# Enhanced Pharmacovigilance Plan

| | |
|---|---|
| **Document Number:** | **c11117613-01** |
| **BI Investigational Product:** | Empagliflozin |
| **BI Study Number:** | 1245.146 |
| **Title:** | A 5-year enhanced Pharmacovigilance surveillance initiative to survey and characterise spontaneous occurrence and experience of ketoacidotic events in patients treated with Empagliflozin –containing products |
| **Brief lay title** | An enhanced form of drug safety monitoring to study the occurrence of ketoacidosis in patients treated with Empagliflozin-containing products |
| **Document version:** | 1.0 |
| **Date of last version of document:** | None |
| **Active substance:** | Empagliflozin (ATC code A10BX12), Empagliflozin/Linagliptin FDC (ATC code A10BD19) and Empagliflozin/Metformin FDC (ATC code A10BD20), |
| **Medicinal product:** | Empagliflozin |
| **Marketing authorization holder:** | Boehringer Ingelheim International GmbH |
| **Objectives:** | The rationale behind this initiative is to perform surveillance of spontaneous adverse event reports from post-marketed experience of ketoacidosis as well as:<br>• To better describe characteristics of patients developing KA under empagliflozin treatment.<br>• To characterise potential predisposing factors in patients developing KA under empagliflozin treatment.<br>• To characterize the clinical presentation of KA in patients taking empagliflozin treatment. |
| **Country(-ies) of study:** | Countries where Empagliflozin-containing products are currently and/or subsequently will be marketed during the 5-year duration of the initiative |
| **Authors:** | Fernando Solimando, Sven Kohler |
| **Marketing authorisation holder(s):** | Boehringer Ingelheim International GmbH |
| **Date:** | 30 June 2016 |

# 1. TABLE OF CONTENTS

# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ARISg | Boehringer Ingelheim Pharmacovigilance Database |
| ATIRMA | Adjunctive-To-Insulin and Renal MechAnistic pilot trial of empagliflozin in T1D M |
| BI | Boehringer Ingelheim |
| BIcMQ | Boehringer Ingelheim customized MedDRA Query |
| DKA | Diabetic Ketoacidosis |
| EMA | European Medicines Agency |
| EMPA-REG | Empagliflozin Cardiovascular Outcomes Trial |
| FDA | Food and Drug Administration |
| FDC | Fixed Dose Combination |
| GAC PV | Global Audit Coordinator - Pharmacovigilance |
| GI | Gastrointestinal |
| HCP | Health Care Professional |
| ICSR | Individual Case Safety Report |
| KA | Ketoacidosis |
| LADA | Latent Auto-immune Diabetes in Adults |
| MAH | Marketing Authorization Holder |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| MLM | Medical Literature Monitoring |
| NTA | Non-Trial Activity |
| OAD | Oral Antidiabetic |
| PMR | Post-Marketing Requirement |
| PV | Pharmacovigilance |
| PYE | Patient-Years of Exposure |
| QM | Quality Medicine |
| RCT | Randomized Controlled Trials |
| RR | Reporting Rates |
| SAE | Serious Adverse Event |
| SGLT2 | Sodium-Glucose Transporter-2 |
| T1DM | Type 1 Diabetes Mellitus |
| T2DM | Type 2 Diabetes Mellitus |

# 3. RESPONSIBLE PARTIES

The responsible parties charged with the design, execution, and analysis and reporting of the initiative including data collection forms, individual case processing, as well as database ownership and maintenance are described in detail in the Boehringer Ingelheim Pharmacovigilance Master File. (Available upon request)

# 4. AMENDMENTS AND UPDATES

| Number | Date | Section of study document | Amendment or update | Reason |
|---|---|---|---|---|
| None | None | None | None | None |

# 5. MILESTONES

| Milestone | Planned/Expected Date |
|---|---|
| Regulatory authority approval | 30 June 2016[1] |
| Start of data collection | 01 September 2016 |
| Data Lock date | 01 September 2021 |
| Study progress report 1 | December 2017 |
| Study progress report 2 | December 2018 |
| Study progress report 3 | December 2019 |
| Study progress report 4 | December 2020 |
| Final report of study results: | 31 December 2021 |

[1]. Continuous reporting of 15-day alert reports will be on-going through the data collection period

