	0	0	1	2
Thyroid function test abnormal	0	1	0	0	0	1
Total lung capacity decreased	6	7	0	0	6	7
Transaminases increased	0	1	0	0	0	1
Urine viscosity increased	0	1	0	0	0	1
Weight abnormal	1	2	0	0	1	2
Weight decreased	12	18	1	1	13	19
Weight increased	382	458	1	1	383	459
White blood cell count decreased	0	2	2	2	2	4
White blood cell count increased	0	1	0	0	0	1
X-ray abnormal	1	1	0	0	1	1
Metabolism and nutrition disorders	**163**	**280**	**11**	**29**	**174**	**309**
Acidosis	0	1	0	0	0	1
Appetite disorder	1	6	0	0	1	6
Decreased appetite	56	116	1	2	57	118
Dehydration	39	59	0	0	39	59
Diabetes mellitus	0	0	2	16	2	16
Diabetes mellitus inadequate control	0	0	8	10	8	10
Diabetic complication	1	1	0	0	1	1
Eating disorder symptom	0	1	0	0	0	1
Feeding disorder	6	12	0	0	6	12
Fluid retention	6	10	0	0	6	10
Food craving	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Glucose tolerance impaired	1	1	0	0	1	1
Hyperglycaemia	0	1	0	0	0	1
Hyperinsulinaemia	0	1	0	0	0	1
Hyperlipidaemia	0	1	0	0	0	1
Hyperphagia	1	1	0	0	1	1
Hypoglycaemia	2	3	0	0	2	3
Hypovitaminosis	0	1	0	0	0	1
Increased appetite	25	37	0	0	25	37
Ketoacidosis	0	0	0	1	0	1
Lactose intolerance	1	2	0	0	1	2
Metabolic disorder	2	2	0	0	2	2
Polydipsia	9	10	0	0	9	10
Poor feeding infant	1	1	0	0	1	1
Vitamin D deficiency	1	1	0	0	1	1
Weight fluctuation	10	10	0	0	10	10
Weight loss poor	1	1	0	0	1	1
Musculoskeletal and connective tissue disorders	**258**	**675**	**6**	**15**	**264**	**690**
Arthralgia	22	45	0	1	22	46
Arthritis	1	4	0	0	1	4
Arthropathy	0	1	0	0	0	1
Back disorder	0	1	0	0	0	1
Back pain	23	59	1	1	24	60
Bone disorder	0	1	0	0	0	1
Bone pain	3	11	0	0	3	11
Chondrosis	1	1	0	0	1	1
Costochondritis	0	1	0	0	0	1
Fibromyalgia	0	1	0	0	0	1
Flank pain	2	18	0	0	2	18
Groin pain	0	1	0	0	0	1
Jaw disorder	0	4	0	0	0	4
Joint contracture	0	1	0	0	0	1
Joint noise	0	1	0	0	0	1
Joint stiffness	1	1	0	1	1	2
Joint swelling	0	2	0	0	0	2
Limb discomfort	8	16	1	1	9	17
Mastication disorder	1	7	0	1	1	8
Mobility decreased	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Muscle contracture	0	2	0	0	0	2
Muscle discomfort	1	1	0	0	1	1
Muscle disorder	0	1	0	0	0	1
Muscle spasms	22	60	0	0	22	60
Muscle tightness	1	2	0	1	1	3
Muscle twitching	5	11	1	1	6	12
Muscular weakness	10	29	0	0	10	29
Musculoskeletal chest pain	7	19	0	0	7	19
Musculoskeletal discomfort	10	19	1	1	11	20
Musculoskeletal disorder	0	1	0	0	0	1
Musculoskeletal pain	0	4	0	0	0	4
Musculoskeletal stiffness	7	38	0	0	7	38
Myalgia	16	32	0	0	16	32
Myokymia	0	1	0	0	0	1
Myositis	0	2	0	0	0	2
Neck mass	1	1	0	0	1	1
Neck pain	26	76	0	2	26	78
Osteitis	1	1	0	0	1	1
Osteoarthritis	1	1	0	0	1	1
Osteochondrosis	0	0	1	2	1	2
Pain in extremity	35	99	0	0	35	99
Pain in jaw	52	90	0	2	52	92
Plantar fasciitis	0	1	0	0	0	1
Posture abnormal	0	1	0	0	0	1
Rheumatoid arthritis	0	0	1	1	1	1
Spinal disorder	1	1	0	0	1	1
Spinal pain	0	1	0	0	0	1
Tendon pain	0	1	0	0	0	1
Tendonitis	0	1	0	0	0	1
Trismus	0	2	0	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**12**	**16**	**26**	**42**	**38**	**58**
Adenoma benign	1	1	0	0	1	1
Benign neoplasm	1	1	0	0	1	1
Brain neoplasm	0	0	1	1	1	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Brain neoplasm malignant	0	0	1	1	1	1
Cancer in remission	1	1	0	0	1	1
Hepatic neoplasm	0	0	0	1	0	1
Laryngeal papilloma	0	1	0	0	0	1
Leukaemia	0	0	0	1	0	1
Lung adenocarcinoma	0	0	0	1	0	1
Lung cancer metastatic	0	0	1	1	1	1
Lung neoplasm	4	4	1	1	5	5
Lung neoplasm malignant	0	0	8	12	8	12
Melanocytic naevus	1	1	0	0	1	1
Metastases to central nervous system	0	0	0	1	0	1
Neoplasm	2	2	0	0	2	2
Neoplasm malignant	0	0	10	15	10	15
Papilloma	2	3	0	0	2	3
Pharyngeal neoplasm	0	0	0	1	0	1
Skin papilloma	0	2	0	0	0	2
Throat cancer	0	0	2	2	2	2
Thyroid cancer	0	0	0	2	0	2
Tongue neoplasm	0	0	1	1	1	1
Tongue neoplasm malignant stage unspecified	0	0	1	1	1	1
Nervous system disorders	**8957**	**19311**	**114**	**260**	**9071**	**19571**
Ageusia	23	56	0	1	23	57
Akathisia	0	1	0	0	0	1
Altered state of consciousness	0	1	1	2	1	3
Amnesia	1	2	0	0	1	2
Anosmia	13	26	0	0	13	26
Aphasia	2	7	0	0	2	7
Ataxia	0	1	0	0	0	1
Autonomic nervous system imbalance	0	4	0	1	0	5
Balance disorder	4	24	0	1	4	25

