Field Safety Notice

FSN-RPD-2015-011

RPD / ClinChem fully automated
Version 4
11-Jun-2015

Sulfasalazine/Sulfapyridine-Drug Interference

Product Name	ALT/ALTL AST/ASTL CKMBL GLDH NH3L
Product Description	For product description please refer to table 3
GMMI / Part No Device Identifier	For catalogue numbers please refer to table 3
Production Identifier (Lot No./Serial No.)	All lot numbers
Type of Action	Field Safety Corrective Action (FSCA)

Dear Valued Customer,

We regret to inform you about a drug interference detected for assays using NAD(H) or NADP(H).
Due to a complaint interference of Sulfasalazine and Sulfapyridine was investigated and confirmed for ALT, AST, CK-MB, GLDH and NH3. Roche received only one complaint regarding this interference issue since introduction of the above mentioned assays many years ago.

Description of Situation

Based on a complaint the potential interference of Sulfasalazine and Sulfapyridine in the Alanine Amino-Transferase (ALT) tests was investigated.

The interference through Sulfasalazine and Sulfapyridine was checked for all tests using NAD(H) or NADP(H). This study was done with the following strongly elevated plasma concentrations which correspond to the CLSI-Guideline EP-7-A2:

- 754 µmol/L Sulfasalazine (300 mg/L)
- 1.2 mmol/L Sulfapyridine (299 mg/L)

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Please be aware the interference depends on the pharmacokinetic and the clinical status of the patient (e.g. liver and kidney function, bowel resection etc.), which makes it impossible to provide exact information about serum drug concentration and half time.

The following table may give an idea for individuals without additional diseases, but Roche cannot take over the responsibility for this information:

Table 1

	Indication	**Normal dose** - p. o. (per os) - in 2 – 4 evenly divided doses	**Max. serum concentration**	**Half-time**
Sulfasalazine	Treatment of inflammatory bowel disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis, inflammatory arthritis, uveitis	**Usual Adult Dose** - 500 mg to 2 g/d **Max. Adult Dose** - 3 g/day (inadequate therapeutic response after 12 weeks) - 3 to 6 g/day (acute Crohn´s disease) ---------- **Usual Pediatric Dose** (>6 years): - 30 to 60 mg/kg/day **Maximum Pediatric Dose** : - 2 g/day	After 3-6 hours	After mono dose: 5.7 hours Multiple doses: 7.6 hours
Sulfapyridine	Seldom used except occasionally for dermatitis herpetiformis and related skin disorders when alternative treatment is unsuitable	250 mg to 4 g/day	Sulfamethoxazole (similar product): after ~2 hours. Blood concentrations of up to100 micrograms/mL occur after a single 2 g oral dose	~ 6 to 12 hours

For further information please refer to the package inserts of the respective drugs or drug manufacturers or for general information regarding Sulfasalazine and Sulfapyridine.

Sources: www.drugs.com, www.medicinescomplete.com

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Investigation Result

The investigation results showed interference of Sulfasalazine and Sulfapyridine in ALT, AST, CK-MB, GLDH, NH3 which use NAD(H) or NADP(H) in the reaction. This interference most probably is caused by the strong absorption of Sulfasalazine and Sulfapyridine at 340 nm which is the measuring wavelength of the tests using NAD(H) or NADP(H).

Sulfasalazine and Sulfapyridine interference will generally affect assays using NAD(H) or NADP(H) reaction principle.

Indicated in the following table is the maximum bias in % for assays which showed interference with 754 µmol/L Sulfasalazine or 1.2 mmol/L Sulfapyridine, respectively:

Table 2

Parameter	Sulfasalazine 754 µmol/L	Sulfapyridine 1.2 mmol/L
ALT	-69%	-24%
AST	>Abs*/-37%	-37%
CK-MB	+72%/-43%	+23%/-26%
GLDH	-67%	-60%
NH3	>Abs*/<Test**	<Test**

* >Abs: The absorbance value to be used for calculation after cell blank correction exceeded the technical limit (33000 Hitachi units). Consequently no result is calculated.

** <Test: The sample concentration is below the lower technical limit. Consequently no result is calculated.

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Table 3:

GMMI	Product name	Product Description	Analyzer
20764957 322	ALTL	Alanine Aminotransferase	COBAS INTEGRA® 400 plus
11876805 216	ALT (ALAT/GPT)	Alanine aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	**MODULAR** P
04570430 190	ALT (ALAT/GPT)	Alanine aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	**MODULAR** P/D
04570448 190	ALT (ALAT/GPT)	Alanine aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	**MODULAR** P/D
04718569 190	ALTL	Alanine aminotransferase acc. IFCC with or without pyridoxal phosphate activation	**cobas c** 111
20764949 322	ASTL	Aspartate Aminotransferase - Pyridoxal phosphate activated	COBAS INTEGRA® 400 plus
11876848 216	AST (ASAT/GOT)	Aspartate aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	**MODULAR** P
04571100 190	AST (ASAT/GOT)	Aspartate aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	**MODULAR** P/D
04571118 190	AST (ASAT/GOT)	Aspartate aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	**MODULAR** P/D
04657543 190	ASTL	Aspartate aminotransferase with/without pyridoxal phosphate activation	**cobas c** 111
05401763 190	CKMBL	Creatine Kinase-MB	**cobas c** 111
11929992 216	GLDH	Glutamate dehydrogenase	**MODULAR** P
05401739 190	NH3L	Ammonia	**cobas c** 111

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Actions taken by Roche Diagnostics

The interference of Sulfasalazine and Sulfapyridine in the affected tests is to be claimed in the respective instructions for use (IFU) to avoid the reporting of potentially false results. This issue may lead to falsely low/high results (according to table 2).
The following supplemental warning notices have been added to the section “Limitations-interference” of the respective package inserts of the affected tests:

- Sulfasalazine: "Physiological plasma concentrations of Sulfasalazine may lead to false results."
- Sulfapyridine: "Physiological plasma concentrations of Sulfapyridine may lead to false results."

Please note that the update of all affected package inserts is ongoing.

Actions to be taken by the customer/user

Please be aware that

- Sulfasalazine and Sulfapyridine in therapeutic concentrations with tests using NAD(H) or NADP(H) in the reaction, may potentially lead to erroneously low/high ALT, AST, CK-MB, GLDH and NH3 results.
- the results of those assays mentioned above may be falsely low/high when the blood sample is taken while Sulfasalazine and Sulfapyridine are present in the body of the patient.
- physicians should be informed that patients currently treated with Sulfasalazine and Sulfapyridine might receive false results of ALT, AST, CK-MB, GLDH and NH3.

Communication of this Field Safety Notice (if appropriate)

This notice must be passed on to all those who need to be aware within your organization or to any organization/individual where the potentially affected devices have been distributed/supplied.
Please transfer this notice to other organizations/individuals on which this action has an impact.

Please maintain awareness of this notice and resulting action for an appropriate period to ensure the effectiveness of the corrective action.

We apologize for any inconvenience this may cause and hope for your understanding and your support.

Sincerely,

Roche Diagnostics Asia Pacific Pte Ltd
Email: sg.regulatory@roche.com

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ACKNOWLEDGMENT RECEIPT

This is to acknowledge the receipt of Roche Safety Board Advisory Notice: FSN-RPD-2015-011, dated 11-Jun-2015, regarding Sulfasalazine/Sulfapyridine drug interference.

Received by:

_____

Name & Signature

_____

Hospital & Stamp

_____

Date

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