

# Field Safety Notice

## FSN-RPD-2014-008

RPD / ClinChem fully automated  
Version 2  
8-May-2015

### Drug Interference in tests based on Trinder Reaction

<b>Product Name</b>	CREA plus, CREP2, LACT2, Lactate, GLU, TRIGL/TG, TRIGGB, TRIG/GB, CHOL/CHOL2, HDL-C plus 3rd generation/HDLC3, LDL_C plus 2nd generation/LDL_C, UA2/UA plus	
<b>Product Description</b>	Creatinine plus, Creatinine plus ver.2, Lactate Gen.2, Lactate, Glucose GOD-PAP, Triglycerides, Triglycerides GPO-PAP, Triglycerides/Glycerol Blanked, Cholesterol CHOD-PAP, Cholesterol Gen.3, HDL-Cholesterol no pretreatment, HDL-Cholesterol plus 3 <sup>rd</sup> generation, LDL-Cholesterol no pretreatment, LDL-Cholesterol plus 2 <sup>nd</sup> generation, Uric Acid ver.2/Uric Acid plus	
<b>GMMI / Part No Device Identifier</b>	CREA plus/CREP2 LACT2/Lactate TRIGL/TG CHOL /CHOL2 HDLC3/HDL-C plus 3rd gen. LDL_C/LDL-C plus 2nd gen. UA2/UA plus TRIGB/ TRIG GB	For catalogue numbers of respective assays, please refer to Table 1.
<b>Production Identifier (Lot No./Serial No.)</b>	All lot numbers	
<b>Type of Action</b>	Field Safety Corrective Action (FSCA)	

Dear Valued Customer,

#### Description of Situation

Roche received complaints about falsely low creatinine (CREA) plus results for patients with a toxic level of Acetaminophen (Paracetamol) under treatment with N-acetylcysteine (NAC).

Other complaints were obtained describing falsely low results of CREA plus after intravenous injection of Metamizole. The CREA plus results were below the measuring range, while plausible results were obtained with the CREA Jaffé method.

# Drug Interference in tests based on Trinder Reaction

Additional studies were initiated to investigate the possible interference with drug metabolites of Acetaminophen and of Metamizole, including the Acetaminophen antidote NAC.

Tests based on the Trinder reaction (abbreviated as “Trinder tests”) use a colorimetric reaction between hydrogen peroxide, a phenol-derivative and aminoantipyrine catalyzed in the presence of peroxidase. Investigations suggest that the peroxidase reaction is interfered by certain drugs, causing falsely low recovery.

## Investigation Result

With the findings from the investigations, more studies were commenced on the emergency parameters (CREA plus, lactate, triglyceride and glucose) that were based on the Trinder reaction. The peroxidase tests with identical POD/H<sub>2</sub>O<sub>2</sub> mechanism were examined for interferences with:

1. Acetaminophen (Paracetamol) and the metabolite N-acetyl-p-benzoquinone imine (NAPQI)
2. N-Acetylcysteine (NAC)
3. Metamizole (Novaminsulfone, Dipyron) and the metabolites 4-Aminoantipyrine (4-AAP) and 4-Methylaminoantipyrine (4-MAP)

According to the current CLSI (Clinical and Laboratory Standards Institute) guideline and Roche’s internal Standard Operating Procedure, the interference investigations were done for 3 different plasma concentrations:

- normal therapeutic range of drug
- 1-fold daily dosage per 5 litres of human plasma
- 5-fold daily dosage per 5 litres human plasma

In all complaints, patient samples were taken shortly after or during intravenous medication.

Investigations showed significant interferences for all emergency parameters based on the Trinder reaction for NAPQI, NAC and Metamizole. This was especially so if the blood sample was taken while a significant plasma concentration of the drug or the drug’s metabolites are still present. The Metamizole metabolites (4-AAP and 4-MAP) and Acetaminophen did not show significant interference.

The other Trinder reaction based tests (cholesterol, HDH-cholesterol, LDL-cholesterol, uric acid) were not investigated. As they do not belong to the emergency panel, there is sufficient time between the administration of a drug, blood sampling and blood testing. These tests, however, will have to be considered in the package insert update due to the existing potential risk of interference caused by identical POD/H<sub>2</sub>O<sub>2</sub> mechanism.

The list of Trinder tests and their corresponding catalogue numbers and analyser types are exemplified in Table 1 below.