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Brain stem infarction	0	0	0	1	0	1
Burning sensation	505	964	1	3	506	967
Burning sensation mucosal	17	23	0	0	17	23
Cerebral disorder	3	5	0	0	3	5
Cerebral haemorrhage	0	0	0	2	0	2
Cerebral hypoperfusion	0	0	0	1	0	1
Cerebral infarction	0	0	2	3	2	3
Cerebral vasoconstriction	0	0	0	1	0	1
Cerebrovascular accident	0	0	5	14	5	14
Cerebrovascular disorder	1	1	0	1	1	2
Cervicogenic headache	0	1	0	0	0	1
Clumsiness	0	1	0	0	0	1
Cluster headache	1	2	0	0	1	2
Cognitive disorder	0	2	0	0	0	2
Coma	0	0	0	1	0	1
Coordination abnormal	1	6	0	0	1	6
Depressed level of consciousness	0	0	0	4	0	4
Disturbance in attention	13	32	0	0	13	32
Dizziness	2418	5706	10	33	2428	5739
Dizziness exertional	1	1	0	0	1	1
Dizziness postural	5	15	0	0	5	15
Dreamy state	0	2	0	0	0	2
Drooling	2	7	0	2	2	9
Dysarthria	2	6	1	1	3	7
Dysgeusia	419	782	0	0	419	782
Dysgraphia	0	1	0	0	0	1
Dyskinesia	1	1	0	0	1	1
Dysstasia	8	17	1	1	9	18
Epilepsy	0	1	3	10	3	11
Facial paralysis	0	0	0	4	0	4
Facial paresis	0	1	0	0	0	1
Facial spasm	2	5	0	0	2	5
Formication	4	4	0	0	4	4

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Hand-eye coordination impaired	0	1	0	0	0	1
Head discomfort	116	210	1	1	117	211
Head titubation	2	2	0	0	2	2
Headache	4782	9873	15	32	4797	9905
Hemianaesthesia	0	0	0	1	0	1
Hyperaesthesia	1	3	0	0	1	3
Hypersomnia	0	4	0	0	0	4
Hypertonia	0	1	0	0	0	1
Hypoaesthesia	69	217	2	6	71	223
Hypogeusia	2	7	0	0	2	7
Hypokinesia	2	5	0	0	2	5
Hyporeflexia	0	1	0	0	0	1
Hyposmia	3	8	0	0	3	8
Hypotonia	1	2	0	0	1	2
Infant irritability	1	1	0	0	1	1
Insomnia	2	2	0	0	2	2
Intracranial pressure increased	0	0	4	6	4	6
Lethargy	5	25	0	0	5	25
Loss of consciousness	1	2	19	50	20	52
Memory impairment	1	15	0	1	1	16
Meningeal disorder	1	1	0	0	1	1
Mental impairment	0	0	1	1	1	1
Migraine	98	194	1	2	99	196
Migraine with aura	0	1	0	0	0	1
Motor dysfunction	1	3	0	0	1	3
Movement disorder	1	2	0	0	1	2
Nervous system disorder	4	10	0	0	4	10
Neuralgia	3	7	0	1	3	8
Neurological symptom	0	1	0	0	0	1
Neurotoxicity	0	0	1	1	1	1
Paraesthesia	63	137	3	3	66	140
Paraesthesia mucosal	0	1	0	0	0	1
Paraparesis	0	0	5	5	5	5
Parosmia	28	56	0	0	28	56

MedDRA SOC MedDRA PT	**Interval Non-serious**	**Cumulative Non-serious**	**Interval Serious**	**Cumulative Serious**	**Interval Total**	**Cumulative Total**
Patient elopement	0	0	0	1	0	1
Poor quality sleep	2	12	0	0	2	12
Post-traumatic epilepsy	1	1	0	0	1	1
Presyncope	31	59	0	0	31	59
Psychomotor hyperactivity	1	1	0	0	1	1
Radiculopathy	1	1	0	0	1	1
Reflexes abnormal	0	1	0	0	0	1
Sedation	0	2	0	0	0	2
Seizure	1	1	4	7	5	8
Sensory disturbance	5	11	0	0	5	11
Sensory loss	3	4	0	0	3	4
Sinus headache	0	2	0	0	0	2
Sleep deficit	0	3	0	0	0	3
Slow speech	0	1	0	0	0	1
Somnolence	53	121	0	0	53	121
Speech disorder	10	30	0	1	10	31
Stupor	0	1	0	0	0	1
Syncope	1	22	30	48	31	70
Taste disorder	138	346	0	0	138	346
Tension headache	4	19	0	0	4	19
Thermohypoaesthesia	0	2	0	0	0	2
Tongue paralysis	0	0	2	3	2	3
Tremor	71	165	1	2	72	167
Unresponsive to stimuli	0	0	1	1	1	1
Uvular spasm	0	1	0	0	0	1
Visual field defect	0	1	0	0	0	1
Visual perseveration	0	1	0	0	0	1
Vocal cord paralysis	2	3	0	0	2	3
Pregnancy, puerperium and perinatal conditions	**1**	**2**	**0**	**0**	**1**	**2**
Morning sickness	1	1	0	0	1	1
Pregnancy	0	1	0	0	0	1
Product issues	**8206**	**18189**	**0**	**0**	**8206**	**18189**
Device battery explosion	1	2	0	0	1	2
Device breakage	54	89	0	0	54	89
Device catching fire	14	21	0	0	14	21

