Safety Update Report

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

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

This Safety Update Report (SUR) is compiled following some key principles of the International Council for Harmonisation (ICH) guideline E2C (R2) and provides a comprehensive and critical analysis of the safety profile of the Electrically Heated Tobacco Product (EHTP) and the Tobacco Heating Device (THD), as part of the Tobacco Heating System (THS) within the period from 01-Jan-2021 to 31-Dec-2021 (Data Lock Point, DLP).

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

The Development International Birth Date (DIBD), which corresponds to the date of first approval for conducting a clinical study for the THS, was 30-Apr-2013. The International Birth Date (IBD), which corresponds to the date of the first market launch worldwide for the THS, was 04-Nov-2014.

Up to the DLP of this SUR (31-Dec-2021), the THS had been marketed in 69 markets worldwide: Albania, Andorra, Armenia, Austria, Belarus, Bosnia & Herzegovina, Bulgaria, Canada, Canary Islands, Colombia, Costa Rica, Croatia, Curacao, Czech Republic, Denmark, Dominican Republic, Egypt, Estonia, France, Georgia, Germany, Greece, Greek Cyprus, Guatemala, Hungary, Indonesia, Israel, Italy, Japan, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Latvia, Lebanon, Lithuania, Malaysia, Maldives, Mexico, Moldova, Monaco, Montenegro, Morocco, Netherlands, New Zealand, North Macedonia, Palestine, Philippines, Poland, Portugal, Reunion, Romania, Russia, Saudi Arabia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Tunisia, Turkish Cyprus, Ukraine, United Arab Emirates, United Kingdom, United States, and Uzbekistan.

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

The Reference Safety Information (RSI) used during the SUR reporting interval for clinical studies and post-marketing safety surveillance was the Summary of Product Information (SPI) version 6.0 for THS (dated 25-May-2021).

The estimated cumulative subject exposure in clinical studies from the DIBD (30-Apr-2013) until the DLP of this SUR was (b) (4) subjects. Cumulatively, (b) (4) subjects were exposed to EHTP in PMI-sponsored pre-market studies up to the DLP of this (b) (4)

During this reporting interval, one PMI-sponsored clinical stud(b) (4)). No studies were closed during this reporting period.

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

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

Of note, the majority of spontaneous reports received by PMI are not medically confirmed, i.e., they were received directly from consumers and not from Health Care Professionals (HCPs). Additionally, the information regarding spontaneous 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 back by PMI; and ii) due to data privacy restrictions in several countries that prohibit storing consumer contact details. Nevertheless, the evaluation of new information as well as the cumulative analysis did not show any change in the safety profile of the THS. PMI will continue to evaluate all new safety information related to the product.

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

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AAA	Abdominal Aortic Aneurysm
AE	Adverse Event
BT	Blend Test
CC	Conventional Cigarette
COT	Commercial Offer Test
DIBD	Development International Birth Date
DLP	Data Lock Point
EHTP	Electrically Heated Tobacco Product
HCP	Health Care Professional
HDP	Hypertensive Disorders of Pregnancy
HNBC	Heat-Not-Burn Cigarette
HTP	Heated Tobacco Product
IBD	International Birth Date
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Report
LBW	Low Birth Weight
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-2021 to 31-Dec-2021 (Data Lock Point, DLP).

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

The THS consists of two main components: the EHTP, which is a tobacco stick, and the THD, which contains the holder and the charger. Depending on the THS version the holder and the charger can be either two separate elements or one element. The EHTP is designed to function with the holder and is composed of a (b) (4) Product technical specifications and constituents, as well as product user instructions, are described in the Summary of Product Information (SPI) for THS version 6.0 (Appendix 1) dated 25-May-2021. The SPI that contains technical specifications concerning the new THS based on the induction technology is under preparation. To date, the safety profile of the blade versus the induction THS does not differ.

The EHTP is commercialized under the brand name Marlboro *HeatSticks*™ or *HEETS*™ depending on the market and is specifically designed to be used with the *IQOS*™ device. The Development International Birth Date (DIBD), which corresponds to the date of first approval for conducting a clinical study for the THS was 30-Apr-2013. The International Birth Date (IBD), which corresponds to the date of the first market launch worldwide for the THS, was 04-Nov-2014.

(b) (4)

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-2021), the THS had been marketed in 69 markets worldwide: Albania, Andorra, Armenia, Austria, Belarus, Bosnia & Herzegovina, Bulgaria, Canada, Canary Islands, Colombia, Costa Rica, Croatia, Curacao, Czech Republic, Denmark, Dominican Republic, Egypt, Estonia, France, Georgia, Germany, Greece, Greek Cyprus, Guatemala, Hungary, Indonesia, Israel, Italy, Japan, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Latvia, Lebanon, Lithuania, Malaysia, Maldives, Mexico, Moldova, Monaco, Montenegro, Morocco, Netherlands, New Zealand, North Macedonia, Palestine, Philippines, Poland, Portugal, Reunion, Romania, Russia, Saudi Arabia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Tunisia, Turkish Cyprus, Ukraine, United Arab Emirates, United Kingdom, United States (U.S.), and Uzbekistan.

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

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

4 CHANGES TO REFERENCE SAFETY INFORMATION

The SPI for THS version 5.0 was updated during the reporting period to version 6.0 (dated 25-May-2021) (Appendix 1). The update did not modify the presented safety information of THS sold under brand name of *IQOS*™ with Marlboro *HeatSticks*™ or *HEETS*™.

The SPI verion 6.0 was used as Reference Safety Information (RSI) for all the clinical studies initiated in countries where the THS is marketed under the brand name IQOS, as well as for post-marketing safety surveillance.

5 ESTIMATED EXPOSURE

5.1 Cumulative Subject Exposure in Clinical Studies

Cumulatively, up to the DLP of this SUR, a total of 12 PMI-sponsored open-label randomized controlled clinical studies had been completed, with one study 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
(b) (4)	Closed	Single use	(b) (4)					
	Closed	Single use						
	Closed	Single use						
	Closed	Single use						
	Closed	5 Days						
	Closed	5 Days						
	Closed	3 Months						
	Closed	3 Months						
	Closed	6 Months						
	Closed	6 Months						
	Closed	Up to 1-year						
	Ongoing	Up to 3-years						
	Closed	3 Months						
Total Exposure	**NA**	**NA**						

[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 (b) (4) is an extension of study (b) (4) (b) (4) are already included in study (b) (4).

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

Table 5-2 Cumulative Subject Demographics in Clinical Studies

Demographics		Total
Gender	Male	(b) (4)
	Female	
	Total	
Race	Caucasian (White)	
	Asian (Japanese)	
	Black or African American	
	Native Hawaiian or Other Pacific Islander	
	American Indian or Alaska Native	
	Other	
	Total	

[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-2021).

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 eight pre-market studies including seven pre-market studies (Blend Tests (BT), Whole Offer Tests (WOT), Commercial Offer Test (COT)), and one Perception and Behaviour Assessment (PBA) study. There were no studies ongoing nor closed during the reporting period of this SUR.

The estimated passive surveillance pre-marketing exposure to the THS in these studies is based on the safety population who was exposed to at least 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-2021), 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)	
(b) (4)	Italy	(b) (4)				Completed
	Italy					Completed
	Switzerland					Completed
	Germany					Completed
	South Korea					Completed
	Russia					Completed
	US					Completed
	Denmark					Completed
Total Exposure	**NA**					**NA**

N=Number of subjects

5.3 Cumulative and Interval Consumer Exposure from Post-Marketing Experience

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

Both the cumulative exposure and the interval exposure covering the reporting interval for THD and EHTP is presented in Table 5-4 below.

Table 5-4 Interval and Cumulative Consumer Exposure

	Interval (n)	Cumulative (n)
THD	(b) (4)	
EHTP		

n=number of units s

6 DATA IN SUMMARY TABULATIONS

6.1 Reference Information

The summary tabulations presented in Appendices 2a-2b-2c of this SUR were generated from the PMI global safety database. The analysis of Adverse Events (AEs) was performed using the Medical Dictionary for Regulatory Activities (MedDRA) versions effective at the time of AE processing (latest version used 24.0).

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

Of note, the majority of the spontaneous reports received by PMI are not medically confirmed, i.e., they are received from consumers directly and not from HCPs.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Studies

Cumulative summary tabulations of Serious Adverse Events (SAEs) received from all PMI-sponsored clinical studies, from the DIBD (30-Apr-2013) until the DLP of this SUR (31-Dec-2021) 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 (b) (4) SAEs reported in (b) (4) ICSRs. A total of (b) (4) SAEs were reported in the THS arms, (b) (4) SAEs in the CC arm, and (b) (4) SAEs in the SA arm.

The most represented SOCs in the THS arms were Infections and infestations ((b) (4)) and Injury, poisoning and procedural complications ((b) (4)). All but (b) (4) SAEs were assessed by principal investigators and by PMI as having no causal relationship to THS use. In case of (b) (4) SAEs, the principal investigator was unable to assess whether they were related to THS use. These SAE concerned (b) (4) entitled "*A controlled, open-label, 3-arm parallel group, multi-center study to evaluate the Abdominal Aortic Aneurysm (AAA) growth rate in adult smoking patients randomized to either cigarette smoking or IQOS use and to compare with the AAA growth rate in patients who had stopped smoking*." This case is presented in Section 7.2 on Ongoing Clinical Studies.

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

Cumulative summary tabulations of SAEs received from all PMI-sponsored pre-market studies up until the DLP of this SUR (31-Dec-2021) are presented in Appendix 2b. The summary tabulations are presented by MedDRA SOC for the THS.

The cumulative summary tabulations present (b) SAEs reported in a total of (b) ICSRs. None of the SAEs were assessed by the principal investigators and by PMI as causally related to THS, and in the case of one SAE, the assessment was not provided by the principal investigator. The most represented SOCs were Injury, poisoning and procedural complications ((b)) and Infections and infestations ((b)).

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 24.0. 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 HCPs.

- Interval summary tabulations of non-serious AEs and SAEs from post-marketing experience show (b) (4) AEs ((b) serious and (b) (4) non-serious) from (b) (4) ICSRs. The most represented SOCs (>5%) were: *Respiratory, thoracic and mediastinal disorders* ((b) (4) , (b) (4) ; (b serious and (b) (4) non-serious), *Gastrointestinal disorders* ((b) (4) , (b) (4) ; (b serious and (b) non-serious), *Nervous system disorders* ((b) (4) , (b) (4) ; (b serious and (b) non-serious), *General disorders and administration site conditions* ((b) (4) , (b) (4) ; (b serious and (b) non-serious), *Injury, poisoning and procedural complications* ((b) (4) , (b) (4) ; (b) serious and (b) non-serious), and *Product issues* ((b) (4) , (b) (4) ; all non-serious).

  The most frequently reported events ((b)) were *Cough* ((b) (4) , (b) (4) ; (serious and (b) non-serious), *Headache* ((b) (4) , (b) (4) ; (serious and (b) non-serious), *Oropharyngeal pain* ((b) (4) , (b) (4) (serious and (b) (4) non-serious), and *Thermal burn* ((b) (4) , (b) (4) ; (serious and (b) non-serious).

  Out of the total (b) (4) SAEs, the most frequently reported (b) (4) were: *Angina pectoris* ((b) (4) , (b) (4)) and *Hypersensitivity* ((b) (4) , (b) (4)).

  As discussed in sections 15.3.1.1 and 15.4.1.1, Hypersensitivity is a known important identified risk for THS products. Concerning the (b) serious events of *Angina*

pectoris, the most frequently reported verbatim ((b) (4)) was "heart pain(s)", which corresponds to the MedDRA coding "*Angina pectoris*". None of these cases of *Angina pectoris* were medically confirmed. In most of these cases, the consumers' medical history was not provided. The mean age of the consumers was 33.73 years. The mean and the median period between the start of THS and the start of the event was 86.38 days and 14.50 days, respectively. Out of these (b) (4) events, (b) (4) t of *Angina pectoris* led to hospitalization. Given the limited information about the events does not allow one to conclude whether the consumer indeed experienced *Angina pectoris*. However, considering the verbatim reported, the mean age of the consumers, and the fact that most of the cases did not lead to hospitalization, it is likely that these cases refer to chest pain or chest discomfort. *Chest pain* and *Chest discomfort* are expected AEs with the use of NRT (e.g. Summary of Product Characteristics for Nicorette 15mg Inhalator, McNeil Products)[3] with a frequency categorized as uncommon (≥1/1 000, <1/100).

- Cumulative summary tabulations of non-serious AEs and SAEs from post-marketing experience show (b) (4) AEs ((b) (4) serious and (b) (4) non-serious) from (b) (4) 5 ICSRs. The most represented SOCs ((b) (4)) were: *Respiratory, thoracic and mediastinal disorders* ((b) (4), (b) (4) ; (b) (4) serious and (b) (4) non-serious), *Gastrointestinal disorders* ((b) (4) serious and (b) (4) non-serious), *Injury, poisoning and procedural complications* ((b) (4) serious and (b) (4) non-serious), *General disorders and administration site* (b) (4) serious and (b) (4) non-serious), *Nervous system d* (b) (4) serious and (b) (4) non-serious), and *Product issues* (b) (4) ; all non-serious).

  The most frequently reported events ((b) (4)) were *Cough* ((b) (4) serious and (b) (4) non-serious), *Thermal burn* (b) (4) serious and (b) (4) non-serious), and *Headache* ((b) (4) serious and (b) (4) non-serious).

  Of the total (b) (4) SAEs reported, the most frequently reported ((b) (4)) were: *Hypersensitivity* ((b) (4)) and *Angina pectoris* ((b) (4)).

  As discussed in sections 15.3.1.1 and 15.4.1.1, *Hypersensitivity* is a known important identified risk for THS products. Concerning the (b) (4) serious events of *Angina pectoris*, the most frequently reported verbatim ((b) (4)) was "heart pain" and "stabbing sensation in the heart", both corresponding to the MedDRA coding "*Angina pectoris*". None of these cases of *Angina pectoris* were medically confirmed. In most of these cases, the consumers' medical history was not provided. The mean age of the consumers was 33.83 years. The mean and the median period between the start of THS and the start of the event was 46.14 days and 4.00 days, respectively. Of these (b) (4) events, (b) (4) events of *Angina pectoris* led to hospitalization, and (b) (4) was life-threatening. The only life-threatening case did not lead to consumer's hospitalization. The consumer mentioned "it was too painful as the heart would stop". Given the limited information about the events does not allow one to conclude whether the consumer indeed experienced *Angina pectoris*. However, considering the verbatim

reported, the mean age of the consumers, the short median latency, and the fact that most of the cases did not lead to hospitalization, it is likely that these cases refer to chest pain or chest discomfort. *Chest pain* and *Chest discomfort* are expected AEs with the use of NRT (e.g. Summary of Product Characteristics for Nicorette 15mg Inhalator, McNeil Products)[3] with a frequency categorized as uncommon (≥1/1,000, <1/100).