# 6. RATIONALE AND BACKGROUND

## 6.1 RATIONALE – DIABETIC KETOACIDOSIS

Diabetic Ketoacidosis (DKA) is a potentially life-threatening complication in patients with diabetes. Usually it is considered a key clinical feature of T1DM (type 1 diabetes mellitus),

where it occurs with an estimated incidence rate of 1-3/ 100 patient years and is associated with insulin deficiency. However, it can also occur in T2DM (type 2 diabetes mellitus) patients under certain circumstances, with a lower estimated incidence of 4-8/ 1000 patient years [R02-0751, R15-5255, R15-5352 , R15-5353, R15-5354, R15-5355].

DKA may be the first presentation of previously undiagnosed diabetes, but it may also occur in people known to have diabetes as a result of a variety of causes, such as concomitant illness or poor compliance with insulin therapy. The symptoms of an episode of DKA usually evolve over the period of about 24 hours and treatment involves primarily insulin to suppress the production of ketone bodies, intravenous fluids to correct dehydration, treatment for any underlying causes such as infections, and close observation to prevent and identify complications. Fortunately due to current advancements in critical patient care, DKA carries a mortality of less than 1% with adequate and timely treatment [P15-07763, R15-4924, R15-3811].

Ketone bodies are produced physiologically, but their production may be increased under certain conditions, such as fasting/ starvation and insulin deficiency. While fasting, glucose metabolism is shifted towards lipid metabolism, with ketones being an alternative energy source. Insulin is the strongest inhibitor of ketogenesis and glucagon is a stimulator of lipolysis and thus also ketogenesis. Ketone bodies are organic acids, but under normal circumstances, ketone body concentrations do not reach high levels to be sufficient for developing an acidosis. However, under increased ketogenesis, ketone body levels may exceed the buffer capacity of serum and tissue and ketoacidosis may develop. [R15-3159, R15-3161, R15-3810, R15-5256]

SGLT2 (sodium glucose co-transporter-2) inhibition leads to insulin independent loss of glucose via the urine and to a reduction in insulin levels, leading to an increased glucagon/ insulin ratio that have been observed under SGLT2 inhibitor treatment, mimicking a prolonged fasting state. Initially gluconeogenesis is increased, but ultimately an increase in lipolysis and lipid utilization results in a shift of substrate utilization from carbohydrates to lipids and is triggering ketone body production. This switch in the energy metabolism has been now consistently described in preclinical models as well as in diabetic patients. The mobilization of fat to sustain energy for the body mass is also the underlying mechanism for the weight loss observed with SGLT2 inhibitor in patients as well as in animal models. The increase in ketone bodies in combination with SGLT2 inhibition seemed to be more pronounced under fasting conditions. However, these increases usually do not seem to exceed to an extent that would cause acidosis. [R13-3150, R14-1979, R15-3159]

An analysis of BI data using a pool of randomized clinical trials (RCT) that investigated empagliflozin in patients with T2DM showed an overall low incidence of DKA across all treatment groups (DKA incidence of approximately 0.5 per 1,000 PYE): 8 events consistent with DKA were reported in more than 12,000 patients with T2D studied throughout Phase 2 and Phase 3 RCTs. No imbalance in DKA events was observed between patients treated with empagliflozin 10 mg (2 events), empagliflozin 25 mg (1 event) and placebo (5 events). In the large, randomised, cardiovascular outcomes trial EMPA-REG OUTCOME with a median follow-up of 3.1 years, the incidence rates of diabetic ketoacidosis AEs were low (with a total of 5 patients in the trial with such events) and comparable in both the empagliflozin and the placebo treatment. Two patients (empagliflozin 10 mg) had DKA AEs leading to

discontinuation of study medication. A total of 4 patients (all empagliflozin) had DKA reported as a serious adverse event (SAE). From T1DM clinical trials, 2 patients from the ATIRMA trial (Adjunctive-To-Insulin and Renal MechAnistic pilot trial of empagliflozin in T1DM (the ATIRMA trial, ClinicalTrials.gov identifier NCT01392560), presented DKA with clear pre-disposing factors (pump failure and gastrointestinal GI disease shortly prior to event). [P13-08968, P13-09179, P14-05959, P15-02849,] The overall incidence has been too low to draw any further conclusions.

