URGENT FIELD SAFETY NOTICE
IMMEDIATE ACTION REQUIRED

Ref No:	**PFSN18 Deviations of high (>4.5) CoaguChek INR values due to calibration with WHO reference standard rTF/16 SBN-CPS-2018-014**
Date:	**22.08.2018**
Type of Action:	**Field Safety Corrective Action (FSCA)**
Product Affected:	CoaguChek XS PT Test PST CoaguChek XS PT Test CoaguChek PT Test
System Affected:	CoaguChek® XS system CoaguChek® INRange system CoaguChek® XS Plus system CoaguChek® XS Pro system CoaguChek® Pro II system
Software Version:	N/A

Product No	Material No	Lot No
CoaguChek XS PT Test PST	07671679190, 07671687019	from 272167 up to 334498
CoaguChek XS PT Test	04625374190, 04625358019, 04625315019	from 272167 up to 334498
CoaguChek PT Test	06688721019	from 272170 up to 353606

Summary of Issue

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)*

Reason for Notice

Description of Situation

Since 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 towards 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 an increase in INR values (6% bias) and shows a higher International Sensitivity Index (ISI):[1]

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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 decided to switch to the new WHO standard and was one of the first companies who delivered CoaguChek test strips calibrated towards this new (rTF/16) standard to markets from January 2018.

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 within the common therapeutic ranges (up to 4.5 INR) and covered by the new (rTF/16) WHO standard (1.5-4.5 INR) a bias of 6% was verified when we compared the new CoaguChek test strips against Innovin-based thromboplastin from the previous (rTF/09) reference WHO standard. This bias is caused by the differences between the previous (rTF/09) and the new (rTF/16) WHO reference standards and was expected to be seen.
- For values >4.5 INR an unexpected increasing positive bias was found between CoaguChek test strips referenced to the latest WHO rTF/16 and Innovin-based laboratory methods referenced to rTF/09.
- No deviations have been experienced with the previous CoaguChek test strips referenced to the previous WHO standard rTF/09. Most laboratory methods are still calibrated against the previous (rTF/09) WHO standard.

Actions taken by Roche Diagnostics

Since a medical risk, due to a possible Vitamin K treatment decision, 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. All values above 4.5 INR, measured with CoaguChek test strips of the affected lot numbers (see above), should be double checked against a laboratory method. As mentioned in the method sheet of the test strips, methods using Innovin as Thromboplastin (Siemens) correlate very well with the CoaguChek system.

The first test strips re-calibrated to rTF/09 will be available from **November 2018** for the following lot numbers:

REF-Number	Product Name	Lot Number (Code Key)
07671679190	CoaguChek XS PT Test PST, 6 tests	≥334499 (S_344)
07671687019	CoaguChek XS PT Test PST, 24 tests	≥334499 (S_344)
04625374190	CoaguChek XS PT Test, 6 tests International	≥334499 (S_344)
04625358019	CoaguChek XS PT Test, 24 tests	≥334499 (S_344)
04625315019	CoaguChek XS PT Test, 2 x 24 tests	≥334499 (S_344)
06688721019	CoaguChek PT Test, 2 x 24 tests	≥361433 (S_062)

Table 2: Availability rTF/09 Lots

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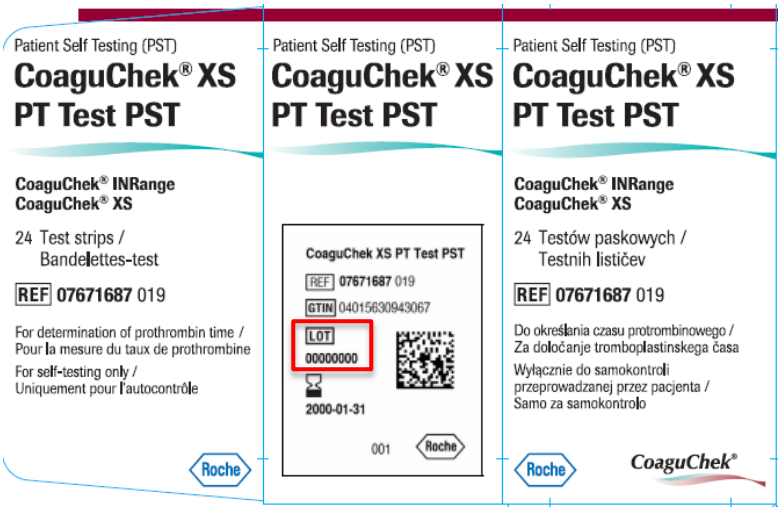
The lot number is printed on the label, which is applied to the test strip box at manufacturing:



*Example for box only

With the above mentioned lots in Table 2 the issue is resolved and values up to 8.0 INR are valid.

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

- values are reliable from 0.8 to 4.5 INR
- the difference of 6%, caused by the new WHO standard, does not expose patients to a medical risk

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

The "Patient-Information-Letter" attached will be provided to patients that have purchased CoaguChek XS PT Test PST and CoaguChek XS PT Test strips directly from Roche.

Action Required

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 lab comparison
   - Values >4.5 INR: Values should be compared with a laboratory method.