## Drug Interference in tests based on Trinder Reaction

Trinder tests <b>Product Name (Product Description)</b>	Analyzer				
	Roche/Hitachi 902 <b>MODULAR P/D</b>	<b>cobas c 111</b>	<b>cobas c 311,</b> 501, 502,	<b>cobas c 701,</b> 702	COBAS INTEGRA® <b>400 plus / 800</b>
<b>CREA plus*</b> (Creatinine plus)	11775685216	n/a	n/a	n/a	n/a
<b>CREP2</b> (Creatinine plus ver.2)	n/a	05401470190	03263991190		03263991190
<b>LACT2</b> (Lactate Gen.2)	n/a		03183700190	05171881190	03183700190
<b>Lactate</b> (Lactate)	11822837190	n/a	n/a	n/a	n/a
<b>GLU</b> (Glucose GOD-PAP)		n/a	n/a	n/a	n/a
<b>TRIGL</b> (Tri-glycerides)	n/a	04657594190	20767107322	05171407190	20767107322
<b>TG</b> (Tri-glycerides GPO-PAP)	11730711216	n/a	n/a	n/a	n/a
<b>TRIGB</b> (Triglycerides /Glycerol Blanked)	n/a	n/a	11877771216		n/a
<b>TRIG/GB</b> (Triglycerides/Glycerol Blanked)	11877771216	n/a	n/a	n/a	n/a
<b>CHOL</b> (Cholesterol CHOD-PAP)	11491458216	n/a	n/a	n/a	n/a
<b>Chol2</b> (Cholesterol Gen.2)	n/a	04718917190	03039773190	05168538190	03039773190
<b>HDL-C plus 3rd generation</b> (HDL-Cholesterol, no pretreatment)	0 04713214190	n/a	n/a	n/a	n/a
<b>HDLC3</b> (HDL-Cholesterol plus 3rd generation)	n/a	05401488190	04399803190	05168805190	04399803190
<b>LDL-C plus 2nd generation</b> (LDL-Cholesterol, no pretreatment)	04714423190	n/a	n/a	n/a	n/a
<b>LDL_C</b> (LDL Cholesterol plus 2nd generation)	n/a	05401682190	03038866322	05171369190	03038866322
<b>UA2</b> (Uric Acid ver.2)	n/a	04657608190	03183807190	05171857190	03183807190
<b>UA plus</b> (Uric Acid plus)		n/a	n/a	n/a	n/a

Table 1: Catalogue number of assay based on Trinder reaction principle

# Drug Interference in tests based on Trinder Reaction

## Actions taken by Roche Diagnostics

In the “Limitations - interference” section of the Trinder test package inserts, the following claims will be added to the respective package inserts:

### **Creatinine plus, lactate, triglyceride:**

“Acetaminophen intoxications are frequently treated with N-Acetylcysteine. N-Acetylcysteine at a plasma concentration above x mg/L\* and the Acetaminophen metabolite N-acetyl-p-benzoquinone imine (NAPQI) independently may cause falsely low results.”

“Venipuncture should be performed prior to the administration of Metamizole. Venipuncture immediately after or during the administration of Metamizole may lead to falsely low results. A significant interference may occur at plasma Metamizole concentrations above x mg/L\*.”

*\*The concentration depends on the test.*

### **Cholesterol, HDL-cholesterol, LDL-cholesterol and uric acid:**

“Acetaminophen intoxications are frequently treated with N-Acetylcysteine. N-Acetylcysteine at the therapeutic concentration when used as an antidote and the Acetaminophen metabolite N-acetyl-p-benzoquinone imine (NAPQI) independently may cause falsely low results.”

“Venipuncture should be performed prior to the administration of Metamizole. Venipuncture immediately after or during the administration of Metamizole may lead to falsely low results.”

### **Urine application for creatinine plus and uric acid:**

“Acetaminophen, Acetylcysteine and Metamizole are metabolized quickly. Therefore, interference from these substances is unlikely but cannot be excluded.”

## Actions to be taken by the customer/user

Please be aware that

- the recovery of Trinder tests may be falsely low when the blood sample is taken while levels of NAC, NAPQI, and Metamizole are still present.
- Venipuncture should be performed prior to the administration of Metamizole. Venipuncture immediately after or during the administration of Metamizole may lead to falsely low results.
- Acetaminophen, N-Acetylcysteine and Metamizole are metabolized quickly. Therefore, interference from these substances is unlikely but cannot be excluded in the creatinine plus and uric acid urine application.



# Drug Interference in tests based on Trinder Reaction

## Communication of this Field Safety Notice

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](mailto:sg.regulatory@roche.com)



# Drug Interference in tests based on Trinder Reaction

## ACKNOWLEDGMENT RECEIPT

This is to acknowledge the receipt of Roche Safety Board Advisory Notice: FSN-RPD-2014-008, dated 08-May-2015, regarding trinder tests drug interference.

Received by:

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Name & Signature

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Hospital & Stamp

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Date