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cc Chairman Medical Board
and Relevant Head of
Departments

Urgent Field Safety Notice

CHC17-06.A.OUS

June, 2017

ADVIA® Chemistry systems

Sulfasalazine and Sulfapyridine Interference with NADH and/or NADPH Reaction Assays

Our records indicate that your facility may have received the following products listed in Tables1 and 2:

Reason for Correction

Table 1. ADVIA Chemistry Products affected by Sulfasalazine and Sulfapyridine

Assay	Test Code	REF Number	Siemens Material Number (SMN)	Lot Number
Ammonia	AMM	04802290	10286035	All
Salicylate	SAL	07989456	10327382	All

Table 2. ADVIA Chemistry Products affected by Sulfasalazine only

Assay	Test Code	REF Number	Siemens Material Number (SMN)	Lot Number
Alanine Aminotransferase (with or without P5P)	ALT, ALTP5P	03036926 P5P: 07371282 07501976 P5P:01411533	10318168 P5P:10326245 10309500 P5P:10315181	All
Alanine Aminotransferase, concentrated (with or without P5P)	ALT_c, ALTP_c	06860469 P5P: 06860477	10283341 P5P:10283342	All

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Sulfasalazine and Sulfapyridine Interference with NADH and/or NADPH reaction Assays

Siemens Healthcare Diagnostics has become aware of sulfasalazine and sulfapyridine drug interference in the assays listed in Table 1 and Table 2 which use NADH and/or NADPH to generate reduction oxidation reactions which produce colorimetric signals. No other ADVIA Chemistry assays exhibited any interference.

Siemens has confirmed that falsely depressed or falsely elevated results may occur on samples drawn from patients taking Sulfasalazine and Sulfapyridine as indicated in the Appendix. Sulfasalazine is the accepted treatment for inflammatory bowel disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis, inflammatory arthritis and uveitis. Sulfapyridine is used occasionally for dermatitis herpetiformis and related skin disorders when alternative treatment is unsuitable.

The Limitations of the Procedure section of the IFU for the ADVIA® Chemistry Ammonia assay will be updated to indicate that: Venipuncture should occur prior to sulfasalazine administration due to the potential for falsely elevated results and sulfapyridine administration due to the potential for falsely depressed results.

The Limitations of the Procedure section of the IFU for the ADVIA® Chemistry Salicylate assay will be updated to indicate that: Venipuncture should occur prior to sulfasalazine administration due to the potential for falsely elevated results and sulfapyridine administration due to the potential for falsely depressed results.

The Limitations of the Procedure section of the IFU for the ADVIA® Chemistry Alanine Aminotransferase (with or without P5P) assay will be updated to indicate that: Venipuncture should occur prior to sulfasalazine administration due to the potential for falsely depressed results.

The Limitations of the Procedure section of the IFU for the ADVIA® Chemistry Alanine Aminotransferase, concentrated (with or without P5P) assay will be updated to indicate that: Venipuncture should occur prior to sulfasalazine administration due to the potential for falsely depressed results.

Baseline assay values before administration of Sulfasalazine or Sulfapyridine therapy would not be affected.

See Appendix for Maximum % bias observed in the studies conducted by Siemens.

Risk to Health

The probability of misinterpretation of results for the assays described in Tables 1 and 2 due to this interference is remote and would be limited to scenarios where a patient has taken Sulfasalazine or Sulfapyridine and had a blood sample drawn before clearance of the drug to a level that does not interfere with laboratory testing. Mitigations include correlation to clinical history and presentation as well as to other diagnostic laboratory testing, serial testing, and/or more vigilant clinical monitoring depending on the analyte. Siemens is not recommending a review of previously generated results.

Actions to be Taken by the Customer:

- Please review this letter with your Medical Director.

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Sulfasalazine and Sulfapyridine Interference with NADH and/or NADPH reaction Assays

- Venipuncture should occur before drug administration of Sulfasalazine or Sulfapyridine as indicated above under Reason For Correction. Baseline assay values before administration of Sulfasalazine or Sulfapyridine therapy would not be affected.
- 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 or 2, immediately contact your local Siemens Customer Care Center or your local Siemens technical support representative.