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

7.1 Completed Clinical Studies

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

7.2 Ongoing Clinical Studies

One PMI-sponsored clinical study ((b) (4)) for the THS was ongoing during the period covered by this SUR.

Study (b) (4) 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, (b) SAEs have been reported in (b) subjects up to 31-Dec-2021.

(b) SAEs in (b) subjects have been reported in THS arm (*Death*, *Cardio-respiratory arrest*, *Pulmonary oedema*, *Patella fracture*, *Atrial fibrillation*, and *Femoral neck fracture*). The fatal case concerns a 71-year-old male Japanese subject with relevant ongoing diseases of AAA (as per inclusion criteria in the study protocol) arterial hypertension and smoking history of 20 cigarettes/day. The subject was randomized to the THS arm on 30-Nov-2018. On 08-Nov-2020, the subject passed away due to a cardiopulmonary arrest. An image autopsy was performed with the findings of a dominant edema in the back of the lungs. It was confirmed that the AAA did not rupture. The cause of the study subject's death remains unknown. The sponsor assessed that there was no reasonable causal relationship between SAEs of *Death*, *Cardio-respiratory arrest*, *Pulmonary oedema*, and THS use. The principal investigator considered these SAEs as unable to be assessed as having a causal relationship to THS use. The events of *Patella fracture* (that occurred as well in the same subject mentioned previously), *Atrial fibrillation*, and *Femoral neck fracture* were assessed as not related to THS use by both the principal investigator and the sponsor.

(b) SAEs in (b) subjects have been reported in Cigarette arm (*Cerebral haemorrhage* *Inflammatory pseudotumour*, and *Tarsal tunnel syndrome*). The first case concerns a 79-year-old male subject with medical history of hypertension and chronic renal failure, ongoing diseases of AAA (as per inclusion criteria in the study protocol) and smoking 25 cigarettes/day. On 16-Dec-2020, the subject died in the hospital due to intracerebral hemorrhage. The event of *Cerebral haemorrhage* was assessed as related to cigarettes by both the principal investigator and the sponsor. The events of *Inflammatory pseudotumour* and *Tarsal tunnel syndrome*, reported in the remaining (b) cases, were assessed as not related to cigarettes by both the principal investigator and the sponsor.

(b) (4) SAEs in (b) subjects were reported in smoking cessation arm ((b) SAEs of *Large intestine polyp*, and (b) SAE of each event *Angina pectoris*, *Appendicitis*, *Cardiac failure*

acute, *Enteritis*, *Gastroenteritis*, *Inguinal hernia*, *Peripheral arterial occlusive disease*, and *Pneumonia*) where the assessment of causal relationship to the products is not applicable.

7.3 Long-term Follow-up in Clinical Studies

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

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

8.1 Completed Passive Surveillance Pre-Market Studies

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

8.2 Ongoing Passive Surveillance Pre-Market Studies

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

8.3 Other Non-Interventional Studies

There was one PMI-sponsored non-interventional study conducted during the previous reporting period. Study (b) (4) is a mixed methods study using qualitative interviews and quantitative exploratory analysis to evaluate content validity of the ABOUT-Health and Functioning questionnaire for users of tobacco and/or nicotine products. The study was conducted in the UK and US.

There were (b) (4) ICSRs received during the current review period reporting (b) non-serious AEs. The events reported more than once included Tongue coated, Dyspnoea, Dyspepsia, Chest pain, Dyspnoea exertional, Cough, Dental plaque, and Acne.

Cumulatively, there were (b) ICSRs reporting (b) non-serious AEs that originated from this study. The most reported AEs ((b)) were: Dyspnoea exertional ((b) (4)), Dry mouth (b) (4) Cough (b) (4) Sluggishness (b) (4) Fatigue (b) (4) Breath odour (b) (4)), Insomnia ((b) (4)), Asthenia ((b) (4)), and Dyspnoea ((b) (4)).

Case analysis did not identify any new safety related findings.

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 until the DLP of this SUR. A total of (b) SAEs in (b) subjects were reported in THS arm. No new participants were enrolled during the interval (01-Jan-2021 to 31-Dec-2021). Among these (b) SAEs, the seriousness criteria were fatal in four SAEs (*Cardiac failure acute*, *Myocardial ischemia*, *Completed suicide*, and *COVID-19*), life-threatening in one SAE (*Acute myocardial infarction*), hospitalization in (b) SAEs, and (b) SAE were classified as important medical events.

The fatal SAEs of *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. 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 result indicated that the cause of death was acute cardiovascular failure due to ischemic heart disease. 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 last fatal SAE of *COVID-19* occurred in a 62-year-old female with medical history of hypertension, varicose vein disease, metabolic X syndrome, and obesity. On 20-Apr-2021, the subject died due to complications after Covid-19. None of these fatal SAEs were assessed as 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

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

- PubMed

(((eclipse OR accord OR "Heatstick" OR "revo") AND cigarette AND heat* NOT (resin OR column)) OR "tobacco heating"[Title/Abstract] OR "heated cigarette*"[Title/Abstract] OR "electrically heated cigarette*"[Title/Abstract] OR "EHCSS"[Title/Abstract] OR "Electrically Heated Cigarette Smoking System*"[Title/Abstract] OR "primarily heat* tobacco"[Title/Abstract] OR "tobacco heating cigarette*"[Title/Abstract] OR "EHCSS-K3"[Title/Abstract] OR "EHCSS-K6"[Title/Abstract] OR "heated tobacco"[Title/Abstract] OR "tobacco heating system"[Title/Abstract] OR ("heat-not-burn"[Title/Abstract] AND "tobacco"[Title/Abstract]) OR "IQOS"[Title/Abstract] OR "HEETS"[Title/Abstract] OR "heatsticks*"[Title/Abstract] OR ("heat-not-burn"[Title/Abstract] AND "tobacco"[Title/Abstract]) OR ("HNB"[Title/Abstract] AND "tobacco"[Title/Abstract]) OR ("THS"[Title/Abstract] AND "tobacco"[Title/Abstract]) OR ("Lil"[Title/Abstract] AND "tobacco"[Title/Abstract]) OR ("TEEPS"[Title/Abstract] AND "tobacco"[Title/Abstract])) OR ("Modified risk tobacco product*"[Title/Abstract])

- Scopus

(ALL ((tobacco W/2 heat*)) OR ALL ("heated tobacco product") OR ALL ("heated tobacco product*") OR ALL ("heated tobacco") OR ALL ("tobacco heating system") OR ALL ("tobacco heating system*") OR ALL ("heat not burn") OR ALL (iqos) OR ALL ("heets") OR ALL (heatstick*) OR ALL ("electrically heated cigarette smoking system") OR ALL ("electrically heated cigarette") OR ALL (ehcss) OR ALL ((heat* W/2 cigarette)) OR ALL ("modified risk tobacco product") OR ALL ("modified risk tobacco product*") OR ALL ((lil W/2 tobacco)) OR ALL ((teeps W/2 tobacco)) OR ALL ((hnb AND tobacco)) OR ALL ((ths AND tobacco)) AND NOT ALL (("third hand smok*" OR "thirdhand smok*"))

- Embase

ths:ab AND tobacco:ab NOT ('third hand smok*' OR 'thirdhand smok*') OR (tobacco NEAR/2 heat*) OR 'heated tobacco product'/exp OR 'heated tobacco product*' OR 'heated tobacco' OR 'tobacco heating system'/exp OR 'tobacco heating system*' OR 'heat not burn' OR iqos OR heets OR heatstick* OR 'electrically heated cigarette smoking system'/exp OR 'electrically heated cigarette' OR ehcss OR (heat* NEAR/2 cigarette) OR 'modified risk tobacco product'/exp OR 'modified risk tobacco product*' OR (lil NEAR/2 tobacco) OR (teeps NEAR/2 tobacco) OR (hnb:ti,ab,kw AND tobacco:ti,ab,kw)

- SciFinder

"heat not burn" OR "tobacco heating system" OR "modified risk tobacco" OR "electrically heated cigarette" OR "heated tobacco"

- Google Scholar

As the search efficiency of Google Scholar is limited when multiple search terms are used, broader-spectrum searches have been implemented, as described below.

("heated cigarette*") OR ("tobacco heating") OR ("heated tobacco") OR ("tobacco heating system") OR ("heat-not-burn" "tobacco") OR ("IQOS") OR ("HEETS") OR ("heatsticks ") OR ("heat not burn" "tobacco") OR ("THS" "tobacco") OR ("HNB" "tobacco"); Articles excluding patents

This comprehensive library was screened for publications containing new safety information associated with the THS products published during the reporting interval from 01-Jan-2021 to 31-Dec-2021 inclusive.

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

Article one by Zaitsu et al.[4] focuses on the impact of heated tobacco products (HTPs) use in pregnant women and possible association with maternal and neonatal risks for hypertensive disorders of pregnancy (HDP) and low birth weight (LBW). Data analyzed in this article originated from a web-based nationwide survey 'COVID-19 and Society' conducted in Japan. The data were collected in October 2020. A total of 923 (558 postdelivery and 365 currently pregnant women) participants were included in the analysis. The authors estimated the age-adjusted ORs and 95% CIs of ever HTP users for HDP and LBW and compared them with those of never HTP users in a logistic regression analysis. The prevalence of ever and current HTP use were 11.7% and 2.7% in postdelivery women and 12.6% and 1.1% in currently pregnant women, respectively. Among currently pregnant women who were former combustible cigarette smokers, 4.4% (4/91) were current HTP users. Among postdelivery women, ever HTP users had a higher HDP incidence (13.8% vs 6.5%, p=0.03; age-adjusted OR=2.48, 95% CI 1.11 to 5.53) and higher LBW incidence (18.5% vs 8.9%, p=0.02; age-adjusted OR=2.36, 95% CI 1.16 to 4.87). The authors concluded that in Japan, the incidence of ever HTP use exceeded 10% among pregnant women, and that HTP use may be associated with maternal and neonatal risks.

PMI comment: The effect of THS use during pregnancy and lactation was recognized as missing information and is closely monitored by PMI. According to the SPI 6.0 dated 25-May-2021, women who are pregnant, breastfeeding, or think they may be pregnant, should quit tobacco and nicotine use altogether.

Article two by Sayin Gülensoy et al.[5] presents a case of a 56-year-old male patient who was admitted with sudden onset of chest pain and shortness of breath. The patient had a history of chronic obstructive lung disease, coronary artery disease, and previous pulmonary embolism. He had smoked approximately 25 pack years and quit. He had been using IQOS for 2.5 years. Thoracic computed tomography scan revealed pleural-based atelectasis and

fibroatelectatic changes in the lower lobe of the right lung, pleural fluid in the right upper lobe, fibroatelectatic changes and pleural thickening in the left lung. Biopsy taken with video-assisted thoracic surgery showed lymphoid aggregation in nodular form and widespread anthracosis around the lung, fibrillar material that double-refracting the light in the alveoli, hyaline membrane-like material in the alveoli, type 2 pneumocyte hyperplasia, an interstitial organization, and a subacute lung injury picture with exogenous lipoid material. These findings were evaluated in accordance with toxic substance-induced chemical pneumonia. The authors concluded that it might be related to 2.5 years of using HTP.

PMI comment: This case has been captured in the PMI global safety database as an ICSRs retrieved through literature screening. The case concerns a middle-aged subject with a positive medical history of chronic obstructive pulmonary disease and pulmonary embolism, and a 25 pack years-smoking history. Subject switched to *IQOS*™ and used it for 2.5 years before the event. No information related to concomitant medications, number of *HEETS*™ used per day and exposure to exogenous inhalants by occupation or environment was provided. Additionally, the authors described dust deposits in many alveoli which caused birefringence in polarized microscopy. Tobacco heated products do not release any dust in their aerosols. Scarce literature about the onset duration of a subacute lung disease by chemical inhalants leading to a chemical pneumonia makes it difficult to assess this case in an appropriate way. Literature about e-cigarette or vaping product use associated lung injury cases showed a mean onset duration of approximately six days (ranging from 0 day to 2 months) prior to presentation of respiratory symptoms including dyspnea, cough, and chest pain. Due to lack of information related to concomitant medications, details on product use, exogeneous exposure to other potential sources, non-evocative temporal relationship, it is currently not possible to assess the causal relationship between the use of the product and the reported adverse event. In alignment with the authors of this article, further studies are needed for a better understanding of the pathophysiological underlying mechanisms in this case.

The last article by Imura and Tabuchi[6] focuses on short-term symptoms related to secondhand HTP aerosol exposure. An internet-based self-reported questionnaire survey was conducted in 2019 as a part of the Japan Society and New Tobacco Internet Survey study. In total, 8784 eligible respondents aged 15–73 years were analyzed. The authors examined the frequency (%) of secondhand combustible cigarette smoke and HTP aerosol exposure, and the exposure-related subjective symptoms (sore throat, cough, asthma attack, chest pain, eye pain, nausea, headache, and other symptoms). Overall, 56.8% of those exposed to secondhand cigarette smoke had any subjective symptoms, compared to 39.5% of those exposed to HTP aerosol. Asthma attacks and chest pains were reported more frequently when associated with secondhand HTP aerosol exposure (10.9 and 11.8%, respectively) than with secondhand cigarette smoke exposure (8.4 and 9.9%, respectively). Sore throat, cough, eye pain, nausea, and headache were also more frequently reported when associated with secondhand cigarette smoke than with secondhand HTP exposure. The authors conclude that this is the first study to examine severe subjective symptoms such as asthma attacks and chest pains, and to suggest that respiratory and cardiovascular abnormalities could be related to secondhand HTP aerosol exposure. Further careful investigations are necessary.

PMI comment: As remarked by the authors, the level of second-hand aerosol or smoke exposure could not be measured; thus, a quantitative analysis could not be performed in this study. Additionally, the authors investigated the symptoms related to second-hand aerosol or smoke exposure but due to a lack of control group, could not compare these symptoms with the ones occurring in not exposed people. Therefore, the degree to which second-hand exposure increases acute symptoms is unknown.

The review of the recently published articles noted herein concerning THS products did not identify any new safety concerns.

12 OTHER PERIODIC REPORTS

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

13 LATE-BREAKING INFORMATION

No potentially important safety findings concerning THS products were identified after the DLP (31-Dec-2021) 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, global websites, non-sponsored social media, and AEs reported by PMI employees involved in the internal panel testing.
2. Signal validation: verification of the existence of a new potential causal association or a new aspect of a known association, with justification for further analysis.
3. Signal assessment: thorough investigation of the validated signal, including the preparation of a Signal Evaluation Report.

