## LETTER TO THE BERKSHIRE CORONER RE CIPROFLOXACIN

FAO Mr P Bedford
HM Senior Coroner for Berkshire
Reading Town Hall,
Blagrave Street,
Reading RG1 1QH

8 March 2017

Dear Sir

**Report to Prevent Further Deaths: Mr Charles Rendell**

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I refer to your letter of 11 January 2017 attaching a report to prevent further deaths, under paragraph 7, schedule 5, of the Coroners and Justice Act 2009 and regulations 28 and 29 of the Coroners (Investigations) Regulations 2013. In this letter I respond to your report on behalf of Bayer plc.

As a preliminary matter, please be aware that patient safety is taken very seriously by Bayer. After receiving notification of Mr Rendell's death and the associated circumstances, we have carefully reviewed all reports of psychiatric effects, specifically attempted and completed suicide associated with use of ciprofloxacin. The review included all sources of information available to us. We have considered these in the context of the information currently provided to prescribers and to patients and the matters raised in your report.

Additionally, while Bayer supplies ciprofloxacin in the UK under the brand name Ciproxin, generic versions of ciprofloxacin are also supplied by other manufacturers and the information provided below may not apply to those products. It is unclear to us whether Mr Rendell took Ciproxin or ciprofloxacin manufactured by another company.

We respond below, in relation to the specific matters of concern set out in your report.

1. Apart from the fact that Mr Rendell had undergone a diagnostic biopsy to test for the possibility of prostate cancer, the only change in his daily routine was the prescription of ciprofloxacin medication.

Bayer was informed that it should not attend the inquest on 5 January 2017 and we therefore have only very limited information in relation to Mr Rendell's medical history and personal circumstances.

We understand, from information received from your office that Mr Rendell was a 76 year old man, who had been prescribed ciprofloxacin 500 mg

twice daily on 19 September 2016, following a needle biopsy for possible prostate cancer. On 24 September 2016 he was apparently found 8 miles away from home and was said to be vacant and confused. He was later found hanged in his garage.

While Bayer is not in a position to respond to your report in relation to Mr Rendell's particular case, the causes of suicide and suicidality are complex and may result from a range of factors including mental illness and negative life events. If Mr Rendell believed that a diagnosis of prostate cancer would be confirmed in his case, it is possible that this would constitute a negative life event.

Data issued by the Office for National Statistics for 2015[1] (the most recent year for which figures are available) showed that men are around 3 times as likely to commit suicide as women across all broad age groups and that hanging is the most common suicide method used in the UK.

2. Ciprofloxacin carries warnings/precautions that, in rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. However, it is unclear how clearly this is made known to ciprofloxacin users.

Manufacturers of medicinal products principally provide information regarding their medicines, to prescribers in the EU/ UK through the Summary of Product Characteristics (SmPC) and to patients, through the Patient Information Leaflet (PIL) supplied with every pack of the relevant medicine. The SmPC and PIL are referred to collectively as product information. The required form and content of SmPCs and PILs is specified in EU Directive 2001/83/EC (implemented in the UK by the Human Medicines Regulations 2012). The particular information included for each medicinal product in the SmPC and PIL, including the relative prominence given to each statement, must be approved by the competent regulatory authority, as reflecting available scientific and technical knowledge, before it is put into circulation. Warnings of potential adverse events or side effects, associated with a medicinal product, are included in product information on a precautionary basis. This means that prescribers and patients will be alerted to the possibility that a particular side effect may occur, if there is some evidence of an association, even if this falls short of establishing a causal relationship.

The competent regulatory authority for the purposes of supply of Ciproxin in the UK, is the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA has therefore considered the available evidence for ciprofloxacin and has approved the information included in the SmPC and PIL for Ciproxin (including in relation to the risk of particular adverse effects)

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1 https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/suicidesintheunitedkingdom/2015registrations

as reflecting the current state of scientific and medical knowledge regarding the product.