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Device colour issue	0	4	0	0	0	4
Device defective	6	25	0	0	6	25
Device delivery system issue	1	2	0	0	1	2
Device deposit issue	1	2	0	0	1	2
Device electrical finding	2	5	0	0	2	5
Device failure	1	4	0	0	1	4
Device inappropriate shock delivery	1	1	0	0	1	1
Device issue	215	949	0	0	215	949
Device leakage	23	44	0	0	23	44
Device malfunction	738	956	0	0	738	956
Device material issue	0	1	0	0	0	1
Device occlusion	2	2	0	0	2	2
Device pacing issue	0	1	0	0	0	1
Device physical property issue	3628	8915	0	0	3628	8915
Device power source issue	4	13	0	0	4	13
Device temperature issue	1	1	0	0	1	1
Product adhesion issue	0	1	0	0	0	1
Product caught fire	9	23	0	0	9	23
Product colour issue	5	6	0	0	5	6
Product complaint	1070	1823	0	0	1070	1823
Product deposit	2	2	0	0	2	2
Product distribution issue	1	1	0	0	1	1
Product label issue	0	1	0	0	0	1
Product leakage	0	2	0	0	0	2
Product odour abnormal	306	645	0	0	306	645
Product physical consistency issue	8	13	0	0	8	13
Product physical issue	1747	3220	0	0	1747	3220
Product quality issue	14	608	0	0	14	608
Product size issue	0	1	0	0	0	1
Product substitution issue	0	3	0	0	0	3

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Product taste abnormal	352	802	0	0	352	802
Suspected counterfeit product	0	1	0	0	0	1
Psychiatric disorders	**432**	**1049**	**9**	**23**	**441**	**1072**
Abnormal dreams	2	2	0	0	2	2
Adjustment disorder	1	1	0	0	1	1
Adjustment disorder with depressed mood	0	1	0	0	0	1
Aggression	1	5	0	0	1	5
Agitation	9	33	0	1	9	34
Anger	1	5	0	0	1	5
Anhedonia	2	2	0	0	2	2
Anxiety	54	141	1	1	55	142
Anxiety disorder	0	3	0	0	0	3
Apathy	4	10	0	0	4	10
Attention deficit hyperactivity disorder	0	1	0	0	0	1
Aversion	0	3	0	0	0	3
Behavioural addiction	0	1	0	0	0	1
Bipolar disorder	0	0	0	1	0	1
Bradyphrenia	1	2	0	0	1	2
Confusional state	6	22	0	0	6	22
Daydreaming	1	6	0	0	1	6
Decreased eye contact	0	1	0	1	0	2
Dependence	3	5	1	1	4	6
Depressed mood	7	20	0	0	7	20
Depression	11	16	0	0	11	16
Depressive symptom	1	1	0	0	1	1
Disorientation	1	19	0	0	1	19
Distractibility	1	2	0	0	1	2
Drug dependence	1	1	0	0	1	1
Dysphemia	2	2	0	0	2	2
Dysphoria	8	9	0	0	8	9
Eating disorder	3	14	0	0	3	14
Emotional disorder	1	1	0	0	1	1
Emotional distress	5	7	0	0	5	7
Euphoric mood	3	15	0	0	3	15

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Fear	6	23	0	0	6	23
Fear of death	1	2	0	1	1	3
Frustration tolerance decreased	0	1	0	0	0	1
Hallucination	0	2	4	4	4	6
Hallucination, auditory	0	1	1	1	1	2
Hallucination, visual	0	0	1	1	1	1
Inappropriate affect	2	2	0	0	2	2
Indifference	0	1	0	0	0	1
Initial insomnia	4	13	0	0	4	13
Insomnia	91	217	0	1	91	218
Irritability	78	128	1	1	79	129
Laziness	1	2	0	0	1	2
Libido decreased	1	5	0	0	1	5
Listless	5	6	0	0	5	6
Mental disorder	3	6	0	1	3	7
Mental status changes	1	2	0	0	1	2
Middle insomnia	0	1	0	0	0	1
Mood altered	13	57	0	0	13	57
Morbid thoughts	0	2	0	0	0	2
Nervousness	18	45	0	0	18	45
Neurosis	0	1	0	0	0	1
Nicotine dependence	8	22	0	0	8	22
Nightmare	1	5	0	0	1	5
Panic attack	22	46	0	3	22	49
Panic disorder	1	4	0	1	1	5
Panic reaction	4	9	0	0	4	9
Paranoia	1	1	0	0	1	1
Personality change	0	1	0	0	0	1
Psychotic disorder	0	1	0	0	0	1
Restlessness	6	8	0	0	6	8
Sleep disorder	16	35	0	1	16	36
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	7	19	0	0	7	19

