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PMI RESEARCH & DEVELOPMENT

THS Additional Safety Data Report

Tobacco Heating System / iQOS

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LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event: Any health-related event associated with the use of a tobacco product in humans that is adverse or unfavorable, whether or not it is considered tobacco-product related (FDA 2012: MRTPA Draft Guidance).
AER	Adverse Event Report
CC	Conventional Cigarettes
FDA	Food and Drug Administration
ICSR	Individual Case Safety Report
iQOS system	iQOS is the brand name of THS
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PBA	Perception and Behavior Assessment
PMI	Philip Morris International
PT	Preferred Term (MedDRA)
SA	Smoking Abstinence
SAE	Serious Adverse Event: A serious adverse event is an adverse event that results in any of the following: death; a life-threatening condition or event; persistent or substantial disability or incapacitation; hospitalization or prolonged hospitalization; or a congenital anomaly or birth defect (FDA 2012: MRTPA Draft Guidance).
SOC	System Organ Class (MedDRA)
THS	Tobacco Heating System
USA	United States of America

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1 INTRODUCTION

This is the THS Additional Safety Data Report prepared for Tobacco Heating Systems 2.2 and 2.4 (THS) Regular and Menthol (THS Menthol) all variants, herein referred to as THS products, summarizing relevant safety data received by Philip Morris International (PMI, herein referred to as the Company, complementary to the THS Safety Update Report 2016 issued 19-Apr-2016.

Section 2 includes the FDA 3500A (MedWatch) Forms for all the individual Serious Adverse Events (SAEs) reported until 30 April 2016 from THS 2.2 clinical studies (8 completed studies and 2 ongoing studies)

Section 3 includes the cumulative summary tables and line listings of THS-emergent adverse events from pre-market safety surveillance, covering six market research studies and one perception and behavior study. The safety data was collected until 31 March 2016. Summary tables and line listings are provided per THS variants.

Section 4 includes the the cumulative summary tables and line listings of THS-emergent adverse events from post-market safety surveillance outside USA, collected until safety data lock point of 31 December 2015. Summary tables and line listings are provided per THS variants.

The summary tabulations and the line listings were generated from the Company Safety database. Argus Pharmacovigilance database was searched for individual case safety reports (ICSRs; also called “cases”) reported from pre-market studies and post-market safety surveillance to the Company.

NOTE

In Argus Safety Database:

- For THS Regular variants, THS Regular Dorado II Fitz was identified as product variant for pre-market study P1_WOT1_KO and was consequently identified as THS Dorado II Ron in Company’s Product Development database.
- For THS Menthol variants, THS Menthol Vinny/Ron was identified as product variant for pre-market studies P1_WOT1_CH and P1_WOT2_IT and was consequently identified as THS Dorado I Vinny Low Menthol in Company’s Product Development database.

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2 SAE INDIVIDUAL CASE SAFETY REPORTS FROM CLINICAL STUDIES

Table 1 lists all individual case safety reports for serious adverse events which occurred during the course of completed and ongoing clinical studies and reported until 30-April-2016.

Table 1 List of SAE Individual Case Safety Reports

Safety Case #	Study code	Preferred term, Latest Update, Date	Case Status
PMI000007	ZRHM-REXA-08-US	Diabetic ketoacidosis, Sinusitis, Follow-up 4, 26 Feb 2015	Closed
PMI000350	ZRHR-ERS-09-US	Metastases to small intestine, Anaemia, Follow-up 4, 17 Feb 2016	Closed
PMI000360	ZRHR-ERS-09-US	Urosepsis, Pyelonephritis acute, Nephrolithiasis, Follow-up 4, 12 Feb 2016	Closed
PMI000369	ZRHR-ERS-09-US	Papillary thyroid cancer, Follow-up 3, 5 Feb 2016	Further information expected
PMI000385	ZRHR-ERS-09-US	Vertebral osteophyte, Cervical myelopathy, Follow-up 1, 25 Jan 2016	Closed
PMI000452	ZRHR-ERS-09-US	Alcohol abuse, Follow-up 3, 22 Apr 2016	Closed
PMI000463	ZRHR-ERS-09-US	Loss of consciousness, Head injury, Seizure, Follow-up 2, 22 Apr 2016	Closed
PMI000466	ZRHR-ERS-09-US	Head injury, Follow-up 1, 29 Jan 2016	Further information expected
PMI000467	ZRHR-ERS-09-EXT-US	Cellulitis staphylococcal, Follow-up 4, 22 Apr 2016	Closed
PMI000470	ZRHR-ERS-09-EXT-US*	Laceration, Initial, 25 Jan 2016	Further information expected
PMI000482	ZRHR-ERS-09-EXT-US	Breast cancer, Follow-up 2, 31 Mar 2016	Further information expected
PMI000500	ZRHR-ERS-09-EXT-US	Costochondritis, Follow-up 1, 24 Mar 2016	Closed
PMI000507	ZRHR-ERS-09-US	Suicidal ideation, Follow-up 1, 5 Apr 2016	Further information expected