Within literature there is increasing number of publications suggesting a potential association between SGLT2 inhibition and ketoacidosis under certain conditions. It is also reported, that patients may present with an atypical and lower blood glucose level than expected for a patient with a DKA. This may be due to the insulin independent mode of action of the SGLT2 inhibition.

Also from spontaneous sources there are an increasing number of reports of DKA events in combination with SGLT2 inhibitors. The reporting rate of events with empagliflozin to date is low, which may be due to the still limited post-marketing exposure. Also the information on the cases is not sufficient to fully assess the association between empagliflozin and the development of DKA, or to identify a subgroup of patients who may be at higher risk.

Under normal circumstances an increase in ketone body levels in patients treated with SGLT2 inhibitors would not be expected to be higher as compared to a usual fasting state and to reach high levels to set patients at risk for developing ketoacidosis (KA). However, there may be some patients who have an increased risk for developing a KA, as the combination may lead to further excess of ketone body formation (similar to starvation ketoacidosis). Also in patients with an impaired β – cell function, which may even still be sufficient under normal circumstances, SGLT2 inhibition may contribute to further decrease in absolute insulin levels and thus leading to increase in ketone body formation. In some excessive decrease in insulin dose may also lead to increase in ketone body formation.

# 7. OBJECTIVES

The KA PMR will be an enhanced Pharmacovigilance surveillance of spontaneous adverse event reports from post-marketed experience of KA events. It is intended to assess and characterize a potential patient population at risk for KA, characterize the circumstances behind predisposing factors, course and treatment of KA in patients undergoing empagliflozin treatment. The duration of the enhanced Pharmacovigilance surveillance activities will be 5 years. Cases will be identified with a pre-specified MedDRA Query, and will be followed up with a specific questionnaire. The objectives of this enhanced Pharmacovigilance surveillance are:

- To better describe characteristics of patients developing KA under empagliflozin treatment.
- To characterize potential predisposing factors in patients developing KA under empagliflozin treatment.
- To characterize the clinical presentation of KA in patients taking empagliflozin treatment.

# 8. METHODS

## 8.1 PLAN DESIGN

The enhanced KA pharmacovigilance plan will address a prospective collection of spontaneous cases of KA herein referred to as Individual Case Safety Reports (ICSR) and subsequent processing (initial and follow up information including a specially designed KA questionnaire) including KA and related reports from worldwide sources (e.g. scientific literature, health care professionals, non-health care professionals and consumers), recorded in the BI PV Database (ARISg) for the purpose of characterising KA in patients undergoing empagliflozin treatment, over a period of 5 years, excluding those cases reported from clinical trials.

## 8.2 SETTING

The case reports to be analysed in this plan will be based on any received ICSRs (which may refer to one or more persons) in which any marketed empagliflozin-containing medication has been reported as a suspect drug, and the reported event in these ICSRs matches any Preferred Term pre-defined by a MedDRA Boehringer Ingelheim Customised Query (BIcMQ consisting of both broad and narrow scope terms, Appendix 1) as a valid case for inclusion in the analysis.

## 8.3 VARIABLES

### 8.3.1 Exposure

Exposure will be defined as at least one successful ingestion of a marketed empagliflozin-containing medicinal product. Patient years of Exposure is defined by calculating the coefficient between the approximate sales data for each of the 2 strengths of Empagliflozin as either individual mono component or fixed dose combination (FDC) expressed in number of tablets sold and the expected number of tablets a patient is expected to ingest in a regular treatment of a 12-month calendar year.

#### 8.3.1.1 KA Questionnaire Form

Once an eligible ICSR has been identified, regardless of seriousness, expedited adverse event reporting procedures will be done (e.g.15-day alert reports and regularly scheduled aggregated reporting). The standard ICSR follow up procedures will be complemented with the KA Questionnaire Form (Appendix 2). The information requested in the KA questionnaire form relates to the patient's diabetic disease history and therapy, as well as any applicable risk factors for the development of KA, and circumstances around diagnosis and treatment of the reported event not already asked in the standard follow up questions (Appendix 3). All data sources and forms applied for each applicable case will be unified into FDA MedWatch forms which are expeditely reported.