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.

ADVIA is a trademark of Siemens Healthcare Diagnostics.

Appendix:

Maximum % bias observed at 300 mg/L of sulfasalazine and sulfapyridine

Assay	**Concentration of analyte in common unit (SI Unit)**	**Maximum% bias observed at 300 mg/L Sulfasalazine**	**Maximum% bias observed at 300 mg/L Sulfapyridine**
Ammonia (AMM)	~60 µg/dL (35 umol/L)	75.9%	-18%
Salicylate (SAL)	~25 mg/dL (1.8 mmol/L)	25%	-24.8%
Alanine Aminotransferase (ALT) and equivalent assay ALT_c	~50 U/L	-25.6%	Interference ≤ 10% observed
ALTP5P , and equivalent assay ALTP_c	~50 U/L	-34.6%	Interference ≤ 10% observed

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FIELD CORRECTION EFFECTIVENESS CHECK

Sulfasalazine and Sulfapyridine Interference with NADH and/or NADPH reaction Assays

This response form is to confirm receipt of the enclosed Siemens Healthcare Diagnostics Urgent Field Safety Notice CHC17-06.A.OUS.CHC dated June, 2017 regarding Sulfasalazine and Sulfapyridine Interference with NADH and/or NADPH reaction Assays. Please read the question and indicate the appropriate answer. Fax this completed form to Siemens Healthcare Diagnostics at the fax number provided at the bottom of this page.

1. I have read and understood the Urgent Field Safety Notice Correction instructions provided in this letter. Yes • No •

Name of person completing questionnaire:

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Please fax this completed form to the Customer Care Center at (65) 6366-3376. If you have any questions, contact your local Siemens technical support representative.

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Urgent Field Safety Notice

CHC-17-06.A.OUS.DM

June 2017

Dimension® clinical chemistry system and Dimension Vista® System

Sulfasalazine and Sulfapyridine Interference with NADH and/or NADPH Reaction Assays

Our records indicate that your facility may have received the following products listed in Table1:

Table 1. Dimension/Dimension Vista Products affected by Sulfasalazine and/or Sulfapyridine

Assay	Test Code	Catalog Number	Siemens Material Number (SMN)	Lot Number
Ammonia	AMM	DF119/ K3119	10711991/ 10711992	All
Alanine Aminotransferase	ALTI	DF143/ K2143	10475530/ 10635565	All
Aspartate Aminotransferase	AST	DF41A/ K2041	10444959/ 10445148	All
Glucose	GLUC/GLU	DF40/ K1039	10444971/ 10445162	All
Creatine Kinase MB	MBI	DF32/ K3032	10464510/ 10464339	All
Thyroxine	T4	DF65/ K6065	10444908/ 10445101	All

Reason for Correction

Siemens Healthcare Diagnostics has become aware of sulfasalazine and sulfapyridine drug interference in the assays listed in Table 1 which use NADH and/or NADPH to generate reduction oxidation reactions which produce colorimetric signals. No other Dimension/Dimension Vista assays exhibited any interference.

Siemens has confirmed that falsely depressed or falsely elevated results may occur on samples drawn from patients taking Sulfasalazine and Sulfapyridine as indicated in the Appendix. Sulfasalazine is the accepted treatment for inflammatory bowel disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis, inflammatory arthritis, and uveitis. Sulfapyridine is used

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occasionally for dermatitis herpetiformis and related skin disorders when alternative treatment is unsuitable.

The Limitations of the Procedure Section of the Instructions For Use (IFU) for the Dimension and Dimension Vista assays listed in Table 1 will be updated as follows:

Dimension Ammonia: Venipuncture should occur prior to sulfapyridine administration due to the potential for falsely depressed results.

Dimension Vista Ammonia: Venipuncture should occur prior to sulfasalazine administration due to the potential for falsely elevated results. Venipuncture should occur prior to sulfapyridine administration due to the potential for falsely depressed results.

Dimension Alanine Aminotransferase: Venipuncture should occur prior to sulfasalazine administration due to the potential for falsely depressed results.

Dimension Vista Alanine Aminotransferase: Venipuncture should occur prior to sulfasalazine and/or sulfapyridine administration due to the potential for falsely depressed results.