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Suicidal ideation	0	0	0	2	0	2
Suicide attempt	0	0	0	1	0	1
Tension	2	12	0	0	2	12
Terminal insomnia	0	1	0	0	0	1
Tic	1	1	0	0	1	1
Tobacco abuse	9	10	0	0	9	10
Tobacco withdrawal symptoms	1	4	0	0	1	4
Renal and urinary disorders	**20**	**58**	**3**	**6**	**23**	**64**
Bladder leukoplakia	0	0	1	1	1	1
Chromaturia	1	6	0	0	1	6
Dysuria	1	3	0	0	1	3
Incontinence	1	1	0	0	1	1
Micturition disorder	0	1	0	0	0	1
Micturition urgency	0	0	0	1	0	1
Pollakiuria	1	6	0	0	1	6
Polyuria	0	1	0	0	0	1
Renal disorder	3	5	0	0	3	5
Renal failure	0	0	0	1	0	1
Renal pain	6	22	0	1	6	23
Urinary incontinence	0	0	1	1	1	1
Urinary retention	0	0	1	1	1	1
Urinary tract discomfort	2	2	0	0	2	2
Urine odour abnormal	5	11	0	0	5	11
Reproductive system and breast disorders	**13**	**32**	**13**	**16**	**26**	**48**
Adnexa uteri pain	1	1	0	0	1	1
Breast discomfort	1	1	0	0	1	1
Breast inflammation	1	1	0	0	1	1
Breast pain	2	3	0	0	2	3
Breast tenderness	1	1	0	0	1	1
Erectile dysfunction	0	5	13	16	13	21
Erection increased	1	1	0	0	1	1
Genital discomfort	1	1	0	0	1	1
Menstrual disorder	0	3	0	0	0	3
Menstruation delayed	1	1	0	0	1	1
Menstruation irregular	1	1	0	0	1	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Organic erectile dysfunction	0	1	0	0	0	1
Pelvic pain	0	1	0	0	0	1
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	1	5	0	0	1	5
Spontaneous penile erection	1	1	0	0	1	1
Testicular swelling	0	1	0	0	0	1
Vaginal flatulence	1	1	0	0	1	1
Respiratory, thoracic and mediastinal disorders	**22687**	**46185**	**185**	**500**	**22872**	**46685**
Adenoidal hypertrophy	1	1	0	0	1	1
Allergic cough	10	20	0	0	10	20
Alveolar proteinosis	0	0	1	1	1	1
Alveolitis	0	1	0	0	0	1
Anoxia	0	0	1	1	1	1
Aphonia	90	270	2	2	92	272
Apnoea	0	0	2	5	2	5
Apnoeic attack	0	0	0	1	0	1
Asphyxia	1	2	2	19	3	21
Aspiration	0	0	1	1	1	1
Asthma	182	320	3	15	185	335
Asthmatic crisis	0	0	0	2	0	2
Bronchial disorder	35	70	1	2	36	72
Bronchial hyperreactivity	3	3	0	0	3	3
Bronchial irritation	26	35	0	0	26	35
Bronchial obstruction	0	0	0	1	0	1
Bronchial oedema	1	1	1	3	2	4
Bronchial secretion retention	0	1	0	0	0	1
Bronchitis	1	1	0	0	1	1
Bronchitis chronic	0	6	0	0	0	6
Bronchospasm	25	38	2	3	27	41
Bronchostenosis	0	0	0	1	0	1
Catarrh	18	38	0	0	18	38
Chest discomfort	11	11	0	0	11	11

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Chest pain	9	9	0	0	9	9
Choking	6	17	4	13	10	30
Choking sensation	746	1216	1	2	747	1218
Chronic obstructive pulmonary disease	3	7	2	2	5	9
Chronic respiratory disease	1	1	0	0	1	1
Cough	6858	13657	20	47	6878	13704
Cough decreased	1	5	0	0	1	5
Cough variant asthma	1	2	0	0	1	2
Cystic lung disease	0	1	0	0	0	1
Decreased bronchial secretion	1	1	0	0	1	1
Diaphragmalgia	1	6	0	0	1	6
Diaphragmatic disorder	1	2	0	0	1	2
Dry throat	1313	2561	2	3	1315	2564
Dysphonia	321	805	2	4	323	809
Dyspnoea	2418	4219	29	66	2447	4285
Dyspnoea at rest	0	0	0	1	0	1
Dyspnoea exertional	12	16	0	0	12	16
Emphysema	3	6	1	2	4	8
Eosinophilic pneumonia acute	0	0	1	3	1	3
Epiglottic cyst	0	1	0	0	0	1
Epistaxis	85	521	1	5	86	526
Haemoptysis	37	175	0	4	37	179
Hiccups	64	149	1	1	65	150
Hyperactive pharyngeal reflex	2	4	0	0	2	4
Hyperventilation	2	6	0	0	2	6
Hypopnoea	6	11	0	0	6	11
Hypoxia	0	0	2	4	2	4
Increased bronchial secretion	1	4	0	0	1	4
Increased upper airway secretion	10	30	0	0	10	30
Increased viscosity of bronchial secretion	3	7	0	0	3	7
Increased viscosity of upper respiratory secretion	2	5	0	0	2	5