## 8.4 DATA SOURCES

The main sources of AE data to be used in this initiative will correspond to ICSRs from unsolicited sources:

- Spontaneous by consumer or Health Care professionals by any way of communication
- Health authorities
- Scientific literature including ICSRs from the European Medicines Agency (EMA)'s Medical Literature Monitoring (MLM) service
- BI sponsored digital media
- Compassionate Use programs or named patient use where AEs are not actively sought
- Adverse events reported through Non-Trial Activities (NTA)

## 8.5 DATA MANAGEMENT

### 8.5.1 ARISg

Adverse Reaction Information System global (ARISg) is a commercially available web-based application used for the global processing of unsolicited and solicited AE reports. The application contains a workflow functionality including data validation to support consistent processing. ARISg also supports ICSR reporting in CIOMS I and MedWatch formats as well as via E2B and aggregate data reporting.

### 8.5.2 Detection of eligible events

Cases eligible for inclusion in this enhanced initiative will be selected based on a pre-defined Broad Scope KA BI customized MedDRA Query (BIcMQ) (Appendix 1).

Eligible ICSRs detected during local literature screening or as part of the global literature screening process, follow the same process.

### 8.5.3 ICSR

ICSR management and reporting is in accordance with standard operating procedures described in the PV Master file.

## 8.6 DATA ANALYSIS

### 8.6.1 Main analysis

Analyses will be based on descriptive statistics of the available sample provided by reports of KA and KA-related events as described above and defined by Narrow Scope KA BIcMQ in the BI Safety Database. The list of preferred terms will be update with each MedDRA version update, and the final analysis will use the MedDRA version valid at the moment data collection period is finalised. An Additional sensitivity analysis based on the broad scope BIcMQ is also intended to be performed.

### 8.6.2 Data collection

The selected analysis methods will be based on the data collected from enhanced post-marketed pharmacovigilance activities which consist of a specifically tailored questionnaire designed to obtain the most comprehensive information about the case report and at the same time acknowledging the limitations and uncertainty of the quantity and quality of data derived from post-marketed adverse event reporting.

**Reporting rate**

Reporting Rate (RR – defined as the coefficient between the number of valid cases and Patient exposure as explained in Section 8.3.1) of KA spontaneous reports based on estimated exposure at time of the report:

The rationale to define and analyse the frequencies based on reporting rates (RRs), as well as the use of descriptive statistics is based on several assumptions:

The size of the population to be surveyed.

The nature of spontaneous adverse event reporting is such that, initial reporting of adverse events is usually high in the period immediately after product launch, or after a recent safety communication or label change. This rate of reporting wanes over time as the safety profile of the drug becomes more known to both prescribers and patients.

Quantifying a risk associated with a given drug becomes more difficult over time mostly due an under-reporting during the post-marketed phase. The magnitude of this underreporting is difficult, if not almost impossible to assess and certain assumptions have to be made in analysing the data collected.

The completeness of certain parameters such as lab values may vary from one report to another and completeness of each AE report depends on the willingness of the AE reporter to provide any queries sent

The analysis of this enhanced pharmacovigilance initiative will be based on:

- Reporting Rate[1][2] of KA per country of occurrence
- Proportion of patients with KA per background antidiabetic medication
- Proportion of patients with KA requiring Hospitalization
- Proportion of patients experiencing KA per age subgroups
- Proportion of patients experiencing KA by gender
- Proportion of predisposing factors.

[1] To be performed on patients with T1DM, T2DM - regardless of background medication
[2] Same analyses will be performed for Euglycaemic KA, non-KA Ketosis and LADA patients

**Further analysis**

Additional Sub-group analyses have been considered based on the design of the KA questionnaire. The planned subgroups are the following:

Subgroups by Patient Age
Subgroups by sex
Subgroups by Background disease (T1DM, T2DM, Ketosis Prone Diabetes[3] and LADA[4])
Subgroups by Background therapy (Insulin, one or various oral antidiabetics (OADs))
Latency (time to onset from initiation of empagliflozin),
Time to onset from a dosage change to the event (if applicable),
Duration of diabetes history
Dose of empagliflozin

**LIMITATIONS OF THE METHODS**
Several limitations have been identified:

Due to the limitations of spontaneous data (mainly related to underreporting), we rely on the use of descriptive statistics for the analyses.
Stimulated reporting can be high during the first few weeks/months after a medicinal product has been made available in the market or a recent safety communication or a label change.
Due to the heterogeneity of reporters in spontaneous adverse event reporting, the quantity and quality of the data received in the forms is expected to be of very high variability unlike the uniform and control standard expected in a clinical trial setting.
Difficulty in authenticating non-Health Care Professional (HCP) reports when the reporter is unable or unwilling to provide source documentation to substantiate the data provided in the AE reports.