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

15 SIGNAL AND RISK EVALUATION

15.1 Summary of Safety Concerns

A summary of the safety concerns at the beginning of the reporting interval of this SUR is presented in Table 15-1 below. New information received during the period covered by this SUR (01-Jan-2021 to 31-Dec-2021) 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)	(b) AEs of hypersensitivity retrieved: Most reported AEs(b)): - Hypersensitivity, (b) - Rash,(b) (4) - Rash macular, (b) - Pharyngeal swelling, (b) - Urticaria, (b) - Lip swelling, (b) - Gingival swelling, (b) - Swollen face, (b) - Swelling tongue, (b) - Mouth swelling, (b)
	Accidental exposure to product by child	Selected Preferred Terms (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	(b) AEs retrieved: - Accidental exposure to product by child, (b) Co-reported AEs representing at least (b) of the total: - Vomiting, (b) - Irritability, (b) - Cough, (b)) - Crying, (b) - Pallor, (b) - Asthenia, (b) - Nausea, (b) - Mood altered, (b) - Respiratory tract irritation (b) - Drooling, (b) - Retching, (b) - Affective disorder, (b)

	Risk	Search criteria for Risk Assessment	Interval Retrieved AEs within Safety Database
			- Somnolence, (b) - Dizziness, (b) (4) - Saliva discolouration, (b) - Hiccups, (b) - Listless, (b) - Diarrhoea (b) (4) - Oropharyngeal discomfort, (b) - Fatigue, (b) - Pyrexia, (b) - Malaise, (b) - Lip discolouration, (b) - Choking, (b) - Device physical property issue, (b)

	Burning sensation	<u>Customized search of MedDRA PTs and *Lowest Level Terms (LLTs)*:</u>
		- 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)*
			(b) <u>AEs retrieved:</u>
			- Burning sensation (b) (4)
			- Burning sensation mucosal, (b)
			- Skin burning sensation, (b)
			- Oral discomfort*, (b) (4)
			(only the following selected *LLTs* under the PT Oral discomfort are included in the risk assessment:
			  - *Lip burning sensation of,* (b)
			  - *Burning lips,* (b)
			  - *Burning mouth* (4) (b)
			  - *Oral mucosal burning sensation,* (b)
			  - *Burning oral sensation,* (b)
			  - *Oral hot feeling,* (b))
			* note that the total number of AEs under the PT Oral discomfort is (b) out of which (b were included in the risk assessment.
			(b) (4)

Important Potential Risks	Thermal burn	<u>Customized search of MedDRA PTs:</u> - Airway burns - Burn oral cavity - Burns first degree - Burns second degree - Burns third degree - Burns fourth degree - Thermal burn - Thermal burns of eye	(b) <u>AEs retrieved</u>: - Thermal burn, (b) (4) - Burn oral cavity, (b) - Burns second degree, (b) - Airway burns, (b) - Burns first degree, (b) - Thermal burns of eye, (b) - Burns third degree, (b)

	Risk	Search criteria for Risk Assessment	Interval Retrieved AEs within Safety Database
Missing Information	Pregnancy and lactation	MedDRA SOC: - "Pregnancy, puerperium and perinatal conditions" MedDRA SMQs (Narrow): - "Neonatal exposures via breast milk" - "Pregnancy, labour and delivery complications and risk factors (excl. abortions and stillbirth)" - "Foetal disorders" - "Functional lactation disorders" - "Neonatal disorders" - "Normal pregnancy conditions and outcomes" -"Termination of pregnancy and risk of abortion"	(b) AEs retrieved: - Exposure during pregnancy, (b) - Maternal exposure during pregnancy, (b) - Morning sickness, (b) - Primigravida, (b) - Abortion spontaneous, (b) - Abortion of ectopic pregnancy, (b) - Ectopic pregnancy, (b) - Maternal exposure timing unspecified, (b) - Normal newborn, (b) - Exposure via breast milk, (b) - Suppressed lactation, (b) - Imminent abortion, (b) - Maternal exposure during breast feeding, (b) Co-reported AEs representing at least 1% of the total: - Passive smoking, (b) - Malaise, (b) - Product complaint, (b) - Nausea, (b) - Nicotine dependence, (b) - Product odour abnormal, (b) - Non-tobacco user, (b) - Headache, (b) - Tobacco user, (b) - Vomiting, (b) - Nervousness, (b) - Increased appetite, (b) - Dizziness, (b) - Throat irritation, (b) - Dry throat, (b) - Drug ineffective, (b) - Ex-tobacco user, (b) - Somnolence, (b) 4) - Illness, (b) - Frustration tolerance decreased, (b) - Oropharyngeal discomfort, (b) - Anxiety, (b) - Intentional product misuse, (b)

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-2021 up to the DLP of this SUR (31-Dec-2021) was performed in the global safety database to retrieve all the hypersensitivity-related events with THS use. The electronic search included non-serious AEs and SAEs from solicited and unsolicited sources and was carried out using the MedDRA SMQ Hypersensitivity (narrow scope).

A total of (b) (4) AEs of hypersensitivity-related events with THS use ((b) (4) serious and (b) (4) non-serious) were received in (b) (4) ICSRs. The most reported AEs ((b) (4)) were: *Hypersensitivity* ((b) (4) (b) (4) serious and (b) (4) non-serious), *Rash macular* (b) (4) serious and (b) (4) non-serious), *Pharyngeal swelling* (b) (4) serious and (b) (4) non-serious), *Urticaria* ((b) (4) serious and (b) (4) non-serious), *Lip swelling* ((b) (4) serious and (b) (4) non-serious), *Gingival swelling* ((b) (4) serious and (b) (4) non-serious), *Swelling face* ((b) (4) all non-serious), *Swollen tongue* ((b) (4) all non-serious), and *Mouth swelling* ((b) (4) serious and (b) (4) non-serious).

The most reported SAEs ((b) (4) were: *Hypersensitivity* (b) (4) resolved or resolving, (b) (4) with unknown outcome, and (b) (4) not resolved), *Angioedema* (b) (4) resolved or resolving, and (b) (4) with unknown outcome), *Anaphylactic shock* ((b) (4) resolved or resolving, (b) (4) with unknown outcome, and (b) (4) not resolved), *Oropharyngeal blistering* ((b) (4) resolved or resolving, and (b) (4) not resolved), and *Laryngeal oedema* ((b) (4) resolved or resolving, and (b) (4) not resolved).

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

The AEs belonging to the MedDRA SMQ Hypersensitivity represented (b) (4) 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 117.33. This calculation is based on the number of cases falling under the MedDRA SMQ Hypersensitivity and reported during the reporting interval of this SUR ((b) (4)). The calculation also includes the number of users during this period, which is estimated to be 16.3 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,[7] the reporting frequency rate for cases falling into the MedDRA SMQ Hypersensitivity was estimated to be 0.12 per 100 users, following correction for under-reporting. Based on the RSI for nicotine replacement therapies (such as Summary of Product Characteristics for Nicorette 15mg Inhalator, McNeil Products)[3],

Hypersensitivity is a common (≥1/100, <1/10) AE. The estimated reporting frequency rate (after correction for under-reporting) for cases falling under the MedDRA SMQ Hypersensitivity for the THS is therefore considered not to be higher than what is already known for nicotine replacement therapies.

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

15.3.1.2 Accidental exposure to product by Child

A search covering the reporting interval of this SUR (01-Jan-2021 to 31-Dec-2021) 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 (b) (4) events of *Accidental exposure to product by child* (serious and (b) (4) non-serious) were received in (b) (4) ICSRs. A total of (b) (4) AEs were co-reported. The first serious case concerns a child who experienced a serious event of *Choking* and non-serious events of *Cough*, *Respiratory tract irritation,* and *Vomiting* after ingesting the leachate of EHTP. No medical intervention was deemed necessary. At the time of reporting, the child recovered from the reported events. The second case presents a neonate who experienced a serious event of *Choking* and a non-serious event of *Respiratory disorder* after ingesting a part of EHTP. No medical intervention was deemed necessary. The outcome of this case was unknown. Next case presents a child who accidentally ingested an EHTP and was hospitalized for observation. No other AEs were reported. The outcome of the event was unknown. Next serious case concerns a child who ingested an entire EHTP and was brought to the hospital. He threw up (non-serious event of *Vomiting*) while having his stomach pumped. The outcome of the event was unknown. The last case concerns a one-year-old infant who experienced a serious event of *Vomiting* after the accidental ingestion of an EHTP. The child was hospitalized until the susceptor was spontaneously excreted. No medical intervention was deemed necessary. The outcome of the events was reported as resolved.

In (b) (4) of ICSRs concerning accidental exposure by children, no health-related events were co-reported (*No adverse event*, (b) (4)). In the remaining cases, the most frequent ((b) (4)) co-reported events were: *Vomiting* (b) (4) *Irritability* (b) (4) *Cough* ((b) (4)), *Crying* ((b) (4)), *Pallor* ((b) (4)), *Asthenia* ((b) (4)), *Nausea* (b) (4) *Mood altered* (b) (4) *Respiratory tract irritation* (b) (4) *Drooling* ((b) (4)), *Retching* ((b) (4)), *Affective disorder* ((b) (4)), *Somnolence* ((b) (4)), *Dizziness* ((b) (4)), *Saliva discolouration* (b) (4) , *Listless* ((b) (4)), *Diarrhoea* ((b) (4)), *Oropharyn*(b) (4)), *Fatigue* (b) (4) *Pyrexia* (b) (4) *Malaise* (b) (4) *Lip*

discolouration (b) (4) *Choking* (b) (4) and *Device physical property issue* (b) (4).

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 (31-Dec-2021) 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 (b) (4) non-serious AEs were received in (b) (4) ICSRs. The retrieved AEs among the selected PT list were: *Burning sensation* (b) (4), *Burning sensation mucosal* (b) (4), and *Skin burning sensation* (b) (4). The AEs retrieved among the selected LLTs under the PT *Oral discomfort* were: *Lip burning sensation of* (b) (4), *Burning lips* (b) (4), *Burning mouth* (b) (4), *Oral mucosal burning sensation* (b) (4), *Burning oral sensation* (b) (4), and *Oral hot feeling* (b) (4). Of note, the total number of AEs under the PT *Oral discomfort* was (b) (4) out of which (b) (4) were included in the risk assessment. The LLTs excluded from the risk assessment were: *Oral discomfort* (b) (4), *Lip discomfort* (b) (4), *Discomfort in mouth* (b) (4), and *Oral cavity discomfort* (b) (4).

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 (31-Dec-2021) 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 (b) (4) AEs ((b) (4) serious and (b) (4) non-serious) were received in (b) (4) ICSRs: *Thermal burn* ((b) (4) serious and (b) (4) non-serious), *Burn oral cavity* ((b) (4); all non-serious), *Burns second degree* ((b) (4) non-serious), *Airway burns* ((b) (4) serious and (b) (4) non-serious), *Burns first degree* ((b) (4) non-serious), *Thermal burns of eye* ((b) (4); serious), and *Burns third degree* ((b) (4); serious).

There were (b) (4) serious cases identified, (b) (4) reporting a serious event of *Thermal burn*, and one case for each event of *Thermal burns of eye*, *Burns third degree*, and *Airway burns*. Out of (b) (4) serious events, (b) (4) involved hospitalization and two were medically important conditions. The reported events concerned an eye, bronchi, voice box, lips, and fingers. In (b) (4) out of (b) (4) cases, the patient underwent a treatment. The event outcome was reported as resolving for (b) (4) events, not resolved for (b) (4) events, and was unknown for the remaining event.

In about (b) (4) of cases, the consumer reported the oral cavity (including mouth, lips, and tongue) as the body site affected. In about (b) (4) of the cases, the reported body site were fingers and/or hands. In (b) (4) of cases, the affected body site was not specified.

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

15.3.3 Update on missing information

15.3.3.1 Pregnancy and Lactation

A search covering the period from 01-Jan-2021 to the DLP of this SUR (31-Dec-2021) was performed in the global safety database to retrieve data related to pregnancy and lactation. The electronic search for pregnancy reports included all non-serious AEs and SAEs from solicited and unsolicited sources and was carried out under the MedDRA SOC "Pregnancy, puerperium and perinatal conditions" and the following MedDRA SMQs (Narrow): "Neonatal exposures via breast milk", "Pregnancy, labour and delivery complications and risk factors (excl. abortions and stillbirth)", "Foetal disorders", "Functional lactation disorders", "Neonatal disorders", "Normal pregnancy conditions and outcomes", "Termination of pregnancy and risk of abortion".

A total of (b) (4) ((b) (4) serious and (b) (4) non-serious) pregnancy related AEs were received in (b) (4) ICSRs: *Exposure during pregnancy* ((b) (4); (b) (4) non-serious), *Maternal exposure during pregnancy* ((b) (4); (b) (4) non-serious), *Morning sickness* ((b) (4); (b) (4) non-serious), *Primigravida* ((b) (4); (b) (4) non-serious), *Abortion spontaneous* ((b) (4); (b) (4) serious), *Abortion of ectopic pregnancy* ((b) (4); (b) (4)), *Ectopic pregnancy* ((b) (4); (b) (4)), *Maternal exposure timing unspecified* ((b) (4); (b) (4)), *Normal newborn* ((b) (4); (b) (4)), *Exposure via breast milk* ((b) (4); (b) (4)), *Suppressed lactation* ((b) (4); (b) (4)), *Imminent abortion* ((b) (4) serious), and *Maternal exposure during breast feeding* ((b) (4); (b) (4)).

There were (b) (4) SAEs concerning pregnancy reported in (b) (4) cases that were identified during the review period. (b) (4) cases report an event of *Abortion spontaneous*. The (b) (4) case provides no additional data. The (b) (4) case concerns a female partner of the IQOS consumer who had a medical history of miscarriage. The (b) (4) case reports a serious event of *Imminent abortion* that concerned the wife of the consumer. The wife reported that "I really dislike how my husband smokes IQOS cigarettes even though I have an imminent abortion." The data provided in this case were limited. The (b) (4) case reports SAE of *Ectopic pregnancy* and *Abortion of ectopic pregnancy*. The consumer stopped smoking as soon she knew about the pregnancy. The outcome of all SAEs was unknown.