   As mentioned in the method sheet of the test strips, methods using Innovin as Thromboplastin (Siemens) correlate very well with the CoaguChek system.

Method Sheet CoaguChek XS PT, XS PT Test PST: […] Clinical studies were conducted in which venous and capillary blood results from the CoaguChek XS/XS Plus/XS Pro Systems were compared with venous blood results obtained using the laboratory reference method Innovin (Dade-Behring). The majority of slopes were found between 0.93 and 1.04 for venous results, and between 0.92 and 1.03 for capillary results […]

Method Sheet CoaguChek PT Test: […] A clinical study was conducted at 4 external sites in which venous

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blood results obtained with CoaguChek PT Test were compared to venous citrated plasma results obtained using the laboratory method Innovin (Siemens) [….]

Please note: Other methods that use e.g. Neoplastin Plus or Thromborel S do not correlate as well with the CoaguChek system.

2. Health Care Professionals (HCP) with patients performing self-testing/self-management:
   - Values ≤4.5 INR: Values are valid and can be used without lab comparison
   - Values >4.5 INR: Values should be compared with a laboratory method.

   As mentioned in the method sheet of the test strips, methods using Innovin as Thromboplastin (Siemens) correlate very well with the CoaguChek system.
   You are requested to please **reactively** hand out the attached "patient information letter" at your discretion, if patients use CoaguChek tests strips of the affected lots calibrated against rTF/16.

3. Insurers & Retailers (wholesalers, pharmacies etc.):
   If patients contact you regarding INR results above their therapeutic range, please advise your customer to contact their local Health Care Professional.

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

Please complete and return the Acknowledgement Form which accompanies this Field Safety Notice by Sept 5th 2018

Please bring this notice to the attention of all personnel in your hospital or Health Care facility who need to be aware of this safety issue.

If you have forwarded the affected product(s) listed above to another laboratory, please provide a copy of this notice to them.

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

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,

Attachments Consumer Letter

Acknowledgement Form

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This action is being conducted with the knowledge of the Medicines and Healthcare Products Regulatory Agency (MHRA), the Health Products Regulatory Authority (HPRA), and other International Regulatory Agencies.

Roche Diagnostics operates a vigilance system that complies with the IVD Directive 98/79 EC

A copy of this notice can also be found on the Roche Dialog Portal

If you require any further information please contact our

Technical Support Hotline

UK: 0808 100 19 20
Ireland: 1800 40 95 64

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Consumer Letter

(CoaguChek XS PT Test PST, CoaguChek XS PT Test, CoaguChek PT Test)

Urgent Field Safety Notice

<Enter address here>

Roche Diagnostics Limited,
Date: 22/08/2018

Ref: PFSN18 Deviations of high (>4.5) CoaguChek INR values due to calibration with WHO reference standard rTF/16 SBN-CPS-2018-014.

We are writing to inform you about an issue concerning your CoaguChek system and test strips. Please read this information carefully.

Dear Customer,

In order to ensure that your CoaguChek values can be compared to values of other devices (e.g. laboratory systems, Point-of-Care systems in your GP office/Coagulation clinic) we calibrate our test strips against the standard from the World-Health-Organization (WHO). This standard was renewed in 2016. Although manufacturers are not obliged to standardize against the newest standard, as a pioneer for the monitoring of so called "Blood Thinners" Roche Diagnostics decided to do so.

Roche Diagnostics has received an increase in complaints regarding deviations against laboratory methods during the last weeks. Therefore, we initiated an in-depth analysis in order to determine the reasons for the observed differences.

The results of the analysis were:

- For values between 0.8 and 4.5 INR: No significant differences are seen and your CoaguChek is reliable.
- For values above 4.5 INR: Greater than expected deviations to the laboratory methods were seen.

What does that mean to me as a patient self-tester?

Each patient has a so called "therapeutic range" she/he should be compliant to. The therapeutic range is defined by the indication you are receiving "Blood Thinners" (e.g. Atrial fibrillation, heart valve, VTE etc.) for. None of the medically used therapeutic ranges exceed the above mentioned value of INR 4.5. Therefore, your system is delivering reliable results for your relevant therapeutic range.

However, according to the package insert you should contact your physician every time you are out of your therapeutic range:

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 limitation caused by this issue should be minimal, except for the fact that you should ask your health care professional for a laboratory cross-check for values above 4.5 INR.

You can continue using your CoaguChek device as you have done before with one limitation: As soon as you measure values above 4.5 INR, please contact your health care professional and ask for parallel testing with a laboratory method in order to decide on your further medication.

Which are the affected test strip lots?

The following lot numbers may be used up to an INR of 4.5. If the values exceed an INR of 4.5, please contact your health care professional.

Product	REF-Number (found on your test strip box)	Lot Number (only valid up to 4.5 INR)
CoaguChek XS PT Test	04625315019 04625358019 04625374190	272167 – 334498
CoaguChek XS PT PST Test	07671679190 07671687019	272167 – 334498

Table 1: Lot numbers affected by the limitation

Will this limitation be forever?