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Irregular breathing	0	4	0	0	0	4
Laryngeal discomfort	4	28	0	0	4	28
Laryngeal disorder	3	5	0	0	3	5
Laryngeal inflammation	3	7	0	0	3	7
Laryngeal obstruction	0	0	0	1	0	1
Laryngeal oedema	1	3	4	20	5	23
Laryngeal pain	15	39	0	0	15	39
Laryngeal ulceration	0	1	0	0	0	1
Laryngospasm	2	8	0	0	2	8
Larynx irritation	6	13	0	1	6	14
Lower respiratory tract congestion	4	8	0	0	4	8
Lung disorder	138	293	3	9	141	302
Lung hyperinflation	1	1	0	0	1	1
Lung infiltration	1	2	0	0	1	2
Mouth breathing	0	1	0	0	0	1
Musculoskeletal chest pain	1	1	0	0	1	1
Nasal congestion	172	402	0	1	172	403
Nasal crusting	4	10	0	0	4	10
Nasal discharge discolouration	0	3	0	0	0	3
Nasal discomfort	27	89	0	0	27	89
Nasal disorder	1	7	0	0	1	7
Nasal dryness	55	156	0	0	55	156
Nasal inflammation	7	16	0	0	7	16
Nasal mucosal blistering	0	1	0	0	0	1
Nasal mucosal discolouration	0	1	0	0	0	1
Nasal mucosal disorder	2	7	0	0	2	7
Nasal mucosal ulcer	1	2	0	0	1	2
Nasal obstruction	0	2	0	0	0	2
Nasal odour	0	1	0	0	0	1
Nasal oedema	2	8	0	0	2	8
Nasal polyps	2	2	0	0	2	2
Nasal pruritus	2	13	0	0	2	13
Nasal ulcer	1	3	0	0	1	3

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Nocturnal dyspnoea	5	8	0	0	5	8
Obstructive airways disorder	11	17	0	1	11	18
Oropharyngeal blistering	0	2	9	25	9	27
Oropharyngeal discolouration	1	4	0	0	1	4
Oropharyngeal discomfort	688	1078	1	1	689	1079
Oropharyngeal pain	4050	7981	13	25	4063	8006
Oropharyngeal plaque	1	3	0	0	1	3
Oropharyngeal scar	0	1	0	0	0	1
Oropharyngeal spasm	1	6	0	1	1	7
Oropharyngeal swelling	0	3	0	0	0	3
Painful respiration	16	26	0	0	16	26
Paranasal sinus hyposecretion	3	3	0	0	3	3
Paranasal sinus inflammation	1	1	0	0	1	1
Pharyngeal cyst	0	1	0	0	0	1
Pharyngeal disorder	21	54	1	1	22	55
Pharyngeal enanthema	1	1	0	0	1	1
Pharyngeal erythema	14	33	0	1	14	34
Pharyngeal exudate	2	2	1	1	3	3
Pharyngeal haemorrhage	0	0	22	66	22	66
Pharyngeal hypoaesthesia	3	19	0	0	3	19
Pharyngeal inflammation	30	77	2	3	32	80
Pharyngeal lesion	0	1	0	0	0	1
Pharyngeal mass	13	13	0	0	13	13
Pharyngeal oedema	1	12	0	0	1	12
Pharyngeal paraesthesia	27	67	1	1	28	68
Pharyngeal swelling	204	592	1	3	205	595
Pharyngeal ulceration	3	7	0	0	3	7
Pleural effusion	3	3	0	0	3	3
Pleuritic pain	2	2	0	0	2	2
Pneumonitis	0	8	1	3	1	11

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Pneumothorax	0	0	3	5	3	5
Pneumothorax spontaneous	0	0	2	2	2	2
Productive cough	562	1452	0	3	562	1455
Pulmonary calcification	1	1	0	0	1	1
Pulmonary congestion	2	4	6	13	8	17
Pulmonary embolism	0	0	2	3	2	3
Pulmonary fibrosis	0	0	1	2	1	2
Pulmonary haemorrhage	0	0	1	2	1	2
Pulmonary infarction	0	0	0	1	0	1
Pulmonary mass	0	2	0	0	0	2
Pulmonary oedema	0	1	6	19	6	20
Pulmonary pain	495	857	2	4	497	861
Pulmonary sarcoidosis	0	0	0	1	0	1
Rales	4	12	0	1	4	13
Reflux laryngitis	0	1	0	0	0	1
Respiration abnormal	14	27	1	1	15	28
Respiratory arrest	0	0	0	2	0	2
Respiratory depression	0	0	1	1	1	1
Respiratory disorder	50	99	0	3	50	102
Respiratory disorder neonatal	1	1	0	0	1	1
Respiratory distress	1	1	0	3	1	4
Respiratory failure	0	0	3	4	3	4
Respiratory fatigue	2	2	0	0	2	2
Respiratory symptom	2	2	0	0	2	2
Respiratory tract congestion	48	55	1	1	49	56
Respiratory tract inflammation	4	8	0	0	4	8
Respiratory tract irritation	71	123	0	0	71	123
Respiratory tract oedema	0	0	4	5	4	5
Rhinalgia	7	34	0	0	7	34
Rhinitis allergic	4	10	0	0	4	10
Rhinitis atrophic	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Rhinorrhoea	91	275	1	5	92	280
Rhonchi	1	2	0	0	1	2
Sinus congestion	7	11	0	0	7	11
Sinus disorder	6	14	0	0	6	14
Sinus pain	2	6	0	0	2	6
Sinusitis noninfective	0	1	0	0	0	1
Sleep apnoea syndrome	2	2	0	0	2	2
Sneezing	63	143	0	2	63	145
Snoring	9	16	0	0	9	16
Sputum discoloured	29	94	0	0	29	94
Sputum increased	2	12	0	0	2	12
Sputum retention	1	11	0	0	1	11
Suffocation feeling	293	484	2	4	295	488
Tachypnoea	1	2	0	0	1	2
Throat clearing	45	65	0	0	45	65
Throat irritation	2674	6178	3	19	2677	6197
Throat lesion	3	8	1	1	4	9
Throat tightness	93	258	0	1	93	259
Tonsillar disorder	20	35	0	0	20	35
Tonsillar erythema	2	3	0	0	2	3
Tonsillar exudate	1	3	0	0	1	3
Tonsillar haemorrhage	0	1	0	1	0	2
Tonsillar hypertrophy	36	101	0	0	36	101
Tonsillar inflammation	7	40	0	1	7	41
Tonsillar ulcer	1	2	0	0	1	2
Tonsillitis	2	2	0	0	2	2
Tonsillolith	1	2	0	0	1	2
Tracheal disorder	2	7	0	0	2	7
Tracheal inflammation	1	4	0	0	1	4
Tracheal oedema	0	0	2	3	2	3
Tracheal pain	6	18	0	0	6	18
Upper airway obstruction	0	0	0	1	0	1
Upper respiratory tract congestion	33	52	0	0	33	52
Upper respiratory tract inflammation	6	10	2	2	8	12