The co-reported AEs representing at least (b) (4) of the total included: *Passive smoking* ((b) (4)), *Malaise* ((b) (4)), *Product complaint* ((b) (4)), *Nausea* ((b) (4)), *Nicotine dependence* ((b) (4)), *Product odour abnormal* ((b) (4)), *Non-tobacco user* ((b) (4)), *Headache* ((b) (4)), *Tobacco user* ((b) (4)), *Vomiting* ((b) (4)), *Nervousness* ((b) (4)), *Increased appetite* ((b) (4)), *Dizziness* ((b) (4)), *Throat irritation* ((b) (4)), *Dry throat* ((b) (4)), *Drug ineffective* ((b) (4)), *Ex-tobacco user* ((b) (4)), *Somnolence* ((b) (4)), *Illness* ((b) (4)), *Frustration tolerance decreased* ((b) (4)), *Oropharyngeal discomfort* ((b) (4)), *Anxiety* ((b) (4)), and *Intentional product misuse* ((b) (4)), all non-serious events.

There was an increase in the number of pregnancy cases when compared with the previous reporting period. This increase was caused by an implementation of a tool on 04-Jan-2021, which routinely screens non-sponsored websites and social media with a defined list of keywords for the identification of AE complaints. The identified valid cases are processed and stored in the global safety database. Among (b) (4) ICSRs identified in this reporting period, (b) (4) ICSRs ((b) (4)) originated from non-sponsored social media.

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.[8,9] One possible reason for such an increase may be the changing exposure to known and unknown risk factors[10] 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.[11] Smoking augments nasal responses to allergen in atopic subjects and increases IgE, immunoglobulin G4, and postallergen histamine levels in nasal lavage fluid.[12,13] Tobacco smoke has a number of harmful effects

on the immune system,[14] *e.g.* on humoral and cellular immunity. The putative direct effect of tobacco smoke on the skin is unclear,[15] but smoke might directly impair skin-barrier function via the effects of reactive oxygen species on keratinocytes.[16,17] Several studies have assessed the association between smoking exposure and allergic diseases.[18] Nicotine replacement therapies based on nasal inhalation of nicotine also showed *Hypersensitivity* as a common (≥1/100, <1/10) undesirable effect (e.g. Nicorette Inhalator). A recently published survey performed on Korean middle and high school students, suggested that both EC and HTP have the potential to cause and aggravate allergic rhinitis through airway inflammation or toxicity.[19]

The SPI version 6.0 dated 25-May-2021, mentions that *Hypersensitivity* events may occur in users of the THS, in particular those with a past medical history of an allergic condition, such as food, pet, or dust allergies. In case of signs and symptoms that may indicate a serious allergic event, users should stop using the THS and contact their physician immediately.

To characterize this risk, a cumulative search from the IBD (04-Nov-2014) to the DLP of this SUR (31-Dec-2021) was performed in the global safety database to retrieve hypersensitivity-related events with THS product use. The electronic search included all non-serious AEs and SAEs from all sources and was carried out under the MedDRA SMQ Hypersensitivity (narrow).

Cumulatively, (b) (4) hypersensitivity-related AEs with THS use ((b) (4) serious and (b) (4) non-serious) were received in (b) (4) ICSRs. The most reported AEs ((b) (4)) were: *Hypersensitivity* (b) (4) serious and (b) (4) non-serious), *Rash* ((b) (4) (b) (4) serious and (b) (4) non-serious), *Pharyngeal swelling* ((b) (4) serious and (b) (4) non-serious), *Rash macular* ((b) (4) serious and (b) (4) non-serious), *Gingival swelling* (b) (4) serious and (b) (4) non-serious), *Lip swelling* (b) (4) serious and (b) (4) non-serious), *Urticaria* ((b) (4) serious and (b) (4) non-serious), *Swollen tongue* (b) (4) serious and (b) (4) non-serious), *Mouth swelling* ((b) (4), n=(b) (4) (serious and (b) (4) non-serious), *Rash pruritic* ((b) (4) serious and (b) (4) non-serious), and *Swelling face* ((b) (4) all non-serious).

The most reported SAEs ((b) (4)) were: *Hypersensitivity* (b) (4) resolved or resolving, (b) (4) with unknown outcome, and (b) (4) not resolved), *Ang*(b) (4) resolved or resolving, (b) (4) with unknown outcome, and (b) (4) not resolved), *Oropharyngeal blistering* (b) (4) with unknown outcome, (b) (4) not resolved, and (b) (4) resolved or resolving), *Rash* ((b) (4) resolved or resolving, (b) (4) not resolved, and (b) (4) with unknown outcome), and *Laryngeal oedema* ((b) (4) not resolved, (b) (4) resolved or resolving, and (b) (4) with unknown outcome).

As mentioned in section 15.3.1.1, the reporting frequency rate of cases of *Hypersensitivity* is estimated to be (b) (4) per 100 users for the current reporting period, after correction for under-reporting. Based on the RSI for nicotine replacement therapies (such as Summary of Product Characteristics for Nicorette 15mg Inhalator, McNeil Products), *Hypersensitivity* is a common (≥1/100, <1/10) AE. The estimated reporting frequency rate (after correction for

under-reporting) of cases of *Hypersensitivity* for the THS is, therefore, considered not to be higher than what is already known for nicotine replacement therapies.

PMI will continue to perform regular review of the events of *Hypersensitivity* upon the THS use to ensure the ongoing evaluation of new safety information.

15.4.1.2 Accidental exposure to product by child

Unintentional ingestion of tobacco products is a major reason for infant and child nicotine exposures worldwide. A European retrospective study published the outcomes of e-liquid exposure incidents reported to 10 Poison Centers[20] 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% $p < 0.001$).[20]

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.[21,22] Chewing tobacco (67.3%) and snuff (25.0%) accounted for most of the other tobacco product exposures.[21] Most children were exposed through ingestion (95.5%) or multiple routes including ingestion (2.8%), and only 1.7% through non-ingestion routes.[21] A recent study aiming to analyse cases of acute exposure to ECs, e-liquids, and heat-not-burn cigarette (HNBC) products containing nicotine based on toxicological consultations at the Czech Republic poisons control centre during a seven-year period (2012–2018) showed similar results.[23] 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%).[23]

Infants are susceptible to accidental tobacco ingestion because of a natural curiosity and a tendency for oral exploration.[24,25] Ingestion of as little as 1mg of nicotine by a small child can produce symptoms such as nausea and vomiting.[26] Severe toxic effects of nicotine ingestion may include weakness, convulsions, unresponsiveness, and impaired respiration, and ultimately, may lead to respiratory arrest and death.[26]

As described in SPI version 6.0 for THS (dated 25-May-2021), toxic effects of nicotine develop rapidly following acute overdose. The current data indicates that 6 to 7mg/kg of acute oral nicotine is an accurate estimate of the acute lethal oral dose in adults. One EHTP contains, on average, 5–6mg of nicotine. The accidental ingestion of EHTP may potentially cause signs and symptoms of nicotine intoxication such as: nausea, hyper-salivation, abdominal pain, vomiting, diarrhoea, cold sweat, headache, dizziness, hearing and visual disturbances, mental confusion, tremor, weakness, weak analgesia, increase of respiratory reflex and coughing, increased bronchial secretions, and increase in heart rate and blood

pressure. The THS should always be kept away from children. In case of accidental ingestion by children, a physician should be contacted immediately.

To characterize the risk of accidental exposure to product by children, a cumulative search from the IBD (04-Nov-2014) until the DLP of this SUR (31-Dec-2021) 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, (b) (4) ((b) (4) serious and (b) (4) non-serious) events of *Accidental exposure to product by child product packaging* were received in (b) (4) ICSRs. In (b) (4) of ICSRs reporting Accidental exposure to product by children, no health-related events were co-reported (*No adverse event*, (b) (4)). In the remaining cases there were a total of (b) (4) co-reported events ((b) (4) serious and (b) (4) non-serious).

The most frequently ((b) (4)) co-reported AEs were: *Vomiting* ((b) (4) serious and (b) (4) non-serious), *Pallor* ((b) (4) serious and (b) (4) non-serious), *Cough* ((b) (4) (b) (4) non-serious), *Nausea* ((b) (4) serious and (b) (4) non-ser(b) (4) (b) (4) non-serious), *Mood altered* ((b) (4) non-ser(b) (4) serious and (b) (4) non-serious), *Asthenia* ((b) (4) serious and (b) (4) non-serious), *Malaise* (b) (4) serious and (b) (4) non-serious), *Hiccups* (b) (4) non-serious), *Fatigue* (b) (4) non-serious), *Somnolence* (b) (4) non-serious), *Retching* ((b) (4) non-serious), *Respiratory tract irritation* ((b) (4) non-serious), *Pyrexia* ((b) (4) serious and (b) (4) non-serious), (b) (4) serious and (b) (4) non-serious).

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

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

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

15.4.1.3 Burning sensation

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

To characterize this risk, a cumulative search from the IBD (04-Nov-2014) until the DLP of this SUR (31-Dec-2021) 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, (b) (4) AEs ((b) (4) serious and (b) (4) non-serious) were received in (b) (4) ICSRs. The retrieved AEs among the selected PT list were: *Burning sensation* ((b) (4) serious and (b) (4) non-serious), *Burning sensation mucosal* ((b) (4) non-serious), and *Skin burning sensation* ((b) (4) non-serious). The AEs retrieved among the selected LLTs under the PT *Oral discomfort* were: *Lip burning sensation of* ((b) (4) serious and (b) (4) non-serious), *Burning lips* (b) (4) serious and (b) (4) non-serious), *Burning mouth* (b) (4) non-serious), *Burning oral sensation* (n=133; all non-serious), *Oral mucosal burning sensation* ((b) (4) non-serious), and *Oral hot feeling* ((b) (4) non-serious). Of note, the total number of AEs under the PT *Oral discomfort* was (b) (4) out of which (b) (4) AEs were included in the risk assessment. The LLTs excluded from the risk assessment were: *Oral discomfort* ((b) (4)), *Lip discomfort* ((b) (4)), *Discomfort in mouth* ((b) (4)), and *Oral cavity discomfort* ((b) (4)).

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.

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.[27] 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[28] 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[29] The failure rate of lithium batteries established during the manufacturing is one in 10 million.[30]

The study by Corey et al. 2018[31] 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.[32] 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.[33], there were an estimated 2,035 EC explosion and burn injuries presented to U.S. hospital emergency departments (95% CI 1107 to 2964) in years 2015 to 2017.

To characterize this risk, a cumulative search from the IBD (04-Nov-2014) to the DLP of this SUR (31-Dec-2021) was performed in the global safety database to retrieve events of thermal burn with THS product use. The electronic search included all non-serious AEs and SAEs from solicited and unsolicited sources. The selected PTs were: *Airway burns*, *Burn oral cavity*, *Burns first degree*, *Burns second degree*, *Burns third degree*, *Burns fourth degree*, *Thermal burns of eye*, and *Thermal burn*.

Cumulatively, (b) (4) AEs ((b serious and (b) (4) non-serious) were received in (b) (4) ICSRs: *Thermal burn* (b) (4) serious and (b) (4) non-serious), *Burn oral cavity* ((b) (4) (serious and (b) non-serious), *Burns second degree* (b) (4) non-serious), *Airway burns* (n=58; 1 serious and 57 non-serious), *Burns first degree* (n=17; all non-serious), *Burns third degree* ((b) (4) serious), and *Thermal burns of eye* ((b) (4) serious and (non-serious).
b

In about (b) (4) of cases, the consumer reported the oral cavity (including mouth, lips, and tongue) as the body site affected. In about (b) (4) of the cases, the reported body site were fingers and/or hands. In (b) (4) of cases, the affected body site was not specified.

Among the (b) (4) serious events of *Thermal burn*, (b) 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, (b) cases reported a burn of lips or hand, in the remaining three cases, the burn site was provided as laryngeal mucosa, throat, voice box, and in one case the site was unspecified.

Among the (b) (4) serious events of *Burns third degree*, (b) (4) case reported a third degree burn to the hand due to an alleged explosion of the device, (b) (4) case reported "very deep subcutaneous burn" of lips and salivary gland resection due to the burn, (b) (4) case reported a burn on consumer's thumb resulting on the loss of the skin after having touched the lid of the device, (b) (4) case reported a third degree burn inside the mouth, and (b) (4) case reported "burned my lower lip, to a stage 3 burn lip".

Among the (b) (4) serious events of *Burn oral cavity*, (b) (4) led to hospitalization. In the (b) (4) 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[34] as it is clear that maternal smoking affects fetal wellbeing and growth.[35,36] Indeed, nicotine is able to cross the placenta, and therefore, may affect foetal development.[37] As pregnancy and lactation constitute exclusion criteria and reason for immediate withdrawal in all completed and ongoing clinical and pre-marketing studies for the THS, its use has not been tested in pregnant and breastfeeding women. An appropriate characterization of the risks to which pregnant women are exposed while using the THS may only be achieved through a long-term monitoring of spontaneous cases reporting AEs associated with the THS usage within this population. Based on the current knowledge and as described in SPI version 6.0 for THS (dated 25-May-2021), 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 (31-Dec-2021)

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, (b) (4) AEs ((b) (4) serious and (b) (4) non-serious) were received in (b) (4) ICSRs including *Exposure during pregnancy* (n=(b) (4) non-serious), *Maternal exposure during pregnancy* (n=37; all non-serious), *Morning sickness* (n=(b) (4) non-serious), *Primigravida* (n=(b) (4) non-serious), *Maternal exposure timing unspecified* (n=(b) (4) non-serious), *Abortion spontaneous* (n=(b) (4) serious), *Maternal exposure during breast feeding* (n=(b) (4) non-serious), *Pregnancy* (n=(b) (4) *Mastitis* (n=(b) (4) serious), *Respiratory disorder neonatal* (n=(b) (4) *Abortion of ectopic pregnancy* (n=(b) (4) *Poor feeding infant* (n=(b) (4) *Ectopic pregnancy* (n=(b) (4); (b) (4)), *Infant irritability* (n=(b) (4) (b) (4)), *Exposure via breast milk* (n=1; non-serious), *Suppressed lactation* (n=1; non-serious), *Imminent abortion* (n=1; serious), and *Normal newborn* (n=1; non-serious).

Cumulatively, there were (b) (4) SAEs concerning pregnancy reported in (b) (4) ICSRs. (b) (4) cases reported an event of *Abortion spontaneous*. The (b) (4) case provided no additional data. The (b) (4) case concerns a female partner of the IQOS™ consumer who has a medical history of miscarriage. The (b) (4) case reported a serious event of *Imminent abortion* that concerns the wife of the consumer. The wife reported that "I really dislike how my husband smokes IQOS cigarettes even though I have an imminent abortion". The data provided in this case were limited. The (b) (4) case reported SAE of *Ectopic pregnancy* and *Abortion of ectopic pregnancy*. The consumer stopped smoking as soon she knew about the pregnancy. The last case reported a SAE of *Mastitis*. The consumer stopped using IQOS due to laryngitis symptoms and when she resumed using it, mastitis occurred. No additional data are available. The outcome of all SAEs was unknown.

