

Urgent Field Safety Notice

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Drug Interference in tests based on Trinder Reaction

Product Name	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	
Product Description	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 rd generation, LDL-Cholesterol no pretreatment, LDL-Cholesterol plus 2 nd generation, Uric Acid ver.2/Uric Acid plus	
GMMI / Part No Device Identifier	CREA plus/CREP2 LACT2/Lactate GLU /Glucose GOD-PAP 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 refer to table 1 on page 3/4
Production Identifier (Lot No./Serial No.)	All lot numbers	
Type of Action	Field Safety Corrective Action (FSCA)	

Dear Valued Customer,

Description of Situation

Roche received complaints about falsely low CREA plus results for patients with a toxic level of Acetaminophen 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.

Trinder Test Drug Interference

Additional studies were needed 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 with by certain drugs, causing falsely low recovery.

Investigation Result

After the investigations confirmed the interference of drugs and metabolites with CREA plus, further studies with emergency parameters based on the Trinder reaction were initiated. The peroxidase tests with identical POD/H₂O₂ mechanism, i.e. CREP2, LACT2, TRIG, GLU GOD PAP, and TRIG/GB were investigated for interferences with:

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

According to the current CLSI 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 liters of human plasma
- 5-fold daily dosage per 5 liters 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 Paracetamol (Acetaminophen), N-Acetylcysteine 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.

For NAC, NAPQI, and Metamizole a significant influence on the Trinder tests was found due to drug interference, depending on the drug plasma level. The Metamizole metabolites 4-AAP and 4-MAP did **not** show a significant interference.

The other Trinder tests CHOL2, HDLC3, LDL_C and UA2 were **not** investigated. These will have to be considered due to the existing potential risk of interference caused by identical POD/H₂O₂ mechanism.

The Trinder test catalogue numbers and analyzer types being updated with this new claim are listed in **Table 1** on the following pages:

Trinder Test Drug Interference

Trinder tests Product Name (Product Description)	Analyzer				
	Roche/Hitachi 902 MODULAR P/D	cobas c 111	cobas c 311, 501, 502	cobas c 701, 702	COBAS INTEGRA® 400 plus / 800
CREA plus* (Creatinine plus)	11775642216 11775685216 11875566216 11875582216	n/a	n/a	n/a	n/a
CREP2 (Creatinine plus ver.2)	n/a	05401470190	03263991190	05168589190	03263991190
LACT2 (Lactate Gen.2)	n/a	05401666190	03183700190	05171881190	03183700190
Lactate (Lactate)	11822837190	n/a	n/a	n/a	n/a
GLU (Glucose GOD-PAP)	11491253216 11929526216 11448668216	n/a	n/a	n/a	n/a
TRIGL (Tri-glycerides)	n/a	04657594190	20767107322	05171407190	20767107322
TG (Tri-glycerides GPO-PAP)	11730711216 11876023216 11876040216 11488872216	n/a	n/a	n/a	n/a
TRIGB (Triglycerides /Glycerol Blanked)	n/a	n/a	11877771216	05976006190	n/a
TRIG/GB (Triglycerides/Glycerol Blanked)	11877771216 11877780190 11877798190	n/a	n/a	n/a	n/a
CHOL (Cholesterol CHOD-PAP)	11489232216 11491458216 11875540216 11875523216	n/a	n/a	n/a	n/a
Chol2 (Cholesterol Gen.2)	n/a	04718917190	03039773190	05168538190	03039773190
HDL-C plus 3rd generation (HDL-Cholesterol, no pretreatment)	04713109190 04713257190 04713214190 04713265190 04713290190 04713311190 04713320190	n/a	n/a	n/a	n/a
HDLC3 (HDL-Cholesterol plus 3rd generation)	n/a	05401488190	04399803190	05168805190	04399803190

Trinder Test Drug Interference

LDL-C plus 2nd generation (LDL-Cholesterol, no pretreatment)	04714423190 04711220190 05230438190 05230446190	n/a	n/a	n/a	n/a
LDL_C (LDL Cholesterol plus 2nd generation)	n/a	05401682190	03038866322	05171369190	03038866322
UA2 (Uric Acid ver.2)	n/a	04657608190	03183807190	05171857190	03183807190
UA plus (Uric Acid plus)	11875426216 11661850216 11929429216 11929437216 11929445216 11929453216	n/a	n/a	n/a	n/a

Actions taken by Roche Diagnostics

In the “Limitations - interference” section of the Trinder test method sheets respective claims are being added, which describe the observed interferences in relation to the interfering drug or its metabolites. The package inserts will be adjusted accordingly, including the information that venipuncture should be performed prior to the administration of Metamizole.

Actions to be taken by the customer/user

Please be aware that

- the recovery of Trinder tests may be falsely low when the 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.

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.

Trinder Test 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.