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Upper respiratory tract irritation	8	14	0	0	8	14
Upper-airway cough syndrome	0	1	0	0	0	1
Vasomotor rhinitis	1	1	0	0	1	1
Vocal cord disorder	23	54	0	1	23	55
Vocal cord dysfunction	2	2	0	0	2	2
Vocal cord inflammation	5	11	0	0	5	11
Vocal cord polyp	0	1	0	0	0	1
Vocal cord thickening	2	4	0	1	2	5
Wheezing	67	109	0	4	67	113
Yawning	4	9	0	0	4	9
Skin and subcutaneous tissue disorders	**1926**	**5552**	**38**	**96**	**1964**	**5648**
Acne	114	432	1	3	115	435
Acne cystic	0	1	0	0	0	1
Acne varioliformis	0	1	0	0	0	1
Alopecia	8	26	1	1	9	27
Angioedema	0	0	16	33	16	33
Blister	123	391	0	3	123	394
Blister rupture	0	8	0	0	0	8
Blood blister	1	4	0	0	1	4
Circumoral oedema	0	1	0	0	0	1
Cold sweat	20	53	0	0	20	53
Dandruff	3	8	0	0	3	8
Dermatitis	18	48	0	0	18	48
Dermatitis acneiform	2	7	0	0	2	7
Dermatitis allergic	9	37	0	0	9	37
Dermatitis atopic	11	15	0	0	11	15
Dermatitis bullous	0	0	0	1	0	1
Dermatitis contact	0	5	0	0	0	5
Dry skin	31	80	1	1	32	81
Dyshidrotic eczema	0	4	0	0	0	4
Eczema	18	27	0	0	18	27
Erythema	121	361	0	1	121	362
Erythema nodosum	0	0	0	1	0	1
Haemorrhage subcutaneous	0	0	2	2	2	2

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Hair colour changes	0	3	0	0	0	3
Hair disorder	2	3	0	0	2	3
Hair texture abnormal	1	1	0	0	1	1
Hyperhidrosis	49	139	0	1	49	140
Hyperkeratosis	1	4	0	0	1	4
Lichen planus	0	0	1	1	1	1
Lichenification	0	1	0	0	0	1
Livedo reticularis	0	1	0	0	0	1
Madarosis	2	3	0	0	2	3
Mechanical urticaria	0	1	0	0	0	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	1	1	0	0	1	1
Nail disorder	0	2	0	0	0	2
Nail hypertrophy	0	1	0	0	0	1
Neurodermatitis	1	1	0	0	1	1
Night sweats	0	1	0	0	0	1
Occupational dermatitis	1	1	0	0	1	1
Oedema blister	0	1	0	0	0	1
Onychoclasis	0	1	0	0	0	1
Onycholysis	0	1	0	0	0	1
Pain of skin	6	14	0	0	6	14
Palmar erythema	2	2	0	0	2	2
Palmoplantar pustulosis	0	1	0	0	0	1
Papule	0	2	0	0	0	2
Perioral dermatitis	0	4	0	0	0	4
Photosensitivity reaction	0	1	0	0	0	1
Pigmentation disorder	2	8	0	1	2	9
Piloerection	0	1	0	0	0	1
Pityriasis rosea	1	1	0	0	1	1
Pruritus	261	919	2	7	263	926
Pruritus allergic	1	1	0	0	1	1
Psoriasis	10	15	0	0	10	15
Purpura	1	2	0	0	1	2
Rash	584	1527	8	25	592	1552

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Rash erythematous	22	73	0	1	22	74
Rash follicular	0	1	0	0	0	1
Rash macular	213	293	2	3	215	296
Rash papular	4	15	1	1	5	16
Rash pruritic	16	91	0	2	16	93
Rash vesicular	3	5	0	0	3	5
Rosacea	0	1	0	0	0	1
Scab	10	45	0	0	10	45
Scar pain	0	1	0	0	0	1
Sebaceous gland disorder	0	2	0	0	0	2
Sebaceous glands overactivity	1	2	0	0	1	2
Seborrhoea	4	6	0	0	4	6
Seborrhoeic dermatitis	3	8	0	0	3	8
Sensitive skin	1	3	0	0	1	3
Skin atrophy	0	1	0	0	0	1
Skin burning sensation	3	9	0	0	3	9
Skin depigmentation	1	5	0	0	1	5
Skin discolouration	21	50	1	1	22	51
Skin discomfort	4	5	0	0	4	5
Skin disorder	47	219	0	0	47	219
Skin exfoliation	42	119	0	0	42	119
Skin fissures	1	4	0	0	1	4
Skin haemorrhage	2	8	0	0	2	8
Skin hypertrophy	2	3	0	0	2	3
Skin induration	0	1	0	0	0	1
Skin irritation	22	53	0	1	22	54
Skin lesion	2	5	0	0	2	5
Skin mass	0	0	1	1	1	1
Skin necrosis	0	0	0	2	0	2
Skin odour abnormal	1	12	0	0	1	12
Skin reaction	1	9	0	0	1	9
Skin striae	2	2	0	0	2	2
Skin swelling	4	12	0	0	4	12
Skin tightness	1	3	0	0	1	3
Skin ulcer	1	2	0	0	1	2
Skin weeping	2	5	0	0	2	5