### 8.6.3 Data quality assurance

All quality assurance audit/inspection procedures for this enhanced pharmacovigilance will follow standard procedures as specified in the BI PV Master file

### 8.6.4 ICSR records

#### 8.6.4.1 Source documents

In line with standard procedure concerning Adverse Events, Adverse Drug Reactions or Other Pharmacovigilance-Related Information", AE collection forms, copies of any correspondence and any additional Information received locally must be maintained and archived locally in the format in which the original source documentation was received (paper, electronic) with the exception of safety reports from Clinical trials which are archived at GPV.

[3] Diabetes Care. 2006 Dec;29(12):2755-7; Diabetes Care. 2014 Apr;37(4):e74-5.
[4] Latent Autoinmune Diabetes in Adults Defined as per ADA criteria: https://diabetes.diabetesjournals.org/content/54/suppl_2/S68

8.6.4.2 Direct access to ICSR source data and documents

GPV will permit initiative-related monitoring, audits, and regulatory inspection, providing direct access to all related source data / documents. ICRFs and all source documents related to initiative-eligible ICSRs must be available at all times for review by auditors and inspection by health authorities (e.g. US Food and Drug Administration, FDA). The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.18.7.2.1 of the BI PV Master File.

BI's Pharmacovigilance System including its quality system, processes and related activities is periodically evaluated by audits. The Quality Medicine (QM) Audit function is responsible for the planning and conduct of audits of the PV system. The QM Audit function reports to the Head Global Quality Medicine who reports to the Head of Global Pharmacovigilance. The Global Audit Coordinator Pharmacovigilance (GAC PV) within the QM Audit function is responsible for coordinating all PV audit activities. This includes the development of the longer term PV audit strategy, and the development and implementation of the Annual Audit Programme.

## 8.7 STATEMENT OF CONFIDENTIALITY

The procedures concerning confidentiality of patient identity as well as any personal data are described in the BI PV Master File.

# 9. REFERENCES

## 9.1 PUBLISHED REFERENCES

P13-08968 Häring H-U, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Woerle HJ, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week randomized, double-blind, placebo controlled trial. Diabetes Care. 2013;36(11):3396–404.

P13-09179 Kovacs CS, Seshiah V, Swallow R, Jones R, Rattunde H, Woerle HJ, et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab. 2014;16(2):147–58.

P14-05959 Häring H-U, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014;37(6):1650–9.

P15-02849 Araki E, Tanizawa Y, Tanaka Y, Taniguchi A, Koiwai K, Kim G, Salsali A, Woerle HJ, Broedl UC. Long-term treatment with empagliflozin as add-on to oral antidiabetic therapy in Japanese patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2015 Jul;17(7):665-74.

P15-07763 Balasubramanyam A, et al. "Syndromes of Ketosis-Prone Diabetes Mellitus" Endocrine Reviews 2008; 29(3):292-302

R02-0751 Expert Committee on the Diagnosis and Classification of Diabetes mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003;26:5–20.

R13-3150 Inagaki et al. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study†.

R14-1979 Kaku K, Watada H, Iwamoto Y, Utsunomiya K, Terauchi Y, Tobe K, et al. Tofogliflozin 003 Study Group. Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: a combined Phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. Cardiovasc Diabetol. 2014 Mar 28;13:65.

R15-3159 Hine J, Paterson H, Abrol E, Russell-Jones D, Herring R. SGLT inhibition and euglycaemic diabetic ketoacidosis. Lancet Diabetes Endocrinol. 2015 May 26. pii: S2213-8587(15)00204-1.

R15-3161 Chen TY, Smith W, Rosenstock JL, Lessnau KD Alife-threatening complication of Atkinsdiet. Lancet 367, 958 (2006)

R15-3810 Frigolet ME, Ramos Barragán VE, Tamez González M. Low-carbohydrate diets: a matter of love or hate. Ann Nutr Metab. 2011 Oct;58(4):320-34.

