Date: Wed, 26 Sep 2018 at 14:02
Subject: Safety Notification: Deviations of high (>4.5) CoaguChek INR values due to calibration with WHO reference standard rTF/16

Dear Customer,

Following up our Recall for product correction notification - "Deviations of high (>4.5) Coaguchek INR values due to masterlot calibration issue" - issued on Wed 19th Sept, we are aware that there is some confusion regarding when to request a repeat laboratory sample. Roche, in consultation with Medsafe (Friday 21st September), reconfirm our recommendation that:

- Coaguchek INR results above 4.5, from lots specified in the attached notification, are confirmed with a laboratory method.

Apologies for the inconvenience, please contact Roche if you have any concerns or questions regarding this notification.

Best Regards
Mark

Mark Kilgour

Marketing Manager

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Recall for Product Correction – Version 2

Deviations of high (>4.5) CoaguChek INR values due to masterlot calibration issue

Date: September 2018 **Bulletin Number: SBN-POC-2018-03** **Roche Reference: SBN-CPS-2018-014**

Affected Product(s):

CoaguChek XS PT Test PST	**07671679190, 07671687019**
CoaguChek XS PT Test	**04625358172, 04625315172**
CoaguChek PT Test	**06688721019**

Affected Lot(s):

CoaguChek XS PT Test PST	**from #272167 (S_303) up to #334498 (S_343)**
CoaguChek XS PT Test	**from #272167 (S_303) up to #334498 (S_343)**
CoaguChek PT Test	**from #272170 (S_054) up to #353606 (S_061)**

System:

CoaguChek® XS System
CoaguChek® INRange system
CoaguChek® XS Plus system
CoaguChek® XS Pro system
CoaguChek® Pro II system

Reason for Version 2:
Expanded workaround options, due to inquiries about the use of other thromboplastins or unaffected CoaguChek test strips for comparison measurement.

☐ **Information** ☐ **Information and Action** ☒ **Feedback form mandatory**

Dear Valued Customer,

We need to inform you that Roche Diagnostics has decided to implement a temporary re-calibration of our CoaguChek PT, XS PT and XS PT PST test strips to the previous WHO Standard rTF*/09. At the same time, we can confirm that all CoaguChek test strips in the market which have been calibrated to the latest WHO standard rTF/16 (please refer to the lot numbers mentioned above) are safe to use for results between 0.8 to 4.5 INR.

**(rTF = human, recombinant thromboplastin / recombinant human tissue factor reagent)*

Description of Situation

Since the market introduction of CoaguChek, test strips have been calibrated against standard reference thromboplastin provided by the WHO. In 2016, a new WHO reference Thromboplastin, rTF/16, was established. This new WHO reference standard is calibrated to INR values between 1.5 and 4.5 INR and is derived from human tissue factors. Compared to the previous WHO standard of human based thromboplastin (rTF/09), it leads to a slight increase in INR values and shows a higher International Sensitivity Index (ISI)[1]:

WHO Standard	ISI
rTF/09	1.08
rTF/16	1.11

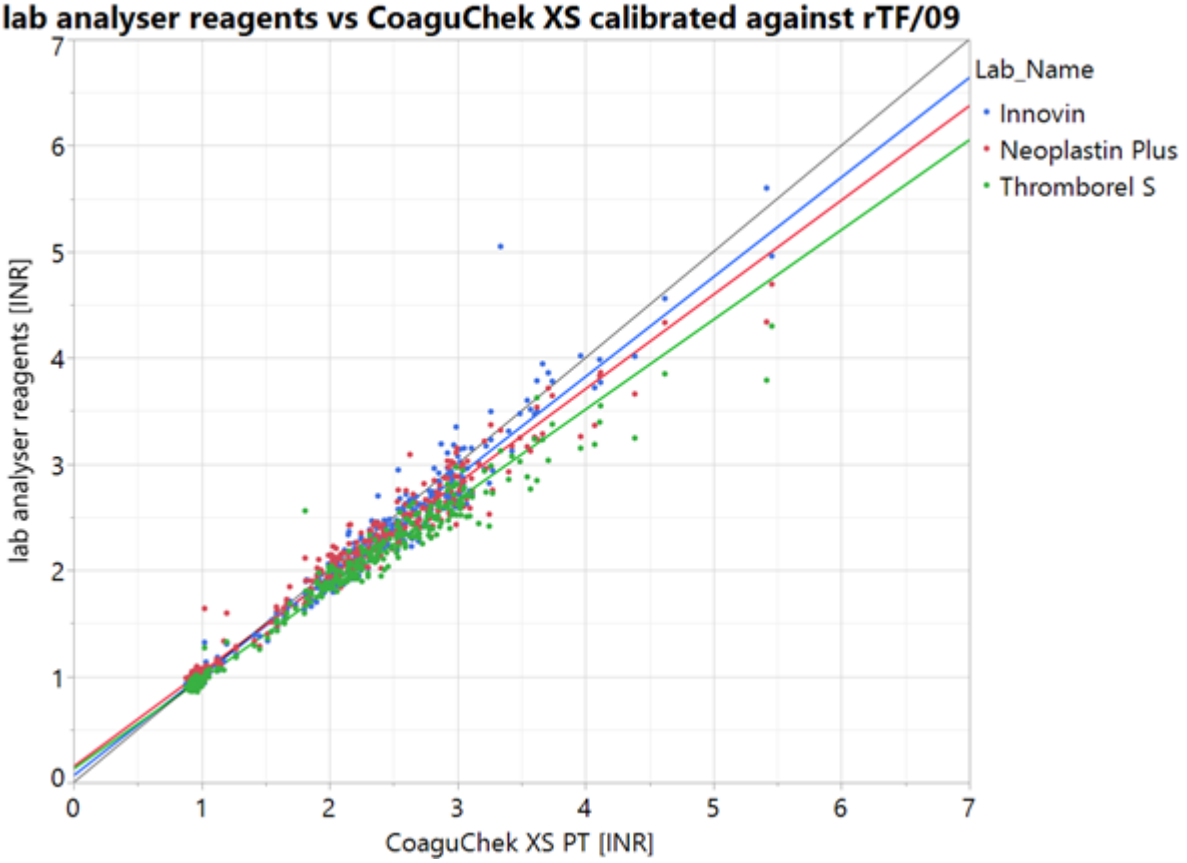
Table 1: ISI values of WHO standards

As the global leader for INR Point-of-Care solutions, Roche was one of the first companies to switch to the new WHO standard. CoaguChek test strips calibrated to this new (rTF/16) standard were delivered to markets worldwide from January 2018 onward.

Roche Diagnostics has received an increased number of complaints regarding deviations of CoaguChek test strips against non-Roche controls as well as laboratory methods during the last weeks. Therefore, we initiated an in-depth analysis in order to determine the reasons for the observed differences.

Our findings:

- For values up to 4.5 INR and calibrated to the new (rTF/16) WHO standard (1.5-4.5 INR), a mean difference of +6% was found when we compared in an internal validation study the new CoaguChek test strips against test strips calibrated to the previous (rTF/09) reference WHO standard.
- In our complaint investigation we have seen an unexpected additional increasing positive bias in the upper INR range (> 4.5 INR).
- Due to these findings, it was decided to limit the use of the currently available CoaguChek (XS PT, XS PT PST, and PT) strips to the range of up to 4.5 INR which is in accordance to the validation of the WHO standard.
- In general, several influencing factors e.g. lot to lot differences, pre-analytics (e.g. sample tubes) can have a significant influence on the comparison of different methods (see graph below).



Graph: Roche Diagnostics, External Masterlot calibration study CoaguChek XS PT, 2017

- No deviations have been experienced with the CoaguChek test strips referenced to the previous WHO standard rTF/09. Most laboratory methods are still calibrated against the previous (rTF/09) WHO standard.
- Internal analysis of complaints showed that after therapy changes (change of dosage, additional medication, hold of medication) the frequency of testing was not always adapted. Therefore, we recommend to follow the local medical guidelines regarding an increased testing frequency after therapy changes.