Dimension Aspartate Aminotransferase: Venipuncture should occur prior to sulfasalazine administration due to the potential for falsely depressed results.

Dimension Vista Aspartate Aminotransferase: Venipuncture should occur prior to sulfasalazine and/or sulfapyridine administration due to the potential for falsely depressed results.

Dimension & Dimension Vista Glucose: Venipuncture should occur prior to sulfasalazine administration due to the potential for falsely depressed results. Venipuncture should occur prior to sulfapyridine administration due to the potential for falsely elevated results.

Dimension Creatine Kinase MB: Venipuncture should occur prior to sulfapyridine administration due to the potential for falsely depressed results.

Dimension Vista Creatine Kinase MB: Venipuncture should occur prior to sulfasalazine administration due to the potential for falsely elevated results.

Dimension & Dimension Vista Thyroxine: Venipuncture should occur prior to sulfasalazine administration due to the potential for falsely elevated results.

Baseline assay values before administration of Sulfasalazine or Sulfapyridine therapy would not be affected.

See Appendix for Maximum % bias observed in the studies conducted by Siemens.

Risk to Health

The probability of misinterpretation of results for the assays described in Table 1 due to this interference is remote and would be limited to scenarios where a patient has taken sulfasalazine or sulfapyridine and had a blood sample drawn before clearance of the drug to a level that does not interfere with laboratory testing. Mitigations include correlation to clinical history and presentation as well as to other diagnostic laboratory testing, serial testing, and/or more vigilant clinical monitoring depending on the analyte. Siemens is not recommending a review of previously generated results.

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Actions to be Taken by the Customer:

- Please review this letter with your Medical Director.
- Venipuncture should occur before drug administration of sulfasalazine or sulfapyridine as indicated above under Reason For Correction. Baseline assay values before administration of Sulfasalazine or Sulfapyridine therapy would not be affected.
- 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.

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.

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Appendix:

Maximum bias observed for sulfasalazine and sulfapyridine with Dimension Assays

Assay	**Concentration of analyte**	**Maximum% bias observed at 300 mg/L [0.75 mmol/L] Sulfasalazine**	**Maximum% bias observed at 300 mg/L [1.2 mmol/L] Sulfapyridine**
Ammonia (AMM)	~426 µg/dL [~250 µmol/L]	<10%	-19%
Alanine Aminotransferase (ALTI)	~55 U/L [~0.92 µkat/L]	-29%	<10%
Aspartate Aminotransferase (AST)	~37 U/L	-10%	<10%
Glucose (GLUC)	~126 mg/dL [~7.0 mmol/L]	-17%	11%
Creatine Kinase MB (MBI)	~20 U/L [0.33 µkat/L]	<10%	-11%
Thyroxine (T4)	~8 µg/dL [~103 nmol/L]	15%	<10%

Maximum bias observed for sulfasalazine and sulfapyridine with Dimension Vista Assays

Assay	**Concentration of analyte**	**Maximum% bias observed at 300 mg/L [0.75 mmol/L] Sulfasalazine**	**Maximum% bias observed at 300 mg/L [1.2 mmol/L] Sulfapyridine**
Ammonia (AMM)	~426 µg/dL [~250 µmol/L]	66%	-19%
Alanine Aminotransferase (ALTI)	~55 U/L [~0.92 µkat/L]	-72%	-19%
Aspartate Aminotransferase (AST)	~37 U/L	-19%	-12%
Glucose (GLU)	~126 mg/dL [~7.0 mmol/L]	-21%	11%
Creatine Kinase MB (MBI)	~20 U/L [0.33 µkat/L]	22%	<10%
Thyroxine (T4)	~8 µg/dL [~103 nmol/L]	18%	<10%

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FIELD CORRECTION EFFECTIVENESS CHECK

Sulfasalazine and Sulfapyridine Interference with NADH and/or NADPH reaction Assays

This response form is to confirm receipt of the enclosed Siemens Healthcare Diagnostics Urgent Field Safety Notice CHC-17-06.A.OUS.DM dated June 2017 regarding Sulfasalazine and Sulfapyridine Interference with NADH and/or NADPH reaction Assays. Please read the question and indicate the appropriate answer. Fax this completed form to Siemens Healthcare Diagnostics at the fax number provided at the bottom of this page.