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Safety Case #	Study code	Preferred term, Latest Update, Date	Case Status
PMI000511	ZRHR-ERS-09-US	Pneumonia mycoplasmal, Initial, 3 Mar 2016	Further information expected
PMI000514	ZRHR-ERS-09-US	Grief reaction, Initial, 7 Mar 2016	Further information expected
PMI000518	ZRHR-ERS-09-EXT-US	Epiglottitis, Follow-up 2, 22 Apr 2016	Further information expected
PMI000551	ZRHR-ERS-09-EXT-US	Influenza, Follow-up 1, 22 Apr 2016	Further information expected
PMI000553	ZRHR-ERS-09-US	Tooth infection, Follow-up 1, 22 Apr 2016	Closed
PMI000559	ZRHR-ERS-09-EXT-US	Blood triglycerides increased, Follow-up 1, 27 Apr 2016	Further information expected
PMI000627	ZRHR-ERS-09-EXT-US	Appendicitis, Initial, 02 May 2016**	Further information expected

* Case PMI000470 was reported during ZRHR-ERS-09-EXT-US study but occurred apparently during ZRHR-ERS-09-US study

**Case was initially reported by the Investigator on 22 Apr 2016 (D0) and the initial Medwatch report was produced on 02 May 2016

See [Appendix 1](#) for full CIOMS/MedWatch reports

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3 PRE-MARKETING SAFETY SURVEILLANCE

3.1 Tables of THS Product Use in Pre-Marketing Studies

Table 2 THS Product variant Use per Study

Study	Product	Product variant	Sample size
P1_WOT1_KO	THS 2.2 Regular	Dorado II/Ron	357
	THS 2.2 Regular	Other than THS Dorado II/Ron	605
	THS 2.2 Menthol	Dorado I/Vinny Low Menthol	592
Total P1_WOT1_KO	NA	NA	1'316
P1_WOT2_IT	THS 2.2 Regular	Dorado II/Ron	292
	THS 2.2 Menthol	Dorado I/Vinny Low Menthol	310
	THS 2.2 Regular and THS 2.2 Menthol ¹	Dorado II/Ron and Dorado I/Vinny Low Menthol	41
Total P1_WOT2_IT	NA	NA	643
P1_WOT1_DE	THS 2.2 Regular	Dorado II/Ron	298
	THS 2.2 Regular	Dorado II/Ron	295
Total P1_WOT1_DE	NA	NA	593
P1_WOT1_CH	THS 2.2 Regular	Dorado II/Ron	344
	THS 2.2 Menthol	Dorado I/Vinny Low Menthol	236
Total P1_WOT1_CH	NA	NA	580

¹ Respondents used both THS regular and THS Menthol.

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Study	Product	Product variant	Sample size
P1_BT1_RU	THS 2.4 Regular	Scion 1/Walt	309
	THS 2.4 Regular	Scion 1/Fitz	302
Total P1_BT1_RU	NA	NA	611
P1_BT1_IT	THS 2.2 Regular	Other than THS Dorado II/Ron	206
	THS 2.2 Regular	Other than THS Dorado II/Ron	211
	THS 2.2 Regular	Dorado II/Ron	210
	THS 2.2 Regular	Other than THS Dorado II/Ron	209
	THS 2.2 Menthol	Other than THS Dorado I/Vinny Low Menthol	211
Total P1_BT1_IT	NA	NA	1'047
THS_PBA_07_US	THS 2.2 Regular	Dorado II/Ron	441
	THS 2.2 Menthol	Dorado I/Vinny Low Menthol	512
	THS 2.2 Regular and THS 2.2 Menthol ²	Dorado II/Ron and Dorado I/Vinny Low Menthol	205
Total P1_PBA_07	NA	NA	1'158

Table 3 Overall THS Products Use in Pre-Marketing Studies

Product	Product variant	Sample size
THS Regular	THS Dorado II/Ron	2'237
	Other than THS Regular THS Dorado II/Ron	1'842
Total THS Regular	NA	4'079

² Respondents used both THS regular and THS Menthol.**Confidentiality Statement**

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Product	Product variant	Sample size
THS Menthol	THS Dorado I/Vinny Low Menthol	1'650
	Other than THS Dorado I/Vinny Low Menthol	211
Total THS Menthol	NA	1'861
THS Regular and THS Menthol	Dorado II/Ron and Dorado I/Vinny Low Menthol	246
Total THS Product Use		6'186

3.2 Cumulative Summary Tabulations

3.2.1 THS Regular Products

3.2.1.1 Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for All THS Regular Products

3.2.1.2 Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for THS Dorado II/Ron

