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Date November 17, 2020

Document Ref# ACHC21-01.A.OUS

Urgent Field Safety Notice ACHC 21-01:

Atellica CH® Analyzer

Etamsylate Interference with Atellica® CH Assays

Dear Sirs,

Our records indicate that your facility may have received the following products:

Table 1. Atellica® CH Affected Products

Assay	Test Code	Siemens Material Number (SMN)	Lot Number
Enzymatic Creatinine_2	ECre_2	11097533	ALL
Japan Enzymatic Creatinine	ECreJ	11319121 (Japan only)	ALL
Fructosamine	Fruc	11097637	ALL
Glucose Oxidase	GluO	11097621	ALL
Lactate	Lac	11097614	ALL
Lactate_2	Lac_2	11532568	ALL
Triglycerides (concentrated)	Trig	11097591	ALL

Reason for Correction

The purpose of this communication is to inform you of an interference identified with the products indicated in Table 1 above and to provide instructions on actions that your laboratory must take.

Siemens Healthcare Diagnostics Inc. has become aware that falsely depressed results may be observed in the presence of etamsylate, a hemostatic drug, with the assays listed in Table 1.

Siemens performed spiking studies to assess the magnitude of interference with etamsylate. Results of the testing are summarized in Table 2 below for the highest evaluated level of etamsylate.

Table 2: Interference Testing Results

Etamsylate Concentration	Assay	Analyte Concentration	Bias (%)
6 mg/dL (228 µmol/L)	ECre_2/EcreJ	0.99 mg/dL (88 µmol/L)	-59%
	Fruc	187 µmol/L	-44%
		257 µmol/L	-44%
	GluO	44 mg/dL (2.4 mmol/L)	-9%
		111 mg/dL (6.2 mmol/L)	-5%
	Lac/Lac_2	16.5 mg/dL (1.8 mmol/L)	-12%
	Trig	135 mg/dL (1.5 mmol/L)	-13%
		196 mg/dL (2.2 mmol/L)	-9%

The Instructions for Use (IFU) for the assays will be updated with the interference information. Please see “Actions Being Taken by Siemens” below.

Risk to Health

In scenarios where creatinine is measured in the presence etamsylate, the potential exists to report falsely depressed values for patient samples, leading to an underestimation of kidney disease and/or the misinterpretation of an increased estimated glomerular filtration rate (eGFR). Creatinine values are not used in isolation, but are correlated with clinical history and symptomology, as well as to other diagnostic laboratory testing such as blood urea nitrogen, electrolytes, albumin, and/or microalbumin.

In scenarios where fructosamine is measured in the presence of etamsylate, the potential exists to report falsely depressed values for patient samples, leading to delayed intervention of hyperglycemia. Clinical impact would be mitigated by continued correlation to clinical history and presentation, follow-up monitoring of glucose levels, and continued serial monitoring of fructosamine.

When glucose is measured in the presence of etamsylate, the potential exists to report falsely depressed values for patient samples possibly leading to inappropriate treatment for hypoglycemia. Mitigations for clinical impact include correlation to clinical history and presentation, as well as continued monitoring of blood glucose values.

The magnitude of interference observed in the presence of etamsylate when measuring lactate and triglycerides would have negligible clinical impact.

Siemens is not recommending a review of previously generated results.

Actions to be Taken by the Customer:

- Be aware of the limitations indicated below in "Actions Being Taken by Siemens".
- Please review this letter with your Medical Director.
- Complete and return the Field Correction Effectiveness Check Form attached to this letter within 30 days.
- If you have received any complaints of illness or adverse events associated with the products listed in Table 1, immediately contact your local Siemens Customer Care Center or your local Siemens technical support representative.