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Skin wrinkling	5	9	0	1	5	10
Solar lentigo	1	2	0	0	1	2
Spider naevus	1	1	0	0	1	1
Sticky skin	0	1	0	0	0	1
Thermal burn	1	1	0	0	1	1
Urticaria	75	281	1	2	76	283
Urticaria chronic	1	1	0	0	1	1
Xeroderma	0	1	0	0	0	1
Yellow skin	1	5	0	0	1	5
Social circumstances	**11**	**36**	**1**	**2**	**12**	**38**
Bedridden	1	1	0	0	1	1
Ex-tobacco user	1	1	0	0	1	1
Impaired driving ability	3	4	0	0	3	4
Loss of personal independence in daily activities	1	6	1	1	2	7
Passive smoking	4	22	0	1	4	23
Tobacco user	1	1	0	0	1	1
Wheelchair user	0	1	0	0	0	1
Surgical and medical procedures	**8**	**23**	**3**	**7**	**11**	**30**
Cardiac operation	1	1	0	0	1	1
Dental operation	0	1	0	0	0	1
Gingival operation	0	1	0	0	0	1
Hospitalisation	0	0	2	3	2	3
Infusion	1	1	0	0	1	1
Lung lobectomy	0	0	1	1	1	1
Lymphadenectomy	0	0	0	1	0	1
Nerve block	0	1	0	0	0	1
Salivary gland resection	0	0	0	1	0	1
Surgery	2	5	0	1	2	6
Thyroid operation	0	1	0	0	0	1
Tooth extraction	3	8	0	0	3	8
Vocal cord operation	1	1	0	0	1	1
Wisdom teeth removal	0	2	0	0	0	2
Wound drainage	0	1	0	0	0	1
Vascular disorders	**295**	**738**	**24**	**51**	**319**	**789**
Aneurysm	0	0	1	2	1	2

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Angiopathy	9	12	0	0	9	12
Arterial occlusive disease	0	0	1	1	1	1
Arterial rupture	0	0	0	1	0	1
Blood pressure fluctuation	21	39	2	2	23	41
Bloody discharge	0	2	0	0	0	2
Capillary fragility	0	1	0	0	0	1
Circulatory collapse	0	0	1	1	1	1
Cyanosis	3	9	0	0	3	9
Embolism	0	0	1	1	1	1
Flushing	9	38	0	2	9	40
Haematoma	0	2	0	0	0	2
Haemorrhage	0	2	3	9	3	11
Hot flush	7	17	0	0	7	17
Hypertension	142	374	4	7	146	381
Hypertensive crisis	0	0	0	2	0	2
Hypotension	15	40	0	1	15	41
Infarction	0	0	3	3	3	3
Internal haemorrhage	0	0	0	1	0	1
Jugular vein distension	1	1	0	0	1	1
Labile blood pressure	0	1	0	0	0	1
Lymphoedema	0	1	0	0	0	1
Orthostatic hypotension	0	1	0	0	0	1
Pallor	45	119	0	8	45	127
Peripheral artery occlusion	0	0	1	1	1	1
Peripheral coldness	4	13	0	0	4	13
Peripheral vascular disorder	6	13	0	0	6	13
Phlebitis	1	2	0	0	1	2
Poor peripheral circulation	1	2	0	0	1	2
Raynaud's phenomenon	1	1	0	0	1	1
Shock	1	1	0	0	1	1
Superficial vein prominence	1	1	0	0	1	1
Thrombosis	0	0	6	7	6	7
Varicose vein	7	12	0	0	7	12

MedDRA SOC MedDRA PT	**Interval Non-serious**	**Cumulative Non-serious**	**Interval Serious**	**Cumulative Serious**	**Interval Total**	**Cumulative Total**
Vascular insufficiency	0	1	0	0	0	1
Vascular occlusion	1	2	1	1	2	3
Vascular pain	4	6	0	0	4	6
Vascular stenosis	2	2	0	0	2	2
Vasculitis	0	0	0	1	0	1
Vasoconstriction	9	14	0	0	9	14
Vasodilatation	2	2	0	0	2	2
Vasospasm	1	3	0	0	1	3
Vein disorder	1	1	0	0	1	1
Vein rupture	1	1	0	0	1	1
Venous occlusion	0	2	0	0	0	2
Grand Total	**75973**	**174335**	**1355**	**3041**	**77328**	**177376**

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-OHS-01-JP	6-month randomized, controlled, open-label, 2-arm parallel group, multicenter study to evaluate the effect of switching from cigarette smoking to the use of IQOS in smokers with generalized chronic periodontitis on the response to mechanical periodontal treatment and oral health status.	Japan	09-Nov-2017	Closed
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	Ongoing
P1-EXC-01-EU	Randomized, controlled, open-label, 4-arm parallel group study to evaluate the effect of switching from cigarette smoking to the use of IQOS in healthy adult current smokers on exercise capacity and trainability	Germany	01-Feb-2019	Closed

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 three Pre-Market Tobacco Product Applications for the IQOS Tobacco Heating System with three variants of Marlboro HeatSticks. The Marketing Orders for three 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); however, the device was not on the market during the reporting period.

