Urgent Field Safety Notice
SBN-CPS-2019-006

CPS / TDM
Version 1
July 2019

ONLINE TDM Vancomycin Gen.3 incorrectly low results

Product Name	ONLINE TDM Vancomycin Gen.3 (VANC3)
System	**cobas c** 311 analyzer **cobas c** 501/502 modules **cobas c** 701/702 modules **cobas c** 503 analytical unit
GMMI / Part No **Device Identifier**	06779336190 ONLINE TDM Vancomycin Gen.3 100 Tests (c 311, c 501/502) 06779344190 ONLINE TDM Vancomycin Gen.3 200 Tests (c 311, c 501/502) 06781632190 ONLINE TDM Vancomycin Gen.3 150 Tests (c 701/702) 08445605190 ONLINE TDM Vancomycin Gen.3 100 Tests (c 503) 08058849190 ONLINE TDM Vancomycin Gen.3 200 Tests (c 503)
SW Version	n/a
Type of Action	Field Safety Corrective Action (FSCA)

Dear Valued Customer,

Description of Situation

Roche has received a small number of reports about incorrectly low results for vancomycin in individual patient samples measured with the ONLINE TDM Vancomycin Gen.3 assay on **cobas c** platforms (VANC3).

Some results were flagged as below the measuring range (<Test; defined by Limit of Quantification (LoQ) 4.0 µg/mL). As the patients were receiving vancomycin pharmacotherapy, the results below the measuring range were unexpected and thus implausible.

Other results were erroneously low within the measuring range without any flag. Internal investigations using alternative reagent formats and techniques (e.g. LC-MS/MS) confirmed that these samples contained vancomycin and therefore the results obtained with ONLINE TDM Vancomycin Gen.3 were incorrect.

Root cause

The VANC3 immunoassay uses a competitive assay format in which microparticles agglutinate (KIMS). In the reported cases the VANC3 reagent reaction kinetic is impaired. The kinetics of the affected samples showed an unusual strong agglutination of the microparticles. This led to the incorrect results below the measuring range (<4.0 µg/mL) observed in the reported cases. With the competitive test format of VANC3 a lower aggregation kinetic would be expected for samples containing vancomycin.

Falsely low results with ONLINE TDM Vancomycin Gen.3

From the reaction kinetics of the incorrectly low results within the measuring range (4.0-80 µg/mL) it is concluded that the affected patient samples contain one or more non-specific interfering substance(s) that enhance the agglutination. Despite several investigations, the interfering substance(s) could not be isolated. Immunofixation was performed on the available samples and a suspicious immunoglobulin pattern was observed. The exact target/epitope of these immunoglobulins could not be determined.

Detectability & Severity

For results below the measuring range, detection is probable, as this scenario is implausible and not expected during vancomycin pharmacotherapy.

For incorrectly low results within the measuring range detection may be unreliable or difficult. Incorrectly low VANC3 test results within the measuring range are difficult to detect if not confirmed by an alternative method.

The frequency of occurrence is remote based on the reported cases per number of tests performed.

Actions taken by Roche Diagnostics

1. Introduction of a prozone check

In order to make customers aware of incorrect results below the measuring range, Roche will implement a 'prozone check' for the VANC3 applications ACN (8)159 for the **cobas c** 311 analyzer, **c** 501/502 and **c** 701/702 modules. This check detects samples with a stronger agglutination than that of a vancomycin-free sample or the zero calibrator. Such affected samples will be flagged with a ">Kin" flag. Updated e-library packages are expected to be available by the end of September 2019.

For the VANC3 application (ACN 21210) on **cobas c** 503 analytical unit a corresponding check (kinetic unstable check) has already been implemented with the launch version. The affected samples will be flagged with ">Kin3".

2. Update of the Instructions for Use (IfU) for VANC3 on all cobas c analyzer

In general, the operator manuals for the **cobas c** systems recommend a dilution or a rerun with decreased sample volume for ">Kin" or ">Kin3" flagged samples. However, for samples with a low recovery below the measuring range a dilution of the affected samples would not correct the recovery and the recommended action for such a sample is to use another assay technique. Therefore, the Instructions for Use (IfU) will be updated to include the following information, expected to be available by the end of September 2019:

"A test result flagged with ">Kin", ">Kin3" indicates unusual reaction kinetics. There is a high probability that the sample contains an interfering substance which accelerates the reaction kinetics. For such very rare samples it is not possible to report a reliable analyte concentration with this assay."

Investigation showed an agglutination of the microparticles that could not always be distinguished from unaffected samples. Therefore, samples with a low recovery within the measuring range cannot be detected by a prozone check. As interfering substances can also lead to an inhibition of the agglutination and consequently to incorrectly high results, it was decided to include the following disclaimer in the IfU:

"In very rare cases (less than 1 reported case per 1 000 000 tests) certain immunoglobulins can unspecifically interfere with the agglutination reaction leading to unreliable results."

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Actions to be taken by the customer/user

The prozone check settings cannot be changed manually but is included in the updated application.

For VANC3 on **cobas c** 311 analyzer and **cobas c** 501/502/701/702 modules we kindly ask you to download the updated VANC3-application. The updated IfU will be available in the e-content portal.

Samples showing incorrectly low VANC3 test results below and within the measuring range should be re-tested with alternative immunoassays or LC-MS/MS.

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 where the devices have been distributed/supplied. (If appropriate).

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 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.

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

<closing salutations>,

Contact Details

To be completed locally:

Name

Title

Company Name

Address

Tel. +xx-xxx-xxxx xxxx

Email name@roche.com