1. I have read and understood the Urgent Field Safety Notice instructions provided in this letter. Yes • No •

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Urgent Field Safety Notice

CHC17-06.A.OUS.SYC

June 2017

Syva® EMIT® 2000

Sulfasalazine and Sulfapyridine Interference with NADH and/or NADPH Reaction Assays

Our records indicate that your facility may have received the following product(s) listed in Table 1.

Reason for Correction

Table 1. Syva® EMIT® 2000 Products affected by Sulfasalazine and Sulfapyridine

Assay	Cat Number	Siemens Material Number (SMN)	Lot Number
Tacrolimus	8R019UL	10445397	All
Sirolimus	8S019UL	10445401	All

Siemens Healthcare Diagnostics has become aware of sulfasalazine and sulfapyridine drug interference in the assays listed in Table 1 which use NADH and/or NADPH to generate redox reactions which produce colorimetric signals. Other Syva® EMIT® assays were tested and did not show any interference.

Siemens has confirmed that erroneous results may occur on samples drawn from patients taking sulfasalazine and sulfapyridine as indicated in the Appendix. Sulfasalazine is an accepted treatment for inflammatory bowel disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis, inflammatory arthritis, and uveitis. Sulfapyridine is used occasionally for dermatitis herpetiformis and related skin disorders when alternative treatment is unsuitable.

The Limitations of the Procedure section of the Instructions For Use (IFU) for the Syva® EMIT® 2000 Tacrolimus assay will be updated to indicate that: Venipuncture should occur prior to sulfasalazine and/or sulfapyridine administration due to the potential for falsely elevated results.

The Limitations of the Procedure section of the IFU for the Syva® EMIT® 2000 Sirolimus assay will be updated to indicate that: Venipuncture should occur prior to sulfasalazine administration due to the potential for falsely elevated results and sulfapyridine administration due to the potential for falsely depressed results.

See Appendix for Maximum % bias observed in the studies conducted by Siemens.

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Risk to Health

The clinical utility of either the Sirolimus or Tacrolimus assay is not impacted as a result of the bias observed due to sulfasalazine or sulfapyridine interference. Sirolimus and Tacrolimus values are not used in isolation to guide clinical decisions as therapeutic ranges for these drugs are dependent upon a number of variables including transplant type, time post-transplant, co-administration of other immunosuppressants, and clinical symptomology consistent with either rejection or toxicity. Siemens is not recommending a review of previously generated results.

Actions to be Taken by the Customer:

- Please review this letter with your Medical Director.
- Venipuncture should occur before drug administration of sulfasalazine or sulfapyridine as indicated above under Reason For Correction. Baseline assay values before administration of sulfasalazine or sulfapyridine therapy are not affected.
- 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.

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.

Appendix:

Maximum bias observed at 0.3 mg/mL (300 mg/L) of Sulfasalazine and Sulfapyridine

Assay	Mean Concentration of Analyte	Maximum% bias observed at 0.3 mg/mL Sulfasalazine	Maximum% bias observed at 0.3 mg/mL Sulfapyridine
Tacrolimus	4.9 ng/mL	17%	14%
Tacrolimus	10.8 ng/mL	13%	10%
Sirolimus	6.1 ng/mL	3%	-15%
Sirolimus	20.0 ng/mL	15%	5%

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FIELD CORRECTION EFFECTIVENESS CHECK

Sulfasalazine and Sulfapyridine Interference with NADH and/or NADPH reaction Assays

This response form is to confirm receipt of the enclosed Siemens Healthcare Diagnostics Urgent Field Safety Notice CHC17-06.A.OUS.SYC dated June 2017 regarding Sulfasalazine and Sulfapyridine Interference with NADH and/or NADPH reaction Assays. Please read the question and indicate the appropriate answer. Fax this completed form to Siemens Healthcare Diagnostics at the fax number provided at the bottom of this page.

1. I have read and understood the Urgent Field Safety Notice instructions provided in this letter. Yes • No •

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