Actions Being Taken by Siemens:

The "Limitations of the Procedure" section of the Atellica CH ECre_2 and ECreJ assay IFUs will be updated to indicate that '*In the presence of etamsylate at 0.5 mg/dL (19 µmol/L), falsely depressed results ≥10% for enzymatic creatinine may be observed. Use of this assay is not recommended for patients being treated with etamsylate.'*

The "Limitations of the Procedure" section of the Atellica CH Fruc assay IFU will be updated to indicate that '*In the presence of etamsylate at 0.8 mg/dL (30 µmol/L), falsely depressed results ≥10% for fructosamine may be observed. Use of this assay is not recommended for patients being treated with etamsylate.'*

The "Limitations of the Procedure" section of the Atellica CH GluO assay IFU will be updated to indicate that *'In the presence of etamsylate at 5 mg/dL (190 µmol/L), falsely depressed results ≥10% for glucose oxidase may be observed.*

The "Limitations of the Procedure" section of the Atellica CH Lac and Lac_2 assay IFUs will be updated to indicate that *'In the presence of etamsylate at 5 mg/dL (190 µmol/L), falsely depressed results ≥10% for lactate may be observed.*

The "Limitations of the Procedure" section of the Atellica CH Trig assay IFU will be updated to indicate that *'In the presence of etamsylate at 4.4 mg/dL (167 µmol/L), falsely depressed results ≥10% for triglycerides may be observed.*

The information related to etamsylate provided in this letter supersedes the information in the current Atellica CH IFUs until each is updated.

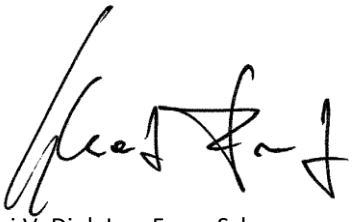
The updated IFUs will be uploaded into Document Library where all registered users who opt in to receive alerts will be notified of the updated IFU.

Please retain this letter with your laboratory records and forward this letter to those who may have received this product.

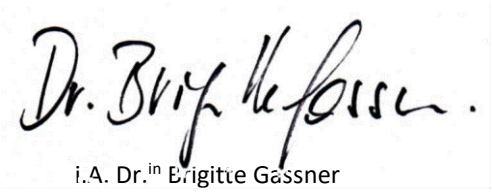
We apologize for the inconvenience this situation may cause. If you have any questions, please contact your Siemens Customer Care Center or your local Siemens Technical Support representative.

Sincerely yours,

Siemens Healthcare Diagnostics GmbH



i.V. Dipl. Ing. Franz Schwarz
Quality Management CEE



i.A. Dr.in Brigitte Gassner
Product Manager Austria & SEE

Addendum I: Frequently Asked Questions:

Addendum I: Frequently Asked Questions:

1. **Is the Jaffe Creatinine (Crea_2) assay impacted by the presence of etamsylate?**
   The Atellica CH Jaffe Crea_2 assay is not impacted by etamsylate interference. The Jaffe methodology uses different reagents and parameters than the ECre_2 assay.

2. **Why was testing performed using 6 mg/dL of etamsylate?**
   This level of etamsylate tested correlates to the C_{max} of approximately 5 mg/dL reported during pharmacokinetic studies following a single dose of 500 mg of etamsylate. Titration experiments were subsequently performed to characterize the potential for interference at decreasing concentrations of etamsylate.

3. **Is etamsylate prescribed worldwide?**
   Etamsylate is currently not available for use in the United States. In some countries, etamsylate is approved only for veterinary use.

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Date November 17, 2020

Document Ref# ACHC21-01.A.OUS.CHC

Urgent Field Safety Notice ACHC 21-01:

ADVIA® 1800 Chemistry System
ADVIA® 2400 Chemistry System
ADVIA® Chemistry XPT System

Etamsylate Interference with ADVIA® Chemistry Assays

Dear Sirs,

Our records indicate that your facility may have received the following products:

Table 1. ADVIA® Chemistry Affected Products

Assay	Test Code	Siemens Material Number (SMN)	Lot Number
Enzymatic Creatinine_2	ECRE_2	10335869	ALL
Fructosamine	FRUC	10361941	ALL
Glucose Oxidase	GLUO	10492319	ALL
Glucose Oxidase Concentrated	GLUO_c	10335872	ALL
Lactate	LAC	10325776	ALL
Triglycerides_2	TRIG_2	10335892	ALL
Triglycerides_2, Concentrated	TRIG_c	10697575	ALL

Reason for Correction

The purpose of this communication is to inform you of an interference identified with the products indicated in Table 1 above and to provide instructions on actions that your laboratory must take.

