

Urgent Field Safety Notice

FSN-RPD-2015-011

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Sulfasalazine/Sulfapyridine-Drug Interference

Product Name	ALT/ALTL/ALTLP/ALTPM AST/ASTL/ASTLP/ASTPM CKMBL/CKMB/CK-MB GLDH/GLDH3 NH3/NH3L
Product Description	For product description please refer to table 3
GMMI / Part No	For catalogue numbers please refer to table 3
Device Identifier	
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)

Sulfasalazine/Sulfapyridine-Drug Interference

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 to 100 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

Sulfasalazine/Sulfapyridine-Drug Interference

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%
NH ₃	>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.

Sulfasalazine/Sulfapyridine-Drug Interference

Table 3:

GMMI	Product name	Product Description	Analyzer
20764957 322	ALTL	Alanine Aminotransferase acc. to IFCC without pyridoxal phosphate activation	cobas c 311/501/ 502
20764957 322	ALTL	Alanine Aminotransferase	COBAS INTEGRA® 400 plus COBAS INTEGRA® 800
04467388 190	ALTLP	Alanine Aminotransferase acc. to IFCC with pyridoxal phosphate activation	cobas c 311/501/ 502
20764957 322	ALTL	Alanine Aminotransferase - Pyridoxal Phosphate Activated	COBAS INTEGRA® 400 plus COBAS INTEGRA® 800
05850797 190	ALT	Alanine Aminotransferase acc. to IFCC without pyridoxal phosphate activation	cobas c 701/702
05531462 190 05531446 190	ALTPM/ASTPM	Alanine Aminotransferase/Aspartate Aminotransferase acc. to IFCC with pyridoxal phosphate activation	cobas c 701/702
10851132 216	ALT (ALAT/GPT)	Alanine aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	Roche/Hitachi 902
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
11877526 216	ALT (ALAT/GPT)	Alanine aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	MODULAR D
11877569 216	ALT (ALAT/GPT)	Alanine aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	MODULAR D
04718569 190	ALTL	Alanine aminotransferase acc. IFCC with or without pyridoxal phosphate activation	cobas c 111
20764949 322	ASTL	Aspartate Aminotransferase acc. to IFCC without pyridoxal phosphate activation	cobas c 311/501/502
20764949 322	ASTL	Aspartate Aminotransferase - Pyridoxal phosphate activated	COBAS INTEGRA® 400 plus COBAS INTEGRA® 800
04467493 190	ASTLP	Aspartate Aminotransferase acc. to IFCC with pyridoxal phosphate activation	cobas c 311/501/502
20764949 322	ASTL	Aspartate Aminotransferase	COBAS INTEGRA® 400 plus COBAS INTEGRA® 800
05850819 190	AST	Aspartate Aminotransferase acc. to IFCC without pyridoxal phosphate activation	cobas c 701/702
05531462 190 05531446 190	ALTPM/ASTPM	Alanine Aminotransferase/Aspartate Aminotransferase acc. to IFCC with pyridoxal phosphate activation	cobas c 701/702
10851124 216	AST (ASAT/GOT)	Aspartate aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	Roche/Hitachi 902

Sulfasalazine/Sulfapyridine-Drug Interference

GMMI	Product name	Product Description	Analyzer
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
11928597 216	AST (ASAT/GOT)	Aspartate aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	MODULAR D
11928635 216	AST (ASAT/GOT)	Aspartate aminotransferase acc. to IFCC with/without pyridoxal phosphate activation	MODULAR D
04657543 190	ASTL	Aspartate aminotransferase with/without pyridoxal phosphate activation	cobas c 111
04525299 190	CKMBL	Creatine Kinase-MB	cobas c 311/501/ 502 COBAS INTEGRA® 400 plus COBAS INTEGRA® 800
05168562 190	CKMB	Creatine Kinase-MB	cobas c 701/702
12132834 216	CK-MB	Creatine Kinase-MB liquid	Roche/Hitachi 902
12132893 216	CK-MB	Creatine Kinase-MB liquid	MODULAR P
03012468 122	CK-MB	Creatine Kinase-MB liquid	MODULAR P
05401763 190	CKMBL	Creatine Kinase-MB	cobas c 111
11929992 216	GLDH3	GLDH Gen.3	cobas c 311/501/ 502 COBAS INTEGRA® 400 plus COBAS INTEGRA® 800
05975956 190	GLDH3	GLDH Gen.3	cobas c 701/702
11929992 216	GLDH	Glutamate dehydrogenase	Roche/Hitachi 902 MODULAR P
03012425 122	GLDH	Glutamate dehydrogenase	MODULAR P
20766682 322	NH3L	Ammonia	cobas c 311/501/502 COBAS INTEGRA® 400 plus COBAS INTEGRA® 800
05975581 190	NH3L	Ammonia	cobas c 701/702
11877984 216	NH3	Ammonia	MODULAR P Roche/Hitachi 902
05401739 190	NH3L	Ammonia	cobas c 111
04931343 022	ALTL	Alanine Aminotransferase acc. to IFCC without pyridoxal phosphate activation	cobas c 711
04467035 022	ASTL	Aspartate Aminotransferase acc. to IFCC without pyridoxal phosphate activation	cobas c 711

Sulfasalazine/Sulfapyridine-Drug Interference

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.

The undersigned confirms that this notice has been notified to the appropriate Regulatory Agency.

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

Sulfasalazine/Sulfapyridine-Drug Interference

Sincerely,

Contact Details

To be completed locally:

Name

Title

Company Name

Address

Tel. +xx-xxx-xxxx xxxx

Email name@roche.com

The following statement is mandatory in FSNs for EEA countries but is not required for the rest of the World:

Include if applicable: The undersigned confirms that this notice has been notified to the appropriate Regulatory Agency.