3.2.1.3 Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for THS Regular other than THS Dorado II/Ron

See [Appendix 2](#)

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3.2.2 THS Menthol Products

3.2.2.1 Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for All THS Menthol Products

3.2.2.2 Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for THS Dorado I/Vinny Low Menthol

3.2.2.3 Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for THS Menthol other than THS Dorado I/Vinny Low Menthol

See [Appendix 3](#)

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3.3 Cumulative Line Listings

3.3.1 THS Regular Products

3.3.1.1 Cumulative Line Listings of Serious and Non-Serious Adverse Events for All THS Regular Products

3.3.1.2 Cumulative Line Listings of Serious and Non-Serious Adverse Events for THS Dorado II/Ron

3.3.1.3 Cumulative Line Listings of Serious and Non-Serious Adverse Events for THS Regular other than THS Dorado II/Ron

See [Appendix 4](#)

3.3.2 THS Menthol Products

3.3.2.1 Cumulative Line Listings of Serious and Non-Serious Adverse Events for All THS Menthol Products

3.3.2.2 Cumulative Line Listings of Serious and Non-Serious Adverse Events for THS Dorado I/Vinny Low Menthol

3.3.2.3 Cumulative Line Listings of Serious and Non-Serious Adverse Events for THS Menthol other than THS Dorado I/Vinny Low Menthol

See [Appendix 5](#)

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4 POST-MARKETING SAFETY SURVEILLANCE

4.1 Cumulative Summary Tabulations

4.1.1 Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events from Spontaneous Reports for All THS Regular Products

4.1.2 Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events from Spontaneous Reports for All THS Menthol Products

4.1.3 Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events from Spontaneous Reports for All IQOS unspecified

See [Appendix 6](#)

4.2 Cumulative Line Listings

4.2.1 Cumulative Line Listing of Serious and Non-Serious Adverse Events from Spontaneous Reports for All THS Regular Products

4.2.2 Cumulative Line Listing of Serious and Non-Serious Adverse Events from Spontaneous Reports for All THS Menthol Products

4.2.3 Cumulative Line Listing of Serious and Non-Serious Adverse Events from Spontaneous Reports for All IQOS unspecified

See [Appendix 7](#)

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5 APPENDICES

[Appendix 1](#) : CIOMS/MedWatch reports for SAE Individual Case Safety reports from clinical studies

[Appendix 2](#) : Pre-marketing Cumulative Summary Tabulations THS Regular Products

Appendix 2.1: Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for All THS Regular Products

Appendix 2.2: Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for THS Dorado II/Ron

Appendix 2.3: Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for THS Regular other than THS Dorado II/Ron

[Appendix 3](#) : Pre-marketing Cumulative Summary Tabulations THS Menthol Products

Appendix 3.1: Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for All THS Menthol Products

Appendix 3.2: Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for THS Dorado I/Vinny Low Menthol

Appendix 3.3: Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events for THS Menthol other than THS Dorado I/Vinny Low Menthol

[Appendix 4](#) : Pre-marketing Cumulative Line Listings THS Regular Products

Appendix 4.1: Cumulative Line Listings of Serious and Non-Serious Adverse Events for All THS Regular Products

Appendix 4.2: Cumulative Line Listings of Serious and Non-Serious Adverse Events for THS Dorado II/Ron

Appendix 4.3: Cumulative Line Listings of Serious and Non-Serious Adverse Events for THS Regular other than THS Dorado II/Ron

[Appendix 5](#) : Pre-marketing Cumulative Line Listings THS Menthol Products

Appendix 5.1: Cumulative Line Listings of Serious and Non-Serious Adverse Events for All THS Menthol Products

Appendix 5.2: Cumulative Line Listings of Serious and Non-Serious Adverse Events for THS Dorado I/Vinny Low Menthol

Appendix 5.3: Cumulative Line Listings of Serious and Non-Serious Adverse Events for THS Menthol other than THS Dorado I/Vinny Low Menthol

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Appendix 6 : Post-marketing Cumulative Summary Tabulations

Appendix 6.1: Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events from Spontaneous Reports for All THS Regular Products

Appendix 6.2: Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events from Spontaneous Reports for All THS Menthol Products

Appendix 6.3: Cumulative Summary Tabulation of Serious and Non-Serious Adverse Events from Spontaneous Reports for All IQOS unspecified

Appendix 7 : Post-marketing Cumulative Line Listings

Appendix 7.1: Cumulative Line Listing of Serious and Non-Serious Adverse Events from Spontaneous Reports for All THS Regular Products

Appendix 7.2: Cumulative Line Listing of Serious and Non-Serious Adverse Events from Spontaneous Reports for All THS Menthol Products

Appendix 7.3: Cumulative Line Listing of Serious and Non-Serious Adverse Events from Spontaneous Reports for All IQOS unspecified

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