The (b) (4) co-reported AEs were all assessed as non-serious. The most reported AEs representing at least (b) (4) of the total included: *Passive smoking* (b) (4) *Malaise* (b) (4) *Nausea* (b) (4) *Product complaint* (b) (4) *Nicotine dependence* (b) (4) *Product odour abnormal* (b) (4) *Cough* (b) (4) *Dizziness* ((b) (4) , *Vomiting* ((b) (4) *Thermal burn* ((b) (4) , *Non-tobacco user* (b) (4) *Abdominal pain upper* (b) (4) *Headache* (b) (4) *Oropharyngeal discomfort* (b) (4) *Tobacco user* (b) (4) *Throat irritation* (b) (4) *Accidental exposure to product by child* (b) (4) and *Nervousness* (b) (4) .

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

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-2021 to 31-Dec-2021.

Of note, the majority of the spontaneous reports received by PMI are not medically confirmed, i.e., they were received from consumers directly and not from HCPs. Additionally, the information regarding spontaneous cases is scarce for at least two main reasons: i) because PMI is not able to contact consumers that do not provide affirmative consent to be contacted back by PMI; and ii) due to data privacy restrictions in several countries that prohibit storing consumer contact details. 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 6.0 dated 25-May-2021

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:	6.0
Release Date:	25 May 2021
Replaces Previous Version:	Version 6.0
Previous Release Date:	02 December 2019

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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
LOQ	Limit of Quantitation
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™, lil™ SOLID with Fiit™, and lil™ HYBRID with Miix™) that heats tobacco without producing combustion. In comparison with cigarette smoke, the formation of harmful and potentially harmful constituents (HPHCs) is substantially reduced (on average by 90%).

As IQOS™ with HeatSticks™/HEETS™, lil™ SOLID with Fiit™, and lil™ HYBRID with Miix™ are heat-not-burn tobacco products that generate on average 90% lower levels of HPHCs compared to cigarette smoke, the information in this document pertaining to IQOS™ with HeatSticks™/HEETS™ is considered to be applicable to lil™ SOLID with Fiit™ and lil™ HYBRID with Miix™.

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

Importantly, the magnitude of reductions in the BoExp levels to selected HPHCs when using the THS[1] were comparable to those observed when smokers stopped smoking cigarettes (1).

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

The purpose of this Summary of Product Information (SPI) is to serve as a reference for professionals (e.g. researchers, health care providers) on how to use the product safely and effectively following product commercialization. In this way, the SPI will also serve as the reference document for safety and efficacy when conducting clinical studies with commercialized products (e.g. for Investigator-Initiated Studies). The SPI is also the document used to determine the expectedness of adverse events (AEs) associated with the use of THS following product commercialization. This document does not replace the THS User Guide.

2 PRODUCT DESCRIPTION

2.1 Product Name

Electrically Heated Tobacco Products (EHTP) are marketed as HeatSticks™/ HEETS™, Fiit™, and Miix™[3]. The EHTP is to be used exclusively with the respective THD. The EHTP and the THD are components of the Tobacco Heating System (THS).

[1] IQOS™ with HeatSticks™/HEETS™

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

[3] The Miix™ consumable consists of an EHTP and a cartridge filled with propylene glycol and vegetable glycerin. There is no nicotine in the cartridge.

2.2 THS components

As previously mentioned, the THS consists 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 element (holder only).

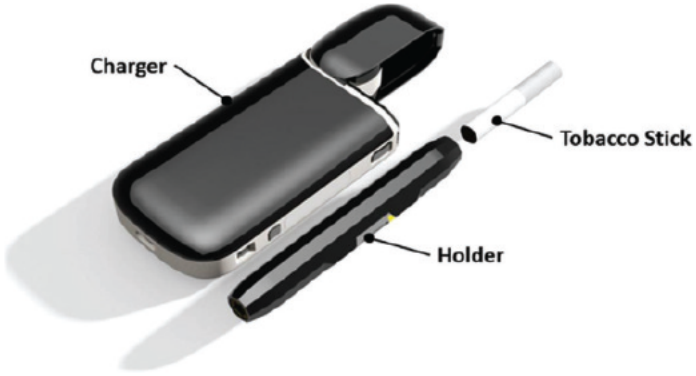

Figure 1 Picture of the THS components[4] (THD with two elements)

2.2.1 The EHTP

The EHTP is designed to function with the holder. It is compos (b) (4)

(b) (4)

[4] IQOS™ with HeatSticks™/HEETS™

All the ingredients have been evaluated from a toxicological point of view and have been approved for use. The EHTP delivers nicotine, which is naturally present in tobacco. (b) (4)

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
(b) (4)	(b) (4)	x	x
		x	x
		x	x
		x	x
			x
		x	x
			x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	
		x	x
		x	
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
			x
			x

Category	Ingredient Name	Regular Variant	Menthol Variant
(b) (4) [redacted]	(b) (4) [redacted]	x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
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		x	x
		x	x
		x	x
		x	x
		x	x
		x	x
		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 an electrical heating unit that heats the EHTP in a controlled manner by using a heater blade.

The THD with two elements includes only the IQOS™ device. Depending on the IQOS™ device version, the holder stores enough energy for one 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. The charger 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 in the holder.

2.2.3 THD with one single element (holder only)

The THD with one element consists of a holder heating the EHTP in a controlled manner by using a heater blade[5] or an external heating[6].

The THD with one element includes the IQOS™ device, the lil™ SOLID device, and the lil™ HYBRID device. Depending on the device, the holder of the THD with one element stores enough energy for approximately 10 inhalation experiences for IQOS™ with HeatSticks™/HEETS™ and 20 inhalation experiences for lil™ SOLID with Fiit™ and lil™ HYBRID with Miix™. The inhalation experience for IQOS™ with HeatSticks™/HEETS™ is 6 minutes or 14 puffs (whichever comes first), while the inhalation experience for lil™ SOLID with Fiit™ and lil™ HYBRID with Miix™ is 4 minutes or 14 puffs (whichever comes first). A LED indicates when the experience can start and when the experience ends.

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

[5] IQOS™ with HeatSticks™/HEETS™, lil™ SOLID

[6] lil™ HYBRID

Figure 3 Pictures of the THD with one single element[7]

2.3 Product Variants

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

2.4 THS[8] Aerosol

Table 2 shows the levels of a selected list of compounds and HPHCs found, under the Health Canada Intense (HCI) machine-smoking conditions[9] in the aerosol of the regular and menthol variants of the THS[4] in comparison with the levels found in a 3R4F reference cigarette. These data show that levels of the majority of HPHCs are reduced on average in the THS by more than 90% compared to the reference cigarette (4, 5). These data for IQOS™ with HeatSticks™/HEETS™ below are also representative of lil™ SOLID with Fiit™, and lil™ HYBRID with Miix™.

[7] lil™ HYBRID (left), IQOS™ with HeatSticks™/HEETS™ (middle), lil™ SOLID (right)

[8] IQOS™ with HeatSticks™/HEETS™

[9] 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[5] (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[10] (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[11] (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

[10] Total particulate matter

[11] 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: confidence interval of the mean.
n.a.: not analyzed.
<: median lower than the limit of quantitation (LOQ), 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 adults who would otherwise continue to use tobacco or nicotine-containing products.

3.2 Product Use

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

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

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).

Women who are pregnant, breastfeeding, or think they may be pregnant, should quit tobacco and nicotine use altogether.

3.3.1 Specific Risks that Lead to a Precaution for Use

3.3.1.1 Hypersensitivity

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

3.3.1.2 Risk of Accidental Exposure to product by Children

The THS must be 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 must be instructed to contact a physician immediately.

3.3.1.3 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, THS users are advised to store the products in a dry and cool place.

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).

A higher water content in the EHTPs may lead to production of aerosol which some users perceive as warm (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 consequently, leads to reduced gum 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/HPHCs (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 the EHTP is ingested (e.g. accidentally by children).

Toxic effects of nicotine develop rapidly following acute overdose. The current data indicate that more than 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, five to six milligrams of nicotine.

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

Other subsequent conditions may also occur such as faintness, prostration, dyspnea, seizures, hypotension; weak, irregular, rapid pulse rate / transient cardiac standstill or paroxysmal atrial

fibrillation. Death may occur within a few minutes following severe nicotine overdose, usually as a result of respiratory failure secondary to paralysis of respiratory muscles.

Acute nicotine intoxication generally requires symptomatic and supportive care. There is no specific antidote for nicotine intoxication. Activated charcoal (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 acute nicotine intoxication 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

(b) (4)

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

November-2014 (Japan) for IQOS™ with HeatSticks™/HEETS™

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

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

6 DATE OF REVISION OF THE TEXT

25-May-2021

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18.2 Appendix 2: Cumulative and Interval Summary Tabulations

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

MedDRA SOC MedDRA PT	CC	THS unspecified	THS Menthol	THS Regular	SA	Total
Blood and lymphatic system disorders	(b) (4)					
Anaemia						
Cardiac disorders						
Acute myocardial infarction						
Angina pectoris						
Atrial fibrillation						
Cardiac failure acute						
Cardio-respiratory arrest						
Gastrointestinal disorders						
Enteritis						
Inguinal hernia						
Large intestine polyp						
Pancreatitis chronic						
General disorders and administration site conditions						
Death						
Infections and infestations						
Appendicitis						
Cellulitis						
Cellulitis staphylococcal						
Epiglottitis						
Gastroenteritis						
Influenza						
Peritonitis						
Pneumonia						
Pneumonia mycoplasmal						
Pyelonephritis acute						
Sinusitis						
Tooth infection						
Urosepsis						
Injury, poisoning and procedural complications						
Clavicle fracture						
Femoral neck fracture						
Foot fracture						
Head injury						
Hip fracture						
Multiple fractures						
Patella fracture						
Pulmonary contusion						
Rib fracture						
Skin laceration						
Traumatic haemothorax						
Metabolism and nutrition disorders						
Diabetic ketoacidosis						

MedDRA SOC MedDRA PT	CC	THS unspecified	THS Menthol	THS Regular	SA	Total
Musculoskeletal and connective tissue disorders	(b) (4)					
Back pain						
Costochondritis						
Jaw cyst						
Vertebral osteophyte						
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Adenocarcinoma of colon						
Breast cancer						
Inflammatory pseudotumour						
Intestinal metastasis						
Papillary thyroid cancer						
Uterine leiomyoma						
Nervous system disorders						
Cerebral haemorrhage						
Myelopathy						
Seizure						
Tarsal tunnel syndrome						
Transient ischaemic attack						
Psychiatric disorders						
Adjustment disorder with depressed mood						
Alcohol abuse						
Completed suicide						
Suicidal ideation						
Renal and urinary disorders						
Nephrolithiasis						
Reproductive system and breast disorders						
Heavy menstrual bleeding						
Ovarian cyst						
Respiratory, thoracic and mediastinal disorders						
Pleural effusion						
Pneumonia aspiration						
Pulmonary oedema						
Social circumstances						
Bereavement						
Vascular disorders						
Peripheral arterial occlusive disease						
Peripheral ischaemia						
Total						

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

MedDRA SOC	MedDRA PT	THS (b) (4)	Total
General disorders and administration site conditions	Adverse event		
	Injury associated with device		
Infections and infestations	Bronchitis		
	Cholecystitis infective		
	Ear infection		
	Osteomyelitis		
	Pneumonia		
	Sepsis		
Injury, poisoning and procedural complications	Accident		
	Concussion		
	Fall		
	Head injury		
	Joint injury		
	Limb injury		
	Muscle strain		
	Nerve injury		
	Road traffic accident		
	Skeletal injury		
	Skin abrasion		
	Thermal burn		
Musculoskeletal and connective tissue disorders	Spinal disorder		
	Spinal pain		
Respiratory, thoracic and mediastinal disorders	Tonsillar cyst		
Surgical and medical procedures	Hospitalization		
Total			