Siemens Healthcare Diagnostics Inc. has become aware that falsely depressed results may be observed in the presence of etamsylate, a hemostatic drug, with the assays listed in Table 1.

Siemens performed spiking studies to assess the magnitude of interference with etamsylate. Results of the testing are summarized in Table 2 below for the highest evaluated level of etamsylate.

Table 2: Interference Testing Results

Etamsylate Concentration	Assay	Analyte Concentration	Bias (%)
6 mg/dL (228 µmol/L)	ECRE_2	0.99 mg/dL (88 µmol/L)	-61%
	FRUC	189 µmol/L	-49%
		263 µmol/L	-45%
	GLUO/GLUO_c	45 mg/dL (2.5 mmol/L)	-12%
		113 mg/dL (6.3 mmol/L)	-5%
	LAC	16.9 mg/dL (1.9 mmol/L)	-10%
	TRIG_2/TRIG_c	136 mg/dL (1.5 mmol/L)	-14%
		197 mg/dL (2.2 mmol/L)	-9%

The Instructions for Use (IFU) for the assays will be updated with the interference information. Please see "Actions Being Taken by Siemens" below.

Risk to Health

In scenarios where creatinine is measured in the presence of etamsylate, the potential exists to report falsely depressed values for patient samples, leading to an underestimation of kidney disease and/or the misinterpretation of an increased estimated glomerular filtration rate (eGFR). Creatinine values are not used in isolation, but are correlated with clinical history and symptomology, as well as to other diagnostic laboratory testing such as blood urea nitrogen, electrolytes, albumin, and/or microalbumin.

In scenarios where fructosamine is measured in the presence of etamsylate, the potential exists to report falsely depressed values for patient samples, leading to delayed intervention of hyperglycemia. Clinical impact would be mitigated by continued correlation to clinical history and presentation, follow-up monitoring of glucose levels, and continued serial monitoring of fructosamine.

When glucose is measured in the presence of etamsylate, the potential exists to report falsely depressed values for patient samples possibly leading to inappropriate treatment for hypoglycemia. Mitigations for clinical impact include correlation to clinical history and presentation, as well as continued monitoring of blood glucose values.

The magnitude of interference observed in the presence of etamsylate when measuring lactate and triglycerides would have negligible clinical impact.

Siemens is not recommending a review of previously generated results.

Actions to be Taken by the Customer:

- Be aware of the limitations indicated below in “Actions Being Taken by Siemens”.
- Please review this letter with your Medical Director.
- Complete and return the Field Correction Effectiveness Check Form attached to this letter within 30 days.
- If you have received any complaints of illness or adverse events associated with the products listed in Table 1, immediately contact your local Siemens Customer Care Center or your local Siemens technical support representative.

Actions Being Taken by Siemens:

The “Limitations of the Procedure” section of the ADVIA Chemistry ECRE_2 assay IFU will be updated to indicate that ‘*In the presence of etamsylate at 0.5 mg/dL (19 µmol/L), falsely depressed results ≥10% for enzymatic creatinine may be observed. Use of this assay is not recommended for patients being treated with etamsylate.’*

The “Limitations of the Procedure” section of the ADVIA Chemistry FRUC assay IFU will be updated to indicate that ‘*In the presence of etamsylate at 0.8 mg/dL (30 µmol/L), falsely depressed results ≥10% for fructosamine may be observed. Use of this assay is not recommended for patients being treated with etamsylate.’*