R15-3811 Freeman TF, Willis B, Krywko DM; Acute intractable vomiting and severe ketoacidosis secondary to the Dukan Diet©. J Emerg Med. 2014 Oct;47(4):e109-12

R15-4924 Diabetes, Obesity and Metabolism 15: 1136–1145, 2013

R15-5255 Douglas R. The Ketogenic Diet Revisited: Back to the Future. Epilepsia 1997

R15-5256 Laffel L. Ketone Bodies: a Review of Physiology, Pathophysiology and Application of Monitoring to Diabetes. Diabetes Metab Res Rev. 1999; 15: 421-426.

R15-5352 Crude and age-adjusted hospital discharge rates for diabetic ketoacidosis (DKA) as first-listed diagnosis per 1,000 diabetic population, United States, 1988 - 2009 (page last reviewed: October 15, 2014). http://www.cdc.gov/diabetes/statistics/dkafirst/fig3.htm (access date: 14 October 2015) ; Atlanta: Centers for Disease Control and Prevention (CDC) (2014)

R15-5353 Hospital discharge rates for diabetic ketoacidosis (DKA) as first-listed diagnosis per 1,000 diabetic population, by age, United States 1988 - 2009 (page last reviewed: October 1, 2014). http://www.cdc.gov/diabetes/statistics/dkafirst/fig4.htm (access date: 14 October 2015) ; Atlanta: Centers for Disease Control and Prevention (CDC) (2014)

R15-5354 Age-adjusted hospital discharge rates for diabetic ketoacidosis (DKA) as first-listed diagnosis per 1,000 diabetic population, by sex, United States 1988 - 2009 (page last reviewed: October 1, 2014). http://www.cdc.gov/diabetes/statistics/dkafirst/fig5.htm (14 October 2015) ; Atlanta: Centers for Disease Control and Prevention (CDC) (2014)

R15-5355 Age-adjusted hospital discharge rates for diabetic ketoacidosis (DKA) as first-listed diagnosis per 1,000 diabetic population, by race, United States, 1988 - 2009 (page last reviewed: October 1, 2014).

# 10. APPENDIX

1. Ketoacidosis BIcMQ (current version as per MedDRA version 19.0)
2. Ketoacidosis Questionnaire Form
3. Standard Adverse Event Follow up Questions

## Appendix 1: BIcMQ Diabetic Ketoacidosis VER 1 FINAL MED 19-0

| | **BIcMQ Diabetic Ketoacidosis** |
|---|---|

| | |
|---|---|
| **Definition:** | Diabetic ketoacidosis (broad) |

| | |
|---|---|
| **Purpose of use** | Type 1 Diabetes Mellitus related trials<br>all trials for SGLT-2 inhibitors (EMA request) |

| | |
|---|---|
| **Version:** | MedDRA 19.0 |

| | |
|---|---|
| **Approved by DMG:** | 06 May 2016 |

| | |
|---|---|
| **Creation narrow:** | per PT list provided by requestor (Fernando Solimando) |

| | |
|---|---|
| **Creation broad:** | per PT list provided by requestor (Fernando Solimando) plus 3 additional PTs requested by EMA (added to broad, although no differentiation between narrow and broad from EMA) |

| | |
|---|---|
| **Maintenance:** | • highlight demoted PTs and send list of new PTs in SOCs:<br>Investigations<br>Metabolism and nutrition disorders<br>Renal and urinary disorders<br>Respiratory, thoracic and mediastinal disorders<br>• Updates to BIcMQ performed with each MedDRA version update |

| | |
|---|---|
| **Discussion:** | Diabetic hyperglycaemic coma, Blood ketone body increased, and Ketosis were added to the first approved version in order to have all EMA PTs included in the BIcMQ. |