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	(b) (4)					
Anaemia						
Blood disorder						
Coagulopathy						
Lymph node pain						
Lymphadenitis						
Lymphadenopathy						
Cardiac disorders						
Acute myocardial infarction						
Angina pectoris						
Angina unstable						
Arrhythmia						
Arteriospasm coronary						
Atrial fibrillation						
Atrioventricular block						
Bradycardia						
Cardiac arrest						
Cardiac discomfort						
Cardiac disorder						
Cardiac dysfunction						
Cardiac failure						
Cardiac failure acute						
Cardiac failure chronic						
Cardiac fibrillation						
Cardiac flutter						
Cardiomegaly						
Cardiopulmonary failure						
Cardiovascular disorder						
Carditis						
Coronary artery disease						
Coronary artery occlusion						
Dressler's syndrome						
Extrasystoles						
Gastrocardiac syndrome						
Left ventricular hypertrophy						
Myocardial infarction						
Myocardial ischaemia						
Palpitations						
Pericardial effusion						
Pericarditis						
Sinus arrhythmia						
Sinus tachycardia						
Tachyarrhythmia						
Tachycardia						
Congenital, familial and genetic disorders						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Albinism	(b) (4)					
Gastrointestinal disorder congenital						
Kenny-Caffey syndrome						
Protuberant ear						
Ear and labyrinth disorders						
Deafness						
Deafness transitory						
Ear congestion						
Ear discomfort						
Ear disorder						
Ear haemorrhage						
Ear pain						
Ear pruritus						
Ear swelling						
Excessive cerumen production						
Hypoacusis						
Inner ear inflammation						
Middle ear inflammation						
Motion sickness						
Otorrhoea						
Sudden hearing loss						
Tinnitus						
Vertigo						
Vertigo positional						
Endocrine disorders						
Autoimmune thyroid disorder						
Goitre						
Hyperthyroidism						
Hypothyroidism						
Thyroid cyst						
Thyroid disorder						
Thyroid mass						
Thyroid pain						
Thyroiditis						
Eye disorders						
Abnormal sensation in eye						
Accommodation disorder						
Asthenopia						
Blepharospasm						
Blindness						
Blindness transient						
Blindness unilateral						
Chromatopsia						
Conjunctival haemorrhage						
Conjunctival irritation						
Conjunctivitis allergic						
Dark circles under eyes						
Diplopia						
Dry eye						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Eczema eyelids	(b) (4)					
Erythema of eyelid						
Excessive eye blinking						
Exophthalmos						
Eye allergy						
Eye colour change						
Eye discharge						
Eye disorder						
Eye haemorrhage						
Eye inflammation						
Eye irritation						
Eye movement disorder						
Eye oedema						
Eye pain						
Eye paraesthesia						
Eye pruritus						
Eye swelling						
Eyelid disorder						
Eyelid function disorder						
Eyelid irritation						
Eyelid oedema						
Eyelid ptosis						
Eyelid rash						
Eyelids pruritus						
Foreign body sensation in eyes						
Lacrimation increased						
Maculopathy						
Metamorphopsia						
Mydriasis						
Ocular discomfort						
Ocular hyperaemia						
Ocular hypertension						
Periorbital pain						
Periorbital swelling						
Photophobia						
Photopsia						
Swelling of eyelid						
Vision blurred						
Visual acuity reduced						
Visual field defect						
Visual impairment						
Vitreous floaters						
Xerophthalmia						
Gastrointestinal disorders						
Abdominal discomfort						
Abdominal distension						
Abdominal pain						
Abdominal pain lower						
Abdominal pain upper						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Abdominal rigidity	(b) (4)					
Abnormal faeces						
Aerophagia						
Allergic stomatitis						
Anaesthesia oral						
Anal incontinence						
Angular cheilitis						
Anorectal discomfort						
Aphthous ulcer						
Aptyalism						
Barrett's oesophagus						
Bowel movement irregularity						
Breath odour						
Burning mouth syndrome						
Cardiospasm						
Change of bowel habit						
Chapped lips						
Cheilitis						
Chronic gastritis						
Coating in mouth						
Colitis						
Colitis ulcerative						
Constipation						
Crohn's disease						
Dental caries						
Dental discomfort						
Dental paraesthesia						
Dental plaque						
Diaphragmatic hernia						
Diarrhoea						
Discoloured vomit						
Dry mouth						
Duodenal ulcer						
Duodenitis						
Dyschezia						
Dyspepsia						
Dysphagia						
Enamel anomaly						
Enlarged uvula						
Enteritis						
Enterocolitis						
Epigastric discomfort						
Erosive duodenitis						
Eructation						
Faeces discoloured						
Faeces hard						
Faeces soft						
Flatulence						
Food poisoning						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Frequent bowel movements	(b) (4)					
Functional gastrointestinal disorder						
Gastric cyst						
Gastric dilatation						
Gastric disorder						
Gastric perforation						
Gastric ulcer						
Gastric ulcer perforation						
Gastritis						
Gastrointestinal disorder						
Gastrointestinal hypermotility						
Gastrointestinal inflammation						
Gastrointestinal motility disorder						
Gastrointestinal oedema						
Gastrointestinal pain						
Gastrointestinal sounds abnormal						
Gastrointestinal tract irritation						
Gastrointestinal ulcer						
Gastrooesophageal reflux disease						
Gingival bleeding						
Gingival blister						
Gingival discolouration						
Gingival discomfort						
Gingival disorder						
Gingival erosion						
Gingival erythema						
Gingival pain						
Gingival pruritus						
Gingival recession						
Gingival swelling						
Gingival ulceration						
Glossitis						
Glossodynia						
Haematemesis						
Haematochezia						
Haemorrhoids						
Hiatus hernia						
Hyperaesthesia teeth						
Hyperchlorhydria						
Hypertrophy of tongue papillae						
Hypoaesthesia oral						
Hypoaesthesia teeth						
Irritable bowel syndrome						
Large intestinal ulcer						
Large intestine perforation						
Leukoplakia oral						
Lip blister						
Lip discolouration						
Lip disorder						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Lip dry	(b) (4)					
Lip erosion						
Lip erythema						
Lip exfoliation						
Lip haemorrhage						
Lip oedema						
Lip pain						
Lip pruritus						
Lip scab						
Lip swelling						
Lip ulceration						
Loose tooth						
Malpositioned teeth						
Mouth cyst						
Mouth haemorrhage						
Mouth swelling						
Mouth ulceration						
Nausea						
Nicotinic stomatitis						
Noninfective gingivitis						
Noninfective sialoadenitis						
Odynophagia						
Oesophageal dilatation						
Oesophageal discomfort						
Oesophageal disorder						
Oesophageal irritation						
Oesophageal obstruction						
Oesophageal oedema						
Oesophageal pain						
Oesophageal rupture						
Oesophagitis						
Oral blood blister						
Oral cavity fistula						
Oral discharge						
Oral discomfort						
Oral disorder						
Oral mucosa erosion						
Oral mucosal blistering						
Oral mucosal discolouration						
Oral mucosal eruption						
Oral mucosal erythema						
Oral mucosal exfoliation						
Oral mucosal roughening						
Oral pain						
Oral papule						
Oral pigmentation						
Oral pruritus						
Palatal disorder						
Palatal oedema						

MedDRA SOC MedDRA PT	Interval Non-	Cumulative Non-	Interval	Cumulative	Interval	Cumulative
Palatal swelling	(b) (4)					
Palatal ulcer						
Pancreatic disorder						
Pancreatitis						
Pancreatitis acute						
Paraesthesia oral						
Peptic ulcer						
Periodontal disease						
Pigmentation lip						
Plicated tongue						
Proctalgia						
Reflux gastritis						
Regurgitation						
Retching						
Saliva altered						
Saliva discolouration						
Salivary duct stenosis						
Salivary gland disorder						
Salivary gland enlargement						
Salivary gland pain						
Salivary hypersecretion						
Scalloped tongue						
Small intestinal obstruction						
Stiff tongue						
Stomatitis						
Stomatitis haemorrhagic						
Swollen tongue						
Teeth brittle						
Teething						
Tongue blistering						
Tongue coated						
Tongue discolouration						
Tongue discomfort						
Tongue disorder						
Tongue dry						
Tongue eruption						
Tongue erythema						
Tongue exfoliation						
Tongue haemorrhage						
Tongue movement disturbance						
Tongue necrosis						
Tongue oedema						
Tongue pruritus						
Tongue rough						
Tongue spasm						
Tongue ulceration						
Tooth deposit						
Tooth discolouration						
Tooth disorder						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Tooth erosion	(b) (4)					
Tooth loss						
Tooth pulp haemorrhage						
Tooth socket haemorrhage						
Toothache						
Trichoglossia						
Varicose veins sublingual						
Vomiting						
General disorders and administration site conditions						
Administration site irritation						
Adverse drug reaction						
Adverse event						
Adverse reaction						
Alcohol interaction						
Application site acne						
Application site alopecia						
Application site burn						
Application site coldness						
Application site discomfort						
Application site dryness						
Application site erythema						
Application site hypersensitivity						
Application site inflammation						
Application site irritation						
Application site joint pain						
Application site pain						
Application site paraesthesia						
Application site rash						
Application site reaction						
Application site swelling						
Application site warmth						
Asthenia						
Chest discomfort						
Chest pain						
Chills						
Condition aggravated						
Crepitations						
Crying						
Cyst						
Death						
Decreased activity						
Device intolerance						
Discharge						
Discomfort						
Disease susceptibility						
Drug ineffective						
Drug intolerance						
Enanthema						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Energy increased	(b) (4)					
Exercise tolerance decreased						
Face oedema						
Facial discomfort						
Facial pain						
Fatigue						
Feeling abnormal						
Feeling cold						
Feeling drunk						
Feeling hot						
Feeling jittery						
Feeling of body temperature change						
Feeling of relaxation						
Foaming at mouth						
Food interaction						
Gait disturbance						
Gait inability						
General physical health deterioration						
Generalised oedema						
Glassy eyes						
Hangover						
Hernia						
Hunger						
Hyperplasia						
Hyperthermia						
Hypothermia						
Ill-defined disorder						
Illness						
Impaired healing						
Induration						
Inflammation						
Influenza like illness						
Injection site discomfort						
Injection site hypersensitivity						
Injection site mass						
Injection site pain						
Injection site urticaria						
Injection site vesicles						
Injury associated with device						
Localised oedema						
Malaise						
Mass						
Mucosa vesicle						
Mucosal atrophy						
Mucosal discolouration						
Mucosal disorder						
Mucosal dryness						
Mucosal erosion						
Mucosal haemorrhage						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Mucosal hypertrophy	(b) (4)					
Mucosal induration						
Mucosal inflammation						
Mucosal membrane hyperplasia						
Mucosal pain						
Mucosal pigmentation						
Mucosal ulceration						
No adverse event						
Nodule						
Non-cardiac chest pain						
Nonspecific reaction						
Obstruction						
Oedema						
Oedema mucosal						
Oedema peripheral						
Organ failure						
Pain						
Performance status decreased						
Peripheral swelling						
Physical deconditioning						
Polyp						
Pre-existing condition improved						
Product intolerance						
Pyrexia						
Screaming						
Secretion discharge						
Sensation of blood flow						
Sensation of foreign body						
Sense of oppression						
Sensitivity to weather change						
Sluggishness						
Swelling						
Swelling face						
Temperature intolerance						
Temperature regulation disorder						
Tenderness						
Therapeutic response increased						
Therapeutic response unexpected						
Thirst						
Thirst decreased						
Tobacco interaction						
Ulcer						
Unevaluable event						
Withdrawal syndrome						
Xerosis						
Hepatobiliary disorders						
Biliary colic						
Cholelithiasis						
Gallbladder disorder						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Hepatic failure	(b) (4)					
Hepatic pain						
Hepatitis						
Hepatomegaly						
Liver disorder						
Liver injury						
Immune system disorders						
Allergic oedema						
Allergic reaction to excipient						
Allergy to animal						
Allergy to chemicals						
Allergy to metals						
Allergy to plants						
Anaphylactic reaction						
Anaphylactic shock						
Anaphylactoid reaction						
Atopy						
Autoimmune disorder						
Decreased immune responsiveness						
Device allergy						
Drug hypersensitivity						
Dust allergy						
Hypersensitivity						
Immune system disorder						
Immunosuppression						
Milk allergy						
Multiple chemical sensitivity						
Mycotic allergy						
Reaction to excipient						
Sarcoidosis						
Seasonal allergy						
Sensitisation						
Smoke sensitivity						
Infections and infestations						
Abscess						
Abscess oral						
Acarodermatitis						
Acne pustular						
Acute sinusitis						
Appendicitis						
Appendicitis perforated						
Bacterial allergy						
Bacterial infection						
Bacterial rhinitis						
Blister infected						
Bronchiolitis						
Bronchitis						
Burn infection						
Candida infection						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Cholecystitis infective	(b) (4)					
Chorioretinitis						
Chronic sinusitis						
Chronic tonsillitis						
Complicated appendicitis						
Conjunctivitis						
Coronavirus infection						
COVID-19						
COVID-19 pneumonia						
Creutzfeldt-Jakob disease						
Cystitis						
Dermatitis infected						
Disseminated tuberculosis						
Diverticulitis						
Dysentery						
Ear infection						
Empyema						
Endocarditis						
Epiglottitis						
Erythema induratum						
Eye infection						
Folliculitis						
Fungal infection						
Fungal pharyngitis						
Furuncle						
Gangrene						
Gastroenteritis						
Gastroenteritis viral						
Gastrointestinal infection						
Gingival abscess						
Gingivitis						
Herpes dermatitis						
Herpes virus infection						
Herpes zoster						
Hordeolum						
Infected skin ulcer						
Infection						
Infection susceptibility increased						
Infective glossitis						
Influenza						
Injection site infection						
Labyrinthitis						
Laryngitis						
Lip infection						
Lower respiratory tract infection						
Lower respiratory tract infection fungal						
Lung abscess						
Mastitis						
Mumps						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Myringitis	(b) (4)					
Nasopharyngitis						
Oral bacterial infection						
Oral candidiasis						
Oral fungal infection						
Oral herpes						
Oral infection						
Oral pustule						
Osteomyelitis						
Otitis externa						
Otitis media						
Periodontitis						
Periorbital infection						
Peritonitis						
Peritonsillar abscess						
Pertussis						
Pharyngeal abscess						
Pharyngitis						
Pharyngitis bacterial						
Pharyngitis streptococcal						
Pharyngotonsillitis						
Pneumonia						
Pneumonia klebsiella						
Pneumonia pneumococcal						
Pneumonia viral						
Pulpitis dental						
Purulence						
Purulent discharge						
Pustule						
Rash pustular						
Respiratory tract infection						
Respiratory tract infection viral						
Rhinitis						
Sepsis						
Sialoadenitis						
Sinusitis						
Skin infection						
Sputum purulent						
Streptococcal infection						
Subcutaneous abscess						
Tetanus						
Tinea infection						
Tongue abscess						
Tongue fungal infection						
Tonsillitis						
Tonsillitis bacterial						
Tooth abscess						
Tooth infection						
Tracheitis						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Tracheobronchitis	(b) (4)					
Tuberculosis						
Upper respiratory fungal infection						
Upper respiratory tract infection						
Urinary tract infection						
Vestibular neuronitis						
Viral infection						
Viral pharyngitis						
Injury, poisoning and procedural complications						
Accident						
Accidental exposure to product						
Accidental exposure to product by child						
Accidental overdose						
Airway burns						
Alcohol poisoning						
Arthropod sting						
Back injury						
Bite						
Blast injury						
Burn oesophageal						
Burn of internal organs						
Burn oral cavity						
Burns first degree						
Burns second degree						
Burns third degree						
Carbon monoxide poisoning						
Chemical burn						
Chemical burn of oral cavity						
Chemical burn of respiratory tract						
Chemical poisoning						
Chillblains						
Clavicle fracture						
Cold burn						
Comminuted fracture						
Concussion						
Contusion						
Dental restoration failure						
Device difficult to use						
Device maintenance issue						
Device use error						
Device use issue						
Ear injury						
Electric shock						
Electrical burn						
Expired product administered						
Exposure during pregnancy						
Exposure to SARS-CoV-2						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Exposure to tobacco	(b) (4)					
Exposure to toxic agent						
Exposure via breast milk						
Exposure via eye contact						
Exposure via inhalation						
Eye contusion						
Eye injury						
Face injury						
Fall						
Foreign body						
Foreign body in eye						
Foreign body in gastrointestinal tract						
Foreign body in mouth						
Foreign body in respiratory tract						
Foreign body in throat						
Fracture displacement						
Gas poisoning						
Gingival injury						
Hair injury						
Head injury						
Heat stroke						
Incorrect route of product administration						
Inflammation of wound						
Injury						
Intentional device misuse						
Intentional overdose						
Intentional product misuse						
Intentional product use issue						
Intercepted wrong patient selecte						
Jaw fracture						
Joint dislocation						
Joint injury						
Lack of administration site rotation						
Laryngeal injury						
Ligament rupture						
Ligament sprain						
Limb injury						
Limb traumatic amputation						
Lip injury						
Maternal exposure during breast feeding						
Maternal exposure during pregnancy						
Maternal exposure timing unspecified						
Metal poisoning						
Mouth injury						
Mucosal excoriation						
Multiple injuries						
Muscle injury						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Muscle strain	(b) (4)					
Nail injury						
Nasal injury						
Nerve injury						
Nervous system injury						
Occupational exposure to product						
Oesophageal injury						
Oesophagitis chemical						
Off label use						
Oral contusion						
Overdose						
Palate injury						
Pharyngeal injury						
Plaque shift						
Pneumoconiosis						
Pneumonitis chemical						
Poisoning						
Post procedural complication						
Product administration error						
Product preparation error						
Product storage error						
Product use complaint						
Product use issue						
Respiratory fume inhalation disorder						
Retinal injury						
Rib fracture						
Road traffic accident						
Scar						
Scratch						
Silicosis						
Skeletal injury						
Skin abrasion						
Skin injury						
Skin laceration						
Skin wound						
Soft tissue foreign body						
Spinal column injury						
Sunburn						
Thermal burn						
Thermal burns of eye						
Tibia fracture						
Tobacco poisoning						
Tongue injury						
Tooth fracture						
Tooth injury						
Toxicity to various agents						
Tracheal injury						
Traumatic haematoma						
Traumatic lung injury						