While Ciproxin has been licensed since 1986 (The Phillipines) and used widely since its marketing authorisation in Europe in 1987, during clinical trials of ciprofloxacin, when usage of the product has been monitored closely under controlled conditions, no cases of self-harm, suicidal ideation and attempted or completed suicide were reported. However, post marketing authorisation very rare cases of self-harming behaviour have been reported in patients prescribed ciprofloxacin in standard clinical use. In view of the nature of post marketing reports, the information provided is sometimes limited or difficult to interpret for example evidence for onset from first dose cannot be reliably assessed. In these cases causality often cannot be attributed solely to ciprofloxacin. An epidemiological study (Jick SS et al (1998)[2] using the UK General Practice Research Database compared the risk of suicidal behaviours among users of quinolones (including ciprofloxacin), other antibiotics and no antibiotics and concluded that there is no material increased risk of suicidal behaviours for users of quinolone antibiotics, compared with the other groups. Your report indicates that you were referred, during the inquest, to a variety of published literature relating to ciprofloxacin and quinolone antibiotics. We would caution the weight placed on these as an objective systematic review of all scientific literature has not been performed upon which to draw firm conclusions. However, depression and psychiatric disorders are identified risks for ciprofloxacin with some evidence that these effects may progress to suicidal thoughts or self-injurious behaviour. .The product information for Ciproxin, approved by the MHRA reflects the current state of scientific and medical information about the product and includes warnings regarding the possibility of such effects on a precautionary basis to ensure that prescribers and patients are fully informed of the potential risks associated with use of the product.

- The SmPC for Ciproxin published electronically by Bayer and through the electronic medicines compendium https://www.medicines.org.uk/emc/ includes the following information to inform prescribers about the possibility of psychiatric effects:

    - Under "Special warnings and precautions for use":

      "Central nervous system ... psychiatric reactions may occur even after first administration of Ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases, Ciprofloxacin should be discontinued."

[2] Jick SS et al. A study of the relation of exposure to quinolones and suicidal behaviour. BJCP 1998; 45(1): 77–81

- Under "Undesirable effects":

  Psychiatric disorders:

  Rare > 1/10,000 to < 1/1000 "Confusion and disorientation. Anxiety reaction. Abnormal dreams. Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) ... Hallucinations."

  Very rare < 1/10,000 "Psychotic reactions (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) ..."

  Frequency not known (but cannot be estimated from the available data) mania and hypomania.

- The PIL for Ciproxin, a copy of which is provided in each pack of the product, starts by advising patients:

  **"Read all of this leaflet carefully before you start taking this medicine because it contains important information for you"** [emboldened in original].

  The PIL then includes the following information to inform patients about the possibility of psychiatric effects:

  - Under "While taking Ciproxin":

  "Tell your doctor immediately if any of the following occurs while taking Ciproxin. Your doctor will decide whether treatment with Ciproxin needs to be stopped ...

  - You may experience psychiatric reactions the first time you take Ciproxin. If you suffer from depression or psychosis your symptoms may become worse under treatment with Ciproxin. In rare cases, depression or psychosis can progress to thoughts of suicide, suicide attempts or completed suicide. If this happens, contact your doctor immediately."

  - Under "Possible side effects"

  "Other side effects which had been observed during treatment with Ciproxin are listed below by how likely they are:

  ...

  Rare (may affect up to 1 in 1,000 people)

...

Confusion, disorientation, anxiety reaction, strange dreams, depression (potentially leading to thoughts of suicide, suicide attempts, or completed suicide) (see Section 2: Warnings and Precautions), or hallucinations.

...

Very rare (may affect up to 1 in 10,000 people).

...

Mental disturbances (psychotic reactions potentially leading to thoughts of suicide, suicide attempts or completed suicide) (see Section 2: Warnings and Precautions)...."

Ciprofloxicin is categorised as a prescription only medicine, which means that it may only be made available following assessment by a healthcare professional and the provision of information to the patient regarding use of the medicine, tailored to their particular medical condition and circumstances, prior to issue of a prescription. Guidance on prescribing issued by the UK General Medical Council emphasises that doctors must keep their knowledge and skills up-to-date and should make use of electronic and other systems that can improve the safety of prescribing. Specific reference is made to the Electronic Medicines Compendium, which lists SmPCs and PILs for medicinal products, including Ciproxin.

Patients are advised to read the PIL relating to their medicine, which supports the information provided by the prescribing healthcare professional, before usage is commenced.

Relevant information about ciprofloxacin is therefore made available to healthcare professionals and to patients through the SmPC and the PIL for Ciproxin. These documents which provide information regarding the potential risks of psychiatric symptoms including suicidal behaviour following use of ciprofloxacin, are readily available to healthcare professionals electronically and to patients in every pack of product.