The “Limitations of the Procedure” section of the ADVIA Chemistry GLUO and GLUO_c assay IFUs will be updated to indicate that *‘In the presence of etamsylate at 5 mg/dL (190 µmol/L), falsely depressed results ≥10% for glucose oxidase may be observed.’*

The “Limitations of the Procedure” section of the ADVIA Chemistry LAC assay IFU will be updated to indicate that *‘In the presence etamsylate at 5 mg/dL (190 µmol/L), falsely depressed results ≥10% for lactate may be observed.’*

The “Limitations of the Procedure” section of the ADVIA Chemistry TRIG_2 and TRIG_c assay IFUs will be updated to indicate that *‘In the presence of etamsylate at 4.4 mg/dL (167 µmol/L), falsely depressed results ≥10% for triglycerides may be observed.’*

The information related to etamsylate provided in this letter supersedes the information in the current ADVIA Chemistry IFUs until each is updated.

The updated IFUs will be uploaded into Document Library where all registered users who opt in to receive alerts will be notified of the updated IFU.

Please retain this letter with your laboratory records and forward this letter to those who may have received this product.

We apologize for the inconvenience this situation may cause. If you have any questions, please contact your Siemens Customer Care Center or your local Siemens Technical Support representative.

Sincerely yours,

Siemens Healthcare Diagnostics GmbH

i.V. Dipl. Ing. Franz Schwarz
Quality Management CEE

i.V. Dr. Brigitte [illegible]
Product Manager Austria & SEE

Addendum I: Frequently Asked Questions:

Addendum I: Frequently Asked Questions:

1. **Are the Jaffe creatinine (CREA_2 and CRE_2c) assays impacted by the presence of etamsylate?**
   The Jaffe creatinine assays (CREA_2 and CRE_2c) are not impacted by etamsylate interference. The Jaffe methodology uses different reagents and parameters than the ECRE_2 assay.

2. **Why was testing performed using 6 mg/dL of etamsylate?**
   This level of etamsylate tested correlates to the C_{max} of approximately 5 mg/dL reported during pharmacokinetic studies following a single dose of 500 mg of etamsylate. Titration experiments were subsequently performed to characterize the potential for interference at decreasing concentrations of etamsylate.

3. **Is etamsylate prescribed worldwide?**
   Etamsylate is currently not available for use in the United States. In some countries, etamsylate is approved only for veterinary use.

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Date November 17, 2020

Document Ref# ACHC21-01.A.OUS.DM

Urgent Field Safety Notice ACHC 21-01:

Dimension® clinical chemistry systems

Etamsylate Interference with Dimension® Assays

Dear Sirs,

Our records indicate that your facility may have received the following products:

Table 1. Dimension® Affected Products

Assay	Test Code	Catalog Number	Siemens Material Number (SMN)	Lot Number	
Enzymatic Creatinine	EZCR	DF270B	10471520	ALL	
Triglycerides	TGL	DF69A	10444906	ALL	

Reason for Correction

The purpose of this communication is to inform you of an interference identified with the products indicated in Table 1 above and to provide instructions on actions that your laboratory must take.

Siemens Healthcare Diagnostics Inc. has become aware that falsely depressed results may be observed in the presence of etamsylate, a hemostatic drug, with the assays listed in Table 1.

Siemens performed spiking studies to assess the magnitude of interference with etamsylate. Results of the testing are summarized in Table 2 below for the highest evaluated level of etamsylate.

Table 2: Etamsylate Interference Testing Results

Etamsylate Concentration	Assay	Analyte Concentration	Bias (%)
6 mg/dL [228 µmol/L]	EZCR	1.03 mg/dL [91 µmol/L]	-47%
	TGL	128 mg/dL [1.4 mmol/L]	-17%
		192 mg/dL [2.2 mmol/L]	-15%

The Instructions for Use (IFU) for the assays will be updated with the interference information. Please see “Actions Being Taken by Siemens” below.