Actions taken by Roche Diagnostics

Since a medical risk, due to inadequate therapeutic measures, for INR ranges >4.5 INR, cannot be excluded, it was decided to re-calculate the calibration for upcoming CoaguChek strip lots according to the previous WHO standard (rTF/09). Moreover, the current CoaguChek test strips, calibrated to the new WHO standard rTF/16, can still be used but are limited to INR values up to 4.5 INR. For all values above 4.5 INR, measured with CoaguChek test strips of the affected lot numbers, the advice under “actions to taken by the customer/user” must be followed.

The first test strips re-calibrated to rTF/09 will be available **beginning / mid-October 2018** for the following lot numbers and availabilities:

Product Code	Product Name	Lot Number (Code Key)	Estimated Availability in stock (NZ)
07671679190	CoaguChek XS PT Test PST, 6 tests	≥334499 (S_344)	Oct 2018
07671687019	CoaguChek XS PT Test PST, 24 tests	≥334499 (S_344)	Nov 2018
04625358172	CoaguChek XS PT Test, 24 tests	≥334499 (S_344)	Oct 2018
04625315172	CoaguChek XS PT Test, 2 x 24 tests	≥334499 (S_344)	Oct 2018
06688721019	CoaguChek PT Test, 2 x 24 tests	≥361433 (S_062)	Nov 2018

Table 2: Availability rTF/09 Lots

Until the new lots are available, rTF/16 calibrated test strips continue to be distributed for the following reasons:

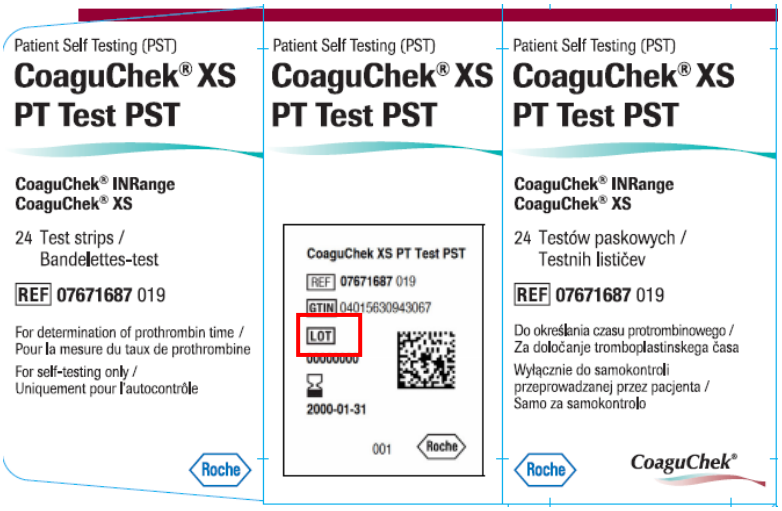
- values are reliable up to 4.5 INR
- the difference in the ranges between 0.8 to 4.5 INR, caused by the rTF/16 calibrated test strips when compared to rTF/09 based test strips, does not expose patients to a medical risk

A re-calibration to the new rTF/16 standard will be carefully evaluated.

In 2019 as an additional measure the respective CoaguChek test strip method sheets will be updated, with regard to method comparison.

Actions to be taken by the customer/user

Check the lot number on the box of strips to see if it is included in the list of affected lots.
The lot number is printed on the label applied to the test strip box, see below illustration:



In order to prevent any risk to your and our valued patients we ask you for the following actions:

1. Health Care Professionals using one of the affected lots in their GP office/hospital:
    - Values ≤4.5 INR: Values are valid and can be used without a comparison test.
    - Values >4.5 INR: If values >4.5 INR are measured a comparison measurement shall be performed with either a laboratory method or unaffected CoaguChek test strips. In addition, the testing frequency shall be increased according to local medical guidelines until results in the therapeutic range of that individual are obtained until recalibrated material is available.

2. Health Care Professionals (HCP) with patients performing self-testing/self-management:
    - Values ≤4.5 INR: Values are valid and can be used without a comparison test.
    - Values >4.5 INR: If values >4.5 INR are measured a comparison measurement shall be performed with either a laboratory method or unaffected CoaguChek test strips. In addition, the testing frequency shall be increased according to local medical guidelines until results in the therapeutic range of that individual are obtained until recalibrated material is available.