3. The literature suggests that this type of side effect can occur even soon after commencing ciprofloxicin at a comparatively low dose. As it is an antibiotic, there is no compelling reason why patients should expect to have this effect unless this fact, and potential symptoms, are brought clearly to their attention by prescribing clinicians.

As indicated above, the reports of cases of suicidal behaviour following use of ciprofloxicin, are derived from post marketing data only and are sometimes very limited and difficult to interpret. Bayer is aware that some individual reports suggest that patients prescribed ciprofloxicin may exhibit

signs of depression, very soon after treatment is commenced, although it is difficult to exclude the potential influence of other factors in these cases. Therefore, as a matter of caution, prescribers are warned in the SmPC for Ciproxin:

"....psychiatric reactions may occur even after first administration of Ciprofloxacin".

In summary therefore, prescribers and patients are warned of the risk of suicidal behaviours following use of ciprofloxacin in the SmPC and PIL supplied by Bayer in relation to Ciproxin. The warnings, as set out above, are explicit and clearly stated. Professional standards require that doctors are familiar with current information relating to the medicines they prescribe; it is a matter for the prescriber to determine the information to be discussed with the patient based on the medical history of the patient and his current condition and personal circumstances. Patients are strongly advised to read the PIL, provided in every pack of product, before use.

4. One of Mr Rendell's family members is a general practitioner in New Zealand. At the inquest, she advised that she had no knowledge of the potential effect of Ciprofloxicin and, in conversation with her colleague, nor did they. I am therefore concerned that this potential risk has not been given sufficient emphasis and that consideration should be given to prescribing clinicians highlighting the symptoms and suggesting to patients that they are alert to the possibility and react appropriately.

The product information supplied by manufacturers of medicinal products in New Zealand is subject to control by the New Zealand competent regulatory authority, Medsafe. The New Zealand Data Sheet (the equivalent of the EU/UK SmPC) and the New Zealand Consumer Medicines Information (the equivalent of the EU/UK PIL) must both be approved by Medsafe before they are put into circulation in New Zealand The fact that there is a different approval process applicable in New Zealand and in the UK, may accordingly result in some differences between the product information supplied with ciprofloxacin products in New Zealand and those supplied in the UK.

Following receipt of your report however we have examined the New Zealand Data Sheet and CMI for Ciproxin and can confirm that they both contain warnings about the possible risk of suicidal behaviour, directed towards prescribing healthcare professionals and patients respectively.

In contrast, the document which you provided and which was, seemingly, supplied to you by the relative of Mr Rendell who is a general practitioner in New Zealand, is a Data Sheet for a generic version of ciprofloxicin supplied in New Zealand by Multichem NZ Limited (i.e. a formulation of ciprofloxacin that is not manufactured or supplied by Bayer). Bayer does not control the content of the information produced by Multichem. It is relevant that the information contained in this document is less detailed than that in the product information supplied by Bayer in relation to Ciproxin (whether in

New Zealand or the UK) and includes no explicit reference to the possibility of suicidal behaviour following use of ciprofloxacin.

In summary, Bayer keeps the product information for its medicines under constant review and, while the data relating to a risk of suicidal behaviour following use of ciprofloxicin are very limited, the UK product information for Ciproxin (both the SmPC and the PIL) includes an appropriate and sufficiently prominent warning to advise prescribers and patients. We recognise that this information is important, but do not believe greater prominence is appropriate, based on the available data and our concern not to detract from other information regarding use of ciprofloxacin. For completeness, we have carried out a review of the UK product information issued by manufacturers of generic formulations of ciprofloxacin and believe that all such information adequately warns prescribers and patients regarding the risk of suicidal behaviour.

We are surprised that Mr Rendell's New Zealand relative was not aware of the content of the New Zealand product information for Ciproxin (which also notifies prescribers of the possibility of suicidal behaviour following treatment with ciprofloxacin), as approved by the New Zealand regulatory authority. This may however be due to the generic versions of ciprofloxacin in New Zealand's product information being less detailed than that of the UK. However, as with the UK, the New Zealand medicines regulatory authority has reviewed and approved the ciprofloxacin information available to prescribers and patients and is entirely satisfied with the adequacy of warnings.

We hope that this letter answers your matters of concern. Please feel free to contact us should you require further information.

Yours faithfully

[redacted]
Head of Pharmacovigilance, Bayer Plc