MedDRA SOC MedDRA PT	Interval Non-	Cumulative Non-	Interval	Cumulative	Interval	Cumulative
Upper limb fracture	(b) (4)					
Vascular injury						
Wound						
Wound complication						
Wound haemorrhage						
Wound secretion						
Wrong technique in device usage process						
Wrong technique in product usage process						
Investigations						
Alanine aminotransferase increased						
Allergy test positive						
Amino acid level increased						
Aspartate aminotransferase						
Aspartate aminotransferase increased						
Biopsy palate abnormal						
Biopsy prostate abnormal						
Blood aluminium increased						
Blood bilirubin increased						
Blood carbon monoxide increased						
Blood cholesterol increased						
Blood count abnormal						
Blood creatinine increased						
Blood glucose abnormal						
Blood glucose decreased						
Blood glucose increased						
Blood immunoglobulin E increased						
Blood mercury abnormal						
Blood pressure abnormal						
Blood pressure decreased						
Blood pressure immeasurable						
Blood pressure increased						
Blood pressure systolic decreased						
Blood pressure systolic increased						
Blood test abnormal						
Blood triglycerides increased						
Blood urine						
Blood urine present						
Body mass index increased						
Body temperature abnormal						
Body temperature decreased						
Body temperature fluctuation						
Body temperature increased						
Breath sounds						
Breath sounds abnormal						
Breath sounds absent						
Cardiac murmur						
Cells in urine						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Chest X-ray abnormal	(b) (4)					
Clostridium test positive						
C-reactive protein increased						
Electrocardiogram abnormal						
Endoscopy upper gastrointestinal tract						
Epinephrine increased						
Gamma-glutamyltransferase increased						
Gastric pH decreased						
General physical condition abnormal						
Haemoglobin increased						
Heart rate						
Heart rate abnormal						
Heart rate decreased						
Heart rate increased						
Heart rate irregular						
Hepatic enzyme increased						
Histamine level increased						
Hormone level abnormal						
Immunoglobulins increased						
Inflammatory marker test						
Inspiratory capacity decreased						
Intraocular pressure increased						
Intraocular pressure test						
Investigation abnormal						
Laboratory test abnormal						
Liver function test abnormal						
Liver function test increased						
Lymph node palpable						
Magnetic resonance imaging ab						
Myocardial strain						
Nicotine test						
Occult blood negative						
Oxygen consumption decreased						
Oxygen consumption increased						
Oxygen saturation decreased						
Oxygen saturation increased						
Physical examination abnormal						
Platelet count decreased						
Product residue present						
Pulmonary function test decreased						
Pulse abnormal						
Pulse pressure increased						
Quality of life decreased						
Respiratory rate decreased						
Respiratory rate increased						
SARS-CoV-2 test negative						
Sputum abnormal						
Thyroid function test abnormal						
Thyroid hormones increased						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Total lung capacity decreased	(b) (4)					
Transaminases increased						
Urine viscosity increased						
Weight abnormal						
Weight decreased						
Weight increased						
White blood cell count decreased						
White blood cell count increased						
X-ray abnormal						
Metabolism and nutrition disorders						
Acidosis						
Appetite disorder						
Decreased appetite						
Dehydration						
Diabetes mellitus						
Diabetes mellitus inadequate control						
Diabetic complication						
Eating disorder symptom						
Feeding disorder						
Fluid intake reduced						
Fluid overload						
Fluid retention						
Food craving						
Glucose tolerance impaired						
Histamine intolerance						
Hyperglycaemia						
Hyperinsulinaemia						
Hyperlipidaemia						
Hyperphagia						
Hypoglycaemia						
Hypovitaminosis						
Increased appetite						
Ketoacidosis						
Lactose intolerance						
Metabolic disorder						
Obesity						
Polydipsia						
Poor feeding infant						
Type 2 diabetes mellitus						
Vitamin D deficiency						
Weight fluctuation						
Weight gain poor						
Weight loss poor						
Musculoskeletal and connective tissue disorders						
Antisynthetase syndrome						
Arthralgia						
Arthritis						
Arthropathy						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Back disorder	(b) (4)					
Back pain						
Bone disorder						
Bone pain						
Costochondritis						
Fibromyalgia						
Flank pain						
Fracture pain						
Groin pain						
Intervertebral disc protrusion						
Jaw disorder						
Joint contracture						
Joint noise						
Joint stiffness						
Joint swelling						
Limb discomfort						
Mastication disorder						
Mobility decreased						
Muscle contracture						
Muscle discomfort						
Muscle disorder						
Muscle spasms						
Muscle tightness						
Muscle twitching						
Muscular weakness						
Musculoskeletal chest pain						
Musculoskeletal discomfort						
Musculoskeletal disorder						
Musculoskeletal pain						
Musculoskeletal stiffness						
Myalgia						
Myokymia						
Myositis						
Neck mass						
Neck pain						
Osteitis						
Osteoarthritis						
Osteochondrosis						
Pain in extremity						
Pain in jaw						
Plantar fasciitis						
Posture abnormal						
Rheumatoid arthritis						
Spinal disorder						
Spinal pain						
Tendon pain						
Tendonitis						
Trismus						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	(b) (4)					
Adenoma benign						
Benign neoplasm						
Brain neoplasm						
Brain neoplasm malignant						
Cancer in remission						
Cancer pain						
Hepatic neoplasm						
Laryngeal papilloma						
Leukaemia						
Lipoma						
Lung adenocarcinoma						
Lung adenocarcinoma stage II						
Lung cancer metastatic						
Lung neoplasm						
Lung neoplasm malignant						
Lymphoma						
Melanocytic naevus						
Metastases to central nervous system						
Metastases to liver						
Metastases to lung						
Neoplasm						
Neoplasm malignant						
Neoplasm skin						
Pancreatic carcinoma						
Papilloma						
Pharyngeal neoplasm						
Prostate cancer						
Rectal cancer						
Recurrent cancer						
Skin papilloma						
Throat cancer						
Thyroid cancer						
Tongue neoplasm						
Tongue neoplasm malignant stage unspecified						
Nervous system disorders						
Ageusia						
Akathisia						
Altered state of consciousness						
Amnesia						
Anosmia						
Aphasia						
Ataxia						
Autonomic nervous system imbalance						
Balance disorder						
Bradykinesia						
Brain stem infarction						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Burning sensation	(b) (4)					
Burning sensation mucosal						
Carotid artery stenosis						
Cerebral disorder						
Cerebral haemorrhage						
Cerebral hypoperfusion						
Cerebral infarction						
Cerebral microinfarction						
Cerebral vasoconstriction						
Cerebrovascular accident						
Cerebrovascular disorder						
Cervicogenic headache						
Circadian rhythm sleep disorder						
Clumsiness						
Cluster headache						
Cognitive disorder						
Coma						
Coordination abnormal						
Depressed level of consciousness						
Disturbance in attention						
Dizziness						
Dizziness exertional						
Dizziness postural						
Dreamy state						
Drooling						
Dysarthria						
Dysgeusia						
Dysgraphia						
Dyskinesia						
Dysstasia						
Dystonia						
Epilepsy						
Exaggerated startle response						
Facial paralysis						
Facial paresis						
Facial spasm						
Formication						
Haemorrhage intracranial						
Hand-eye coordination impaired						
Head discomfort						
Head titubation						
Headache						
Hemianaesthesia						
Hemiplegia						
Hyperaesthesia						
Hypersomnia						
Hypertonia						
Hypoaesthesia						
Hypogeusia						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Hypokinesia	(b) (4)					
Hyporeflexia						
Hyposmia						
Hypotonia						
Infant irritability						
Intracranial pressure increased						
Lethargy						
Loss of consciousness						
Memory impairment						
Meningeal disorder						
Mental impairment						
Migraine						
Migraine with aura						
Monoplegia						
Motor dysfunction						
Movement disorder						
Myoclonus						
Nervous system disorder						
Neuralgia						
Neurological symptom						
Neurotoxicity						
Nystagmus						
Paraesthesia						
Paraesthesia mucosal						
Paraparesis						
Parosmia						
Patient elopement						
Post-traumatic epilepsy						
Presyncope						
Psychomotor hyperactivity						
Reflexes abnormal						
Sedation						
Seizure						
Sensory disturbance						
Sensory loss						
Sinus headache						
Sleep deficit						
Slow speech						
Somnolence						
Speech disorder						
Stupor						
Syncope						
Taste disorder						
Tension headache						
Thermohypoaesthesia						
Tongue paralysis						
Transient ischaemic attack						
Tremor						
Unresponsive to stimuli						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Uvular spasm	(b) (4)					
Vibratory sense increased						
Visual perseveration						
Visuospatial deficit						
Vocal cord paralysis						
Pregnancy, puerperium and perinatal conditions						
Abortion of ectopic pregnancy						
Abortion spontaneous						
Ectopic pregnancy						
Imminent abortion						
Morning sickness						
Normal newborn						
Pregnancy						
Product issues						
Device battery explosion						
Device breakage						
Device catching fire						
Device colour issue						
Device connection issue						
Device defective						
Device delivery system issue						
Device deposit issue						
Device electrical finding						
Device failure						
Device inappropriate shock delivery						
Device issue						
Device leakage						
Device malfunction						
Device material issue						
Device occlusion						
Device pacing issue						
Device physical property issue						
Device power source issue						
Device temperature issue						
Manufacturing issue						
Manufacturing production issue						
Out of specification test results						
Physical product label issue						
Product adhesion issue						
Product availability issue						
Product caught fire						
Product coating issue						
Product colour issue						
Product complaint						
Product contamination						
Product deposit						
Product distribution issue						
Product label issue						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Product leakage	(b) (4)					
Product odour abnormal						
Product physical consistency issue						
Product physical issue						
Product quality issue						
Product size issue						
Product substitution issue						
Product taste abnormal						
Suspected counterfeit product						
Suspected product quality issue						
Undersensing						
Psychiatric disorders						
Abnormal dreams						
Adjustment disorder						
Adjustment disorder with depressed mood						
Affect lability						
Affective disorder						
Aggression						
Agitation						
Anger						
Anhedonia						
Anxiety						
Anxiety disorder						
Apathy						
Attention deficit hyperactivity disorder						
Aversion						
Behavioural addiction						
Bipolar disorder						
Bradyphrenia						
Breathing-related sleep disorder						
Bruxism						
Completed suicide						
Confusional state						
Daydreaming						
Decreased eye contact						
Decreased interest						
Dependence						
Depressed mood						
Depression						
Depressive symptom						
Disinhibition						
Disorientation						
Distractibility						
Drug dependence						
Dysphemia						
Dysphoria						
Eating disorder						
Emotional disorder						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Emotional distress	(b) (4)					
Euphoric mood						
Factitious disorder						
Fear						
Fear of death						
Feeling guilty						
Feeling of despair						
Feelings of worthlessness						
Frustration tolerance decreased						
Hallucination						
Hallucination, auditory						
Hallucination, visual						
Illness anxiety disorder						
Impatience						
Inappropriate affect						
Indifference						
Initial insomnia						
Insomnia						
Intentional self-injury						
Irritability						
Laziness						
Libido decreased						
Listless						
Mental disorder						
Mental fatigue						
Mental status changes						
Middle insomnia						
Mood altered						
Mood swings						
Morbid thoughts						
Nervousness						
Neurosis						
Nicotine dependence						
Nightmare						
Obsessive-compulsive disorder						
Panic attack						
Panic disorder						
Panic reaction						
Paranoia						
Personality change						
Poor quality sleep						
Psychotic disorder						
Restlessness						
Self esteem decreased						
Sleep disorder						
Sleep disorder due to general medical condition, insomnia type						
Speech sound disorder						
Stress						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Suicidal ideation	(b) (4)					
Suicide attempt						
Tension						
Terminal insomnia						
Thinking abnormal						
Tic						
Tobacco abuse						
Tobacco withdrawal symptoms						
Renal and urinary disorders						
Bladder irritation						
Bladder leukoplakia						
Calculus urinary						
Chromaturia						
Dysuria						
Incontinence						
Micturition disorder						
Micturition urgency						
Nephrolithiasis						
Pollakiuria						
Polyuria						
Renal disorder						
Renal failure						
Renal pain						
Urinary incontinence						
Urinary retention						
Urinary tract discomfort						
Urine odour abnormal						
Reproductive system and breast disorders						
Adnexa uteri pain						
Breast discomfort						
Breast inflammation						
Breast pain						
Breast tenderness						
Cervical friability						
Dysmenorrhoea						
Erectile dysfunction						
Erection increased						
Genital discomfort						
Menometrorrhagia						
Menstrual disorder						
Menstruation delayed						
Menstruation irregular						
Nipple swelling						
Oligomenorrhoea						
Organic erectile dysfunction						
Pelvic pain						
Penile discharge						
Prostatic disorder						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Prostatitis	(b) (4)					
Sexual dysfunction						
Spontaneous penile erection						
Suppressed lactation						
Testicular swelling						
Uterine disorder						
Uterine haemorrhage						
Vaginal flatulence						
Respiratory, thoracic and mediastinal disorders						
Adenoidal hypertrophy						
Allergic bronchitis						
Allergic cough						
Allergic sinusitis						
Alveolar proteinosis						
Alveolitis						
Anoxia						
Aphonia						
Apnoea						
Apnoeic attack						
Asphyxia						
Aspiration						
Asthma						
Asthmatic crisis						
Bronchial disorder						
Bronchial hyperreactivity						
Bronchial irritation						
Bronchial obstruction						
Bronchial oedema						
Bronchial secretion retention						
Bronchial varices						
Bronchiectasis						
Bronchitis chronic						
Bronchospasm						
Bronchostenosis						
Catarrh						
Choking						
Choking sensation						
Chronic obstructive pulmonary disease						
Chronic respiratory disease						
Cough						
Cough decreased						
Cough variant asthma						
Cystic lung disease						
Decreased bronchial secretion						
Diaphragmalgia						
Diaphragmatic disorder						
Dry throat						
Dysphonia						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Dyspnoea	(b) (4)					
Dyspnoea at rest						
Dyspnoea exertional						
Emphysema						
Eosinophilic pneumonia acute						
Epiglottic cyst						
Epistaxis						
Haemoptysis						
Hiccups						
Hyperactive pharyngeal reflex						
Hyperventilation						
Hypopnoea						
Hypoxia						
Increased bronchial secretion						
Increased upper airway secretion						
Increased viscosity of bronchial secretion						
Increased viscosity of upper respiratory secretion						
Irregular breathing						
Laryngeal discomfort						
Laryngeal disorder						
Laryngeal inflammation						
Laryngeal obstruction						
Laryngeal oedema						
Laryngeal pain						
Laryngeal ulceration						
Laryngitis allergic						
Laryngospasm						
Larynx irritation						
Lower respiratory tract congestion						
Lung disorder						
Lung hyperinflation						
Lung infiltration						
Mouth breathing						
Nasal congestion						
Nasal crusting						
Nasal cyst						
Nasal discharge discolouration						
Nasal discomfort						
Nasal disorder						
Nasal dryness						
Nasal inflammation						
Nasal mucosal blistering						
Nasal mucosal discolouration						
Nasal mucosal disorder						
Nasal mucosal ulcer						
Nasal obstruction						
Nasal odour						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Nasal oedema	(b) (4)					
Nasal polyps						
Nasal pruritus						
Nasal septum disorder						
Nasal ulcer						
Nocturnal dyspnoea						
Obstructive airways disorder						
Oropharyngeal blistering						
Oropharyngeal discolouration						
Oropharyngeal discomfort						
Oropharyngeal pain						
Oropharyngeal plaque						
Oropharyngeal scar						
Oropharyngeal spasm						
Oropharyngeal swelling						
Painful respiration						
Paranasal sinus discomfort						
Paranasal sinus hyposecretion						
Paranasal sinus inflammation						
Pharyngeal cyst						
Pharyngeal disorder						
Pharyngeal enanthema						
Pharyngeal erythema						
Pharyngeal exudate						
Pharyngeal haemorrhage						
Pharyngeal hypoaesthesia						
Pharyngeal inflammation						
Pharyngeal lesion						
Pharyngeal mass						
Pharyngeal oedema						
Pharyngeal paraesthesia						
Pharyngeal swelling						
Pharyngeal ulceration						
Pleural effusion						
Pleural thickening						
Pleuritic pain						
Pneumonitis						
Pneumothorax						
Pneumothorax spontaneous						
Productive cough						
Pulmonary calcification						
Pulmonary congestion						
Pulmonary embolism						
Pulmonary fibrosis						
Pulmonary haemorrhage						
Pulmonary infarction						
Pulmonary mass						
Pulmonary oedema						
Pulmonary pain						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Pulmonary sarcoidosis	(b) (4)					
Rales						
Reflux laryngitis						
Respiration abnormal						
Respiratory arrest						
Respiratory depression						
Respiratory disorder						
Respiratory disorder neonatal						
Respiratory distress						
Respiratory failure						
Respiratory fatigue						
Respiratory muscle weakness						
Respiratory symptom						
Respiratory tract congestion						
Respiratory tract inflammation						
Respiratory tract irritation						
Respiratory tract oedema						
Rhinalgia						
Rhinitis allergic						
Rhinitis atrophic						
Rhinorrhoea						
Rhonchi						
Sinus congestion						
Sinus disorder						
Sinus pain						
Sleep apnoea syndrome						
Sneezing						
Snoring						
Sputum discoloured						
Sputum increased						
Sputum retention						
Suffocation feeling						
Tachypnoea						
Throat clearing						
Throat irritation						
Throat lesion						
Throat tightness						
Tonsillar cyst						
Tonsillar disorder						
Tonsillar erythema						
Tonsillar exudate						
Tonsillar haemorrhage						
Tonsillar hypertrophy						
Tonsillar inflammation						
Tonsillar ulcer						
Tonsillolith						
Tracheal disorder						
Tracheal inflammation						
Tracheal oedema						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Tracheal pain	(b) (4)					
Upper airway obstruction						
Upper respiratory tract congestion						
Upper respiratory tract inflammation						
Upper respiratory tract irritation						
Upper-airway cough syndrome						
Vasomotor rhinitis						
Vocal cord disorder						
Vocal cord dysfunction						
Vocal cord inflammation						
Vocal cord polyp						
Vocal cord thickening						
Wheezing						
Yawning						
Skin and subcutaneous tissue disorders						
Acne						
Acne cystic						
Acne varioliformis						
Alopecia						
Angioedema						
Blister						
Blister rupture						
Blood blister						
Circumoral oedema						
Cold sweat						
Cold urticaria						
Dandruff						
Decubitus ulcer						
Dermal cyst						
Dermatitis						
Dermatitis acneiform						
Dermatitis allergic						
Dermatitis atopic						
Dermatitis bullous						
Dermatitis contact						
Dilated pores						
Dry skin						
Dyshidrotic eczema						
Eczema						
Erythema						
Erythema nodosum						
Haemorrhage subcutaneous						
Hair colour changes						
Hair disorder						
Hair texture abnormal						
Hand dermatitis						
Hidradenitis						
Hyperhidrosis						
Hyperkeratosis						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Keratosis pilaris	(b) (4)					
Leukoplakia						
Lichen planus						
Lichenification						
Livedo reticularis						
Madarosis						
Mechanical urticaria						
Miliaria						
Nail bed bleeding						
Nail bed inflammation						
Nail discolouration						
Nail disorder						
Nail hypertrophy						
Neurodermatitis						
Night sweats						
Occupational dermatitis						
Oedema blister						
Onychoclasis						
Onycholysis						
Pain of skin						
Palmar erythema						
Palmoplantar pustulosis						
Papule						
Perioral dermatitis						
Petechiae						
Photosensitivity reaction						
Pigmentation disorder						
Piloerection						
Pityriasis rosea						
Pruritus						
Pruritus allergic						
Psoriasis						
Purpura						
Rash						
Rash erythematous						
Rash follicular						
Rash macular						
Rash papular						
Rash pruritic						
Rash vesicular						
Rosacea						
Scab						
Scar pain						
Sebaceous gland disorder						
Sebaceous glands overactivity						
Seborrhoea						
Seborrhoeic dermatitis						
Sensitive skin						
Skin atrophy						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Skin burning sensation	(b) (4)					
Skin depigmentation						
Skin discolouration						
Skin discomfort						
Skin disorder						
Skin exfoliation						
Skin fissures						
Skin haemorrhage						
Skin hypertrophy						
Skin induration						
Skin irritation						
Skin lesion						
Skin mass						
Skin necrosis						
Skin odour abnormal						
Skin plaque						
Skin reaction						
Skin striae						
Skin swelling						
Skin tightness						
Skin ulcer						
Skin weeping						
Skin wrinkling						
Solar lentigo						
Spider naevus						
Sticky skin						
Urticaria						
Urticaria chronic						
Xeroderma						
Yellow skin						
Social circumstances						
Alcohol use						
Bedridden						
Crime						
Ex-tobacco user						
Impaired driving ability						
Impaired work ability						
Loss of personal independence in daily activities						
Non-tobacco user						
Passive smoking						
Patient dissatisfaction with device						
Patient dissatisfaction with treatment						
Patient uncooperative						
Pollution						
Primigravida						
Tobacco user						
Unhealthy diet						
Wheelchair user						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Surgical and medical procedures	(b) (4)					
Cardiac operation						
Cardioversion						
Dental disorder prophylaxis						
Dental operation						
Endodontic procedure						
Gingival operation						
Hospitalisation						
Infusion						
Injection						
Lung lobectomy						
Lung operation						
Lymphadenectomy						
Mechanical ventilation						
Nerve block						
Oxygen therapy						
Routine health maintenance						
Salivary gland resection						
Skin graft						
Surgery						
Thyroid operation						
Tonsillectomy						
Tooth extraction						
Vocal cord operation						
Wisdom teeth removal						
Wound drainage						
Vascular disorders						
Aneurysm						
Angiopathy						
Arterial occlusive disease						
Arterial rupture						
Arterial spasm						
Arteriosclerosis						
Blood pressure fluctuation						
Bloody discharge						
Capillary disorder						
Capillary fragility						
Circulatory collapse						
Cyanosis						
Embolism						
Flushing						
Haematoma						
Haemorrhage						
Hot flush						
Hyperaemia						
Hypertension						
Hypertensive crisis						
Hypotension						
Infarction						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Internal haemorrhage	(b) (4)					
Jugular vein distension						
Labile blood pressure						
Lymphoedema						
Orthostatic hypotension						
Pallor						
Peripheral artery occlusion						
Peripheral coldness						
Peripheral vascular disorder						
Phlebitis						
Poor peripheral circulation						
Raynaud's phenomenon						
Shock						
Superficial vein prominence						
Thrombophlebitis						
Thrombosis						
Varicose vein						
Vascular insufficiency						
Vascular occlusion						
Vascular pain						
Vascular rupture						
Vascular stenosis						
Vasculitis						
Vasoconstriction						
Vasodilatation						
Vasospasm						
Vein disorder						
Vein rupture						
Venous occlusion						
Total						