Risk to Health

In scenarios where creatinine is measured in the presence of etamsylate, the potential exists to report falsely depressed values for patient samples, leading to an underestimation of kidney disease and/or the misinterpretation of an increased estimated glomerular filtration rate (eGFR). Creatinine values are not used in isolation, but are correlated with clinical history and symptomology, as well as to other diagnostic laboratory testing such as blood urea nitrogen, electrolytes, albumin, and/or microalbumin.

The magnitude of interference observed in the presence of etamsylate when measuring triglycerides in patient samples would have negligible clinical impact.

Siemens is not recommending a review of previously generated results.

– Actions to be Taken by the Customer:

- Be aware of the limitations indicated below in "Actions Being Taken by Siemens".
- Please review this letter with your Medical Director.
- Complete and return the Field Correction Effectiveness Check Form attached to this letter within 30 days.
- If you have received any complaints of illness or adverse events associated with the products listed in Table 1, immediately contact your local Siemens Customer Care Center or your local Siemens technical support representative.

Actions Being Taken by Siemens:

The "Limitations of the Procedure" section of the Dimension EZCR assay IFU will be updated to indicate that: *'In the presence of etamsylate at 0.4 mg/dL [15 µmol/L], falsely depressed results ≥10% for enzymatic creatinine may be observed. Use of this assay is not recommended for patients being treated with etamsylate.'*

The "Limitations of the Procedure" section of the Dimension TGL assay IFU will be updated to indicate that: *'In the presence of etamsylate at 2 mg/dL [76 µmol/L], falsely depressed results ≥10% for triglyceride may be observed.'*

The information related to etamsylate provided in this letter supersedes the information in the current Dimension IFUs until each is updated.

The updated IFUs will be uploaded into Document Library where all registered users who opt in to receive alerts will be notified of the updated IFU.

Please retain this letter with your laboratory records and forward this letter to those who may have received this product.

We apologize for the inconvenience this situation may cause. If you have any questions, please contact your Siemens Customer Care Center or your local Siemens Technical Support representative.

Siemens Healthcare Diagnostics GmbH
Management: Joachim Bogner, Stefan Scheidler, Sonja Wehsely

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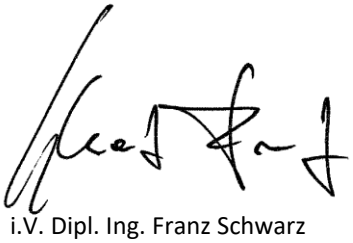
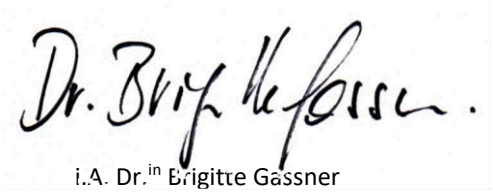
Legal Form: Gesellschaft mit beschraenkter Haftung; Company Seat: Vienna; Commercial Court Registration: FN 135042 t; Commercial Court: Vienna; DVR: 0816540

Sincerely yours,

Siemens Healthcare Diagnostics GmbH



i.V. Dipl. Ing. Franz Schwarz
Quality Management CEE



i.A. Dr.in Brigitte Gassner
Product Manager Austria & SEE

Addendum I: Frequently Asked Questions:

1. **Is the Jaffe Creatinine (CRE2) assay impacted by the presence of etamsylate?**
   The Jaffe CRE2 assay is not impacted by etamsylate interference. The Jaffe methodology uses different reagents and parameters than the EZCR assay.

2. **Why was testing performed using 6 mg/dL of etamsylate?**
   This level of etamsylate tested correlates to the C_{max} of approximately 5 mg/dL reported during pharmacokinetic studies following a single dose of 500 mg of etamsylate. Titration experiments were subsequently performed to characterize the potential for interference at decreasing concentrations of etamsylate.

3. **Is etamsylate prescribed worldwide?**
   Etamsylate is currently not available for use in the United States. In some countries etamsylate is approved only for veterinary use.