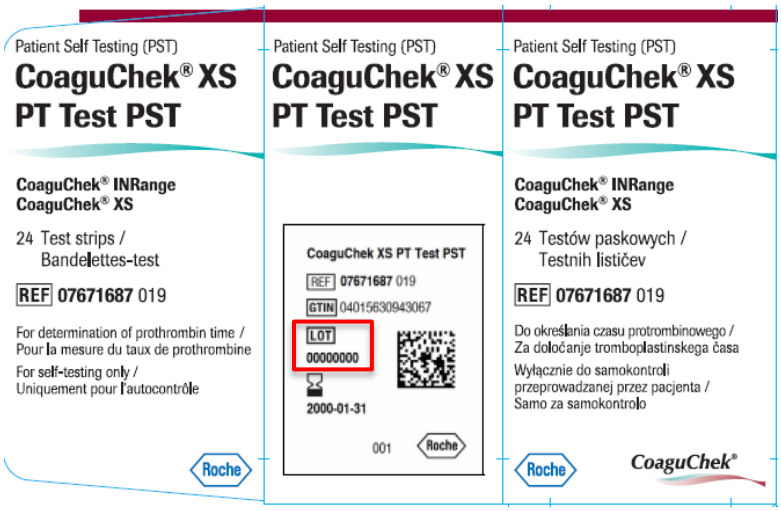
No – Roche Diagnostics has already started to produce new CoaguChek test strips, which will not have this limitation anymore and those strips will be available from **November 2018** as follows:

REF-Number	Product Name	From Lot Number and (Code Key)
07671679190	CoaguChek XS PT Test PST, 6 tests	334499 (S_**344**)
07671687019	CoaguChek XS PT Test PST, 24 tests	334499 (S_**344**)
04625374190	CoaguChek XS PT Test, 6 tests Interna-tional	334499 (S_**344**)
04625358019	CoaguChek XS PT Test, 24 tests	334499 (S_**344**)
04625315019	CoaguChek XS PT Test, 2 x 24 tests	334499 (S_**344**)

Table 2: Availability of new lots

How do I recognize which CoaguChek test strip lot/code chip number I have?

The lot number is printed on the label, which is applied to the test strip box at manufacturing:



**Example for box only*

The code chip number is printed on the code chips (as shown below).

Who can I call for more advice?

Please contact your Roche Diagnostics Customer Care Centre under the following numbers:

Calling from the UK call 0808 100 7666, if calling from Ireland call 1 800 99 2868.

Please choose **option 4** to reach our Support Team.

We apologise for any inconvenience caused by this issue to you.

Sincerely,

Roche Diagnostics

Consumer Letter

(CoaguChek XS PT Test PST, CoaguChek XS PT Test, CoaguChek PT Test)

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<Enter address here>

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22/08/2018

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CoaguChek XS PT PST Test	07671679190 07671687019	272167 – 334498

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04625374190	CoaguChek XS PT Test, 6 tests International	334499 (S_344)
04625358019	CoaguChek XS PT Test, 24 tests	334499 (S_344)
04625315019	CoaguChek XS PT Test, 2 x 24 tests	334499 (S_344)

Table 2: Availability of new lots

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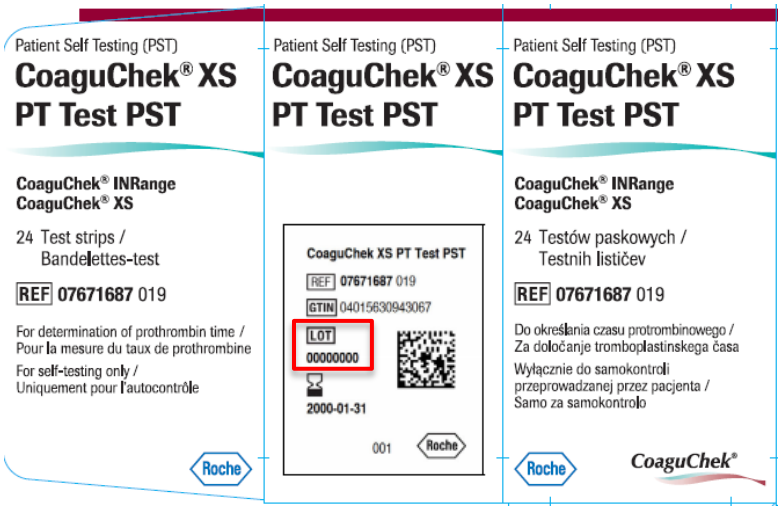

**Example for box only*

The code chip number is printed on the code chips (as shown below).

Who can I call for more advice?

Please contact your Roche Diagnostics Customer Care Centre under the following numbers:

Calling from the UK call 0808 100 7666, if calling from Ireland call 1 800 99 2868.

Please choose **option 4** to reach our Support Team.

Please complete the **Acknowledgement Form** which accompanies this Field Safety Notice and return this to Roche using the pre-paid returns label and envelope provided. Please ensure the Acknowledgement form is returned by 5th September 2018.

We apologise for any inconvenience caused by this issue to you.

Sincerely,

Roche Diagnostics

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