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-2020 to 31-Dec-2020 and cumulatively from 30-Apr-2019 to 31-Dec-2020. The summary tabulation of identified AEs organized by MedDRA SOC is presented in Table 18-1. Of note, most of the spontaneous reports received by PMI are not medically confirmed, i.e. they were received from consumers directly and not via health care professionals.

A total of 25 non-serious AEs was received from 10 ICSRs in the U.S. during the reporting period. The most frequently reported AEs (>5%) were: Product complaint (n=3, 12.00%), Device physical property issue (n=2, 8.00%), No adverse event (n=2, 8.00%), Accidental exposure to product by child (n=2, 8.00%), Thermal burn (n=2, 8.00%), Cough (n=2, 8.00%), and Headache (n=2, 8.00%). No SAEs were received from the U.S. during the period covered by this SUR.

As mentioned in the SPI version 5.0 for THS (dated 02-Dec-2019), Cough and Headache are already known class effect AEs associated with the use of nicotine-containing products. The event of Thermal burn is recognized as an Important Potential risk associated with use of THS and stays under PMI monitoring.

The most represented SOCs (>5%) were: Product issues (n=7, 28.00%), Respiratory, thoracic and mediastinal disorders (n=5, 20.00%), Injury, poisoning and procedural complications (n=4, 16.00%), Gastrointestinal disorders (n=3, 12.00%), Nervous system disorders (n=3, 12.00%), and General disorders and administration site conditions (n=2, 8.00%).

Cumulatively, there were 61 non-serious AEs received from 27 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**	**1**	**0**	**0**	**0**	**1**
Palpitations	0	1	0	0	0	1
Gastrointestinal disorders	**3**	**10**	**0**	**0**	**3**	**10**
Abdominal discomfort	1	1	0	0	1	1
Abdominal distension	1	1	0	0	1	1
Chapped lips	0	1	0	0	0	1
Cheilitis	0	1	0	0	0	1
Dyspepsia	0	1	0	0	0	1
Nausea	1	2	0	0	1	2
Oral discomfort	0	1	0	0	0	1
Swollen tongue	0	1	0	0	0	1
Tongue disorder	0	1	0	0	0	1
General disorders and administration site conditions	**2**	**5**	**0**	**0**	**2**	**5**
Chest discomfort	0	1	0	0	0	1
Fatigue	0	1	0	0	0	1
No adverse event	2	3	0	0	2	3
Hepatobiliary disorders	**0**	**1**	**0**	**0**	**0**	**1**
Hepatic pain	0	1	0	0	0	1
Infections and infestations	**0**	**1**	**0**	**0**	**0**	**1**
Pharyngitis streptococcal	0	1	0	0	0	1
Injury, poisoning and procedural complications	**4**	**7**	**0**	**0**	**4**	**7**
Accidental exposure to product by child	2	3	0	0	2	3
Device difficult to use	0	1	0	0	0	1
Thermal burn	2	3	0	0	2	3
Investigations	**0**	**1**	**0**	**0**	**0**	**1**
Transaminases increased	0	1	0	0	0	1
Nervous system disorders	**3**	**4**	**0**	**0**	**3**	**4**
Burning sensation	1	1	0	0	1	1
Headache	2	3	0	0	2	3
Product issues	**7**	**14**	**0**	**0**	**7**	**14**
Device issue	0	1	0	0	0	1
Device physical property issue	2	5	0	0	2	5
Product complaint	3	5	0	0	3	5
Product distribution issue	1	1	0	0	1	1
Product physical issue	1	2	0	0	1	2
Psychiatric disorders	**0**	**3**	**0**	**0**	**0**	**3**
Anxiety	0	1	0	0	0	1

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Irritability	0	1	0	0	0	1
Panic attack	0	1	0	0	0	1
Respiratory, thoracic and mediastinal disorders	**5**	**13**	**0**	**0**	**5**	**13**
Cough	2	4	0	0	2	4
Dysphonia	0	1	0	0	0	1
Dyspnoea	0	2	0	0	0	2
Epistaxis	0	1	0	0	0	1
Oropharyngeal pain	1	2	0	0	1	2
Snoring	1	1	0	0	1	1
Throat irritation	0	1	0	0	0	1
Throat tightness	1	1	0	0	1	1
Vascular disorders	**1**	**1**	**0**	**0**	**1**	**1**
Cyanosis	1	1	0	0	1	1
Grand Total	**25**	**61**	**0**	**0**	**25**	**61**

18.6 Appendix 5: Signatures

PMI_SURV_2020_SUR01

Period Covered: 01-Jan-2020 to 31-Dec-2020

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

Justification	**Name/*Title***	**Signature**	**Date**
Author	Kamila Kowa/ *Senior Product Surveillance Scientist*	Kamila Kowa (Apr 20, 2021 15:21 GMT+2)	Apr 20, 2021
Review	Nicolas Blanc/ *Manager Medical Operations*	Nicolas Blanc (Apr 21, 2021 17:50 GMT+2)	Apr 21, 2021
Approval	Stephen Malcolm/ *Director Safety Surveillance, New Capabilities*	Stephen Malcolm (Apr 27, 2021 12:08 GMT+2)	Apr 27, 2021
Approval	Annie Heremans/ *Chief Medical Officer*	Annie Heremans (Apr 27, 2021 12:51 GMT+2)	Apr 27, 2021

IQOS SUR2020_v1.0_20Apr2021_US

Final Audit Report 2021-04-27

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By:	Rafael Munoz (b)(4)
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