**DKA BIcMQ MedDRA Version 18.0**

| SEARCH TYPE | SCOPE | LABEL | LEVEL | DECODE | CODE | PRIMSOC | PTRANGE | CATEGORY | SELECT |
|---|---|---|---|---|---|---|---|---|---|
| BIcMQ | NARROW | DKA | PT | Diabetic ketoacidosis | 10012671 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | NARROW | DKA | PT | Diabetic ketoacidotic hyperglycaemic coma | 10012672 | Nervous system disorders | | | INCLUDE |
| BIcMQ | NARROW | DKA | PT | Ketoacidosis | 10023379 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Acetonaemia | 10000410 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Acidosis | 10000486 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Anion gap abnormal | 10002523 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Anion gap increased | 10002528 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Blood ketone body | 10057593 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Blood ketone body increased | 10057594 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Blood ketone body present | 10057598 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Diabetic hyperglycaemic coma | 10012668 | Nervous system disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Ketonuria | 10023388 | Renal and urinary disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Ketosis | 10023391 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Kussmaul respiration | 10023499 | Respiratory, thoracic and mediastinal disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Metabolic acidosis | 10027417 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Urine ketone body | 10059222 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Urine ketone body present | 10057597 | Investigations | | | INCLUDE |

**DKA BIcMQ MedDRA Version 19.0**

| SEARCH TYPE | SCOPE | LABEL | LEVEL | DECODE | CODE | PRIMSOC | PTRANGE | CATEGORY | SELECT |
|---|---|---|---|---|---|---|---|---|---|
| BIcMQ | NARROW | DKA | PT | Diabetic ketoacidosis | 10012671 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | NARROW | DKA | PT | Diabetic ketoacidotic hyperglycaemic coma | 10012672 | Nervous system disorders | | | INCLUDE |
| BIcMQ | NARROW | DKA | PT | Ketoacidosis | 10023379 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Acetonaemia | 10000410 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Acidosis | 10000486 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Anion gap abnormal | 10002523 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Anion gap increased | 10002528 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Blood ketone body | 10057593 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Blood ketone body increased | 10057594 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Blood ketone body present | 10057598 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Blood pH abnormal | 10005705 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Blood pH decreased | 10005706 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Diabetic hyperglycaemic coma | 10012668 | Nervous system disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Ketonuria | 10023388 | Renal and urinary disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Ketosis | 10023391 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Kussmaul respiration | 10023499 | Respiratory, thoracic and mediastinal disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Metabolic acidosis | 10027417 | Metabolism and nutrition disorders | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Urine ketone body | 10059222 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Urine ketone body present | 10057597 | Investigations | | | INCLUDE |
| BIcMQ | BROAD | DKA | PT | Diabetic Metabolic Decompensation | 10074309 | Endocrine Disorders | | | INCLUDE |

## Appendix 2: Ketoacidosis Questionaire Form VER6 10June2016


# Ketoacidosis Event Form

Dear Health Care Provider,

Thank you for bringing this event to our attention. In order to fully understand the event, we would like to ask you for a few details. In answering the questions on the following pages, you will allow Boehringer Ingelheim to keep the safety information for physicians and patients accurate. Thank you for your help.

BI Product: _____

BI Case ID (filled out by BI): _____

Reporter: _____

Reported Event: _____ Start date of Event: _____

*Please complete the following form*

**PATIENT HISTORY:**

| Current Disease | Type 1 Diabetes | Type 2 diabetes | LADA | Others (Please specify) |
|---|---|---|---|---|
| **Type of Diabetes (Indicate duration in years)** | | | | |
| | Antibodies positive? (Y/N):<br><br>Ketosis Prone? (Y/N): | | | |
| **Patient's body weight and height** | Weight: _____ (Kg) (Lbs) Height: _____ cm. in.<br>BMI:_____ | | | |
| **Patient Ethnicity:** | Verify with clinical trial CRF | | | |

| | Yes (start-stop dates) | No |
|---|---|---|
| **Is the patient currently on insulin therapy?** | | |

| | Yes | No |
|---|---|---|
| **If yes to previous question: Were there any recent changes to daily insulin dose?** | | |
| | If Yes, what changes were made? (Please specify): | |

| | | Yes | If yes: Start/stop dates And dose | No |
|---|---|---|---|---|
| **Is the patient taking other oral/injectable anti-diabetic agents other than insulin?** | Metformin | | | |
| | Sulfonylureas | | | |
| | Thiazolidinediones | | | |
| | DPP-4 inhibitors | | | |
| | GLP-1 Analogues | | | |
| | SGLT-2 Inhibitors | | | |
| | Other (Specify): | | | |