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	(b) (4)						
Chest discomfort							
Rash							
Chest pain							
Urticaria							
Epistaxis							
Bacterial pneumonia							
Acute Eosinophilic Pneumonia							

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
	(b) (4)						

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

Study Protocol Number	Study title	Country	Study start	Status
(b) (4)	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
(b) (4)	A mixed methods study using qualitative interviews in the US & UK and quantitative exploratory analysis to evaluate content validity of the ABOUT-Health and Functioning questionnaire for users of tobacco and/or nicotine products	UK, US	03-Jun-2020	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).

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-2021 to 31-Dec-2021 and cumulatively from 30-Apr-2019 to 31-Dec-2021. The summary tabulation of identified AEs organized by MedDRA SOC is presented in Table 18-1. Of note, none of the spontaneous reports received by PMI during the reporting period were medically confirmed, i.e. they were received from consumers directly and not via HCPs.

A total of (b) (4) non-serious AEs was received from (b) (4) ICSRs in the U.S. during the reporting period. The most frequently reported AEs (b) (4) were: Cough (b) (4) Product complaint (b) (4) Nausea (b) (4) Oropharyngeal pain (b) (4) and Headache (b) (4)). No SAEs were received from the U.S. during the period covered by this SUR. As mentioned in the SPI version 6.0 for THS (dated 25-May-2021), Cough, Nausea, Oropharyngeal pain, and Headache are already known class effect AEs associated with the use of nicotine-containing products.

The most represented SOCs (b) (4)) were: Product issues (b) (4) Respiratory, thoracic and mediastinal disorders (b) (4) Gastrointestinal disorders (b) (4)), Nervous system disorders (b) (4) Injury, poisoning and procedural complications (b) (4) and General disorders and administration site conditions (b) (4) .

Cumulatively, there were (b) (4) non-serious AEs received from (b) (4) ICSRs in the U.S. Cumulatively, (b)) 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	(b) (4)					
Palpitations						
Gastrointestinal disorders						
Abdominal discomfort						
Abdominal distension						
Abdominal pain upper						
Chapped lips						
Cheilitis						
Coating in mouth						
Diarrhoea						
Dry mouth						
Dyspepsia						
Dysphagia						
Glossitis						
Nausea						
Oral discomfort						
Retching						
Stomatitis						
Swollen tongue						
Tongue disorder						
General disorders and administration site conditions						
Chest discomfort						
Chest pain						
Fatigue						
Feeling abnormal						
No adverse event						
Pain						
Unevaluable event						
Hepatobiliary disorders						
Hepatic pain						
Immune system disorders						
Hypersensitivity						
Infections and infestations						
Pharyngitis streptococcal						
Injury, poisoning and procedural complications						
Accidental exposure to product by child						
Burn oral cavity						
Device difficult to use						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Exposure during pregnancy	(b) (4)					
Intentional product misuse						
Thermal burn						
Investigations						
Blood pressure increased						
Heart rate increased						
Hormone level abnormal						
Transaminases increased						
Nervous system disorders						
Anosmia						
Burning sensation						
Dizziness						
Dysgeusia						
Headache						
Somnolence						
Taste disorder						
Product issues						
Device breakage						
Device issue						
Device malfunction						
Device physical property issue						
Product complaint						
Product distribution issue						
Product odour abnormal						
Product physical issue						
Product quality issue						
Product taste abnormal						
Psychiatric disorders						
Agitation						
Anxiety						
Confusional state						
Irritability						
Nicotine dependence						
Panic attack						
Sleep disorder						
Respiratory, thoracic and mediastinal disorders						
Asthma						
Cough						
Dysphonia						
Dyspnoea						
Epistaxis						
Nasal discomfort						

MedDRA SOC MedDRA PT	Interval Non-serious	Cumulative Non-serious	Interval Serious	Cumulative Serious	Interval Total	Cumulative Total
Oropharyngeal discomfort	(b) (4)					
Oropharyngeal pain						
Respiratory tract irritation						
Snoring						
Throat irritation						
Throat tightness						
Vascular disorders						
Cyanosis						
Total						

18.6 Appendix 6: Signatures

PMI_SURV_2022_SUR01

Period Covered: 01-Jan-2021 to 31-Dec-2021

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

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

Justification	**Name/*Title***	**Signature**	**Date**
Author	(b) (4), (b) (6) ***Senior Safety Lead***	(b) (4), (b) (6)	Apr 19, 2022
Review	(b) (4), (b) (6) ***Manager Medical Operations***		Apr 19, 2022
Approval	(b) (4), (b) (6) ***Global Head Safety Surveillance***		Apr 19, 2022
Approval	(b) (4), (b) (6) ***Chief Medical Officer***		Apr 19, 2022

IQOS Sur2021 US

Final Audit Report 2022-04-19

Created:	2022-04-19
By:	(b) (4), (b) (6)
Status:	Signed
Transaction ID:	(b) (4), (b) (6)

"IQOS Sur2021 US" History

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Agreement completed.
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