HCPs are requested to please **reactively** hand out the attached "Patient-Information-Letter" at their discretion, if patients use CoaguChek tests strips of the affected lots calibrated against rTF/16.

3. Wholesalers, Retailers
   Please forward this notice and/or the attached "patient information letter" (where applicable) to all your affected customers.
   If patients contact you regarding INR results above their therapeutic range, please advise your customer to contact their local Health Care Professional.

4. All customers:
    - Read and familiarise all staff working with these Coaguchek products of the potential risk and follow the actions recommended in this letter.
    - Please replace the previous notice with this version and retain in a prominent place in your organisation until the new test strip lots are in use.
    - Please complete the attached acknowledgement form and return to Roche Diagnostics NZ by fax or email as soon as possible.

Once you have received the new rTF/09 calibrated test strip lots you can return to your usual testing and treatment procedures.

<u>Please note with respect to the impact towards patients on patient self-testing:</u>
All package inserts of CoaguChek test strips used by patients (XS PT/XS PT PST) contain the following advice:

CoaguChek XS PT Test:
"If the measured PT result is unusually high or low repeat the test. If the PT result is still outside the therapeutic range specified by your treating physician, immediately contact your physician and ask for the appropriate (anticoagulant) measures to take in order to reduce risks that could be encountered due to excessive anticoagulation (danger of bleeding) or insufficient anticoagulation (risk of thrombosis)."

CoaguChek XS PT Test PST:
"If the measured result is outside the therapeutic range specified by your treating physician, repeat the test. If the result is still outside the therapeutic range immediately contact your physician and ask for the appropriate (anticoagulant) measures to take."

Therefore, the above mentioned limitation of the measuring range will have only small impact to the current procedure of managing patients performing patient self-testing. The risk of unnecessary Vitamin-K intake due to deviated high INR values (>4.5) is mitigated by the interaction with the physician.

<u>Please note with respect to the impact towards patients on patient self-management:</u>
Patient self-managers are trained to contact their physicians as soon as they measure values above 4.5 INR. Therefore, patients can continue using their CoaguChek device as before with one limitation: When they measure values above 4.5 INR, they should ask their physician for a parallel testing with a laboratory method in order to decide on further medication. As a result, the above mentioned limitation of the measuring range (>4.5) will have only small impact to the current procedure of managing patients performing patient self-management. The risk of

unnecessary Vitamin-K intake due to deviated high INR values (>4.5) is mitigated by the interaction with the physician.

Communication of this Product Correction

This notice must be passed on to all those who need to be aware within your organisation or to any organisation/individual where the potentially affected devices have been distributed/supplied.

Please transfer this notice to other organisations/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.

This action is being taken in consultation with Medsafe, Ministry of Health (Ref # 23547)

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

Kind Regards,

Keryn Smith
Product Manager, Point of Care
Roche Diagnostics

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References:

1) van den Besselaar AMHP, Chantarangkul V, Angeloni F, Binder NB, Byrne M, Dauer R, Gudmundsdottir BR, Jespersen J, Kitchen S, Legnani C, Lindahl TL, Manning RA, Martinuzzo M, Panes O, Pengo V, Riddell A, Subramanian S, Szederjesi A, Tantanate C, Herbel P, Tripodi A. International collaborative study for the calibration of proposed International Standards for thromboplastin, rabbit, plain, and for thromboplastin, recombinant, human, plain. J Thromb Haemost 2018; 16: 142–9.

Acknowledgement of In Vitro Diagnostics Device Notification

Please complete this form and return to: Roche Diagnostics NZ
Attention: Alison Rhodes

Recall for Product Correction – Version 2

I have read and understood the instructions related to the following product**:**

Deviations of high (>4.5) CoaguChek INR values due to masterlot calibration issue

Returning Organisation:

Name:

Address:

Telephone Number:

Fax:

Details of person making the declaration

Name:

Position:

Date:

Signature:

Fax to: 09 276 8917 or email to: keryn.smith@roche.com