| Predisposing condition | Yes | No | Comment (if applicable) |
|---|---|---|---|
| **Prior history of DKA** | | | |
| **Recent weight loss** | | | |
| **Low carb diet** | | | |
| **Increased exercise** | | | |
| **Alcohol Abuse/Recent binge drinking** | | | |
| **Acute febrile infection/illness** | | | |
| **Recent history of gastroenteritis** | | | |
| **Pancreatitis** | | | |
| **Dehydration** | | | |
| **Recent surgery** | | | |
| **Recent CV/MI episode** | | | |
| **Other** | | | |

**COMPLICATIONS DURING EPISODE:**

| Signs and Symptoms | Yes | No | Comment (if applicable) |
|---|---|---|---|
| **Altered state of consciousness?** | | | |
| **Other complications deemed relevant?** | | | |
| **Duration of stay in hospital** | | | |

**INITIAL LABORATORY VALUES:**

Please provide as well (if available) any relevant laboratory results:

| Lab Parameter | Date | Value/Unit | Reference Range |
|---|---|---|---|
| **Blood pH** | | | |
| **β Hydroxybutyrate (blood)** | | | |
| **Ketone (urine)** | | | |
| **Anion Gap** | | | |
| **Bicarbonate** | | | |
| **PCO2** | | | |
| **Blood Glucose** | | | |
| **Creatinine** | | | |
| **Sodium** | | | |
| **Potassium** | | | |
| **Lactic Acid** | | | |
| **Other** | | | |

**FOLLOW-UP LABORATORY VALUES (If performed and available)**

| Lab Parameter | Date | Value/Unit | Reference Range |
|---|---|---|---|
| **Blood pH** | | | |
| **β Hydroxybutyrate (blood)** | | | |
| **Ketone (urine)** | | | |
| **Anion Gap** | | | |
| **Bicarbonate** | | | |
| **PCO2:** | | | |
| **Blood Glucose** | | | |
| **Creatinine** | | | |
| **Sodium** | | | |
| **Potassium** | | | |
| **Lactic Acid** | | | |
| **Other** | | | |

**MEDICAL TREATMENT:**

| Treatment | Yes | No |
|---|---|---|
| **Fluid replacement?** | | |
| **I.V. Insulin?** | | |
| **Electrolyte Correction?** | | |
| **Other:** | | |
| **Other:** | | |

**OUTCOME OF THE EVENT:**

| Treatment | Please ☑ |
|---|---|
| **Recovered** | |
| **Recovered with sequelae** | |
| **Not yet recovered** | |
| **Fatal** | |
| **Unknown** | |

Please use reverse side to report any other relevant information. Thanks!

## Appendix 3: Standard Questions 06 MAY 2016

### Standard Adverse Event Follow up Questions

The following questions are asked upon receipt of any adverse event report received by BI Drug Safety regardless of source, seriousness or diagnosis:

1. What is the patient's gender?
2. What is the patient's age?
3. What is the BI suspect drug?
4. For what indication was the BI suspect drug used in this patient?
5. Which dose and formulation of BI suspect drug was administered?
6. What is the start and end date of administration of BI suspect drug?
7. Is the lot number for the BI suspect drug available?
8. Was the patient adhering to the drug regimen? If not, please specify.
9. Which adverse event(s) occurred while the patient was on BI drug?
10. What is the onset date of the adverse event(s)?
11. What is the end date of adverse event(s)?
12. How long after initiation of the BI suspect drug did the adverse event(s) occur?
13. What is the outcome of the adverse event(s)?
14. Was the patient receiving any treatment for the adverse event(s)? If so, please specify the treatment administered.
15. Did the adverse event(s) improve or resolve after discontinuation of medication?
16. If medication was re-introduced, did the adverse event(s) re-occur?
17. Do you see a causal relationship between the suspect drug(s) and the adverse event(s)?
18. Was the patient taking other medications (incl. OTC and herbal drugs) at the time of event? If so, do you see a causal relationship to the event?
19. Did the patient have any other medical disorders at the time of adverse event(s)?
20. Did the patient have any relevant diseases in her/his medical history?
21. If the patient died: What was the primary cause of death according to death certificate? Is an autopsy report available?