Medicines & Healthcare products
Regulatory Agency

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Ms Alison Mutch
Senior Coroner for South Manchester
By Email: [redacted]

Reference: [redacted]

23 January 2025

Dear Ms Mutch,

Regulation 28 Report into the death of Linda McLaughlin

Thank you for your Regulation 28 Report relating to the death of Linda McLaughlin on 27 October 2023 which was received on 31 October 2024. I would like to offer my sincere condolences to Mrs McLaughlin's family on their tragic loss. I apologise for a delay in responding to you, contact was made with your office by telephone, to explain the situation on 5 November 2024.

As described in your report Mrs McLaughlin was diagnosed with Chronic Myeloid Leukaemia (CML) in 2014 and was treated with nilotinib. Following response to treatment she was in molecular remission by October 2021. Nilotinib treatment continued at a low dose. Mrs McLaughlin subsequently went on to be diagnosed with interstitial lung disease in May 2023 which was treated with steroids and her nilotinib was stopped. In October 2023 Mrs McLaughlin developed bronchopneumonia and sadly died as a result.

I note the Regulation 28 report was initially sent to NHS England and in their response dated 5 August 2024, NHS England suggested your concerns should also be sent to the MHRA.

Your report identified the following matters of concern relating to nilotinib (Tasigna):

1. The inquest heard evidence that the complication Mrs McLaughlin developed is rare but recognised internationally. However, it is not widely known about and as a consequence of lack of awareness even amongst oncologists/haematologists it may not be recognised that a patient has symptoms of interstitial lung disease and as a consequence referral and treatment that could slow the disease progression may be delayed.

2. The inquest was told that the consenting process for starting a patient on a drug such as nilotinib would not ordinarily include mentioning rare complications such as interstitial lung disease. The family gave evidence that in this case this is something that would have been carefully weighed in the decision to proceed with the treatment.

3. In this case the inquest was told that a decision was taken to continue with nilotinib despite being in remission. The inquest was told that there is growing evidence that some people do not need to stay on these drugs for life if in remission but there is no clear guidance for the approach to take. As a consequence, patients may remain on the drug longer than necessary.

I will address each of these concerns in turn but first provide some background on the MHRA.

The MHRA regulates medicines, medical devices, and blood components for transfusion in the United Kingdom to ensure that they meet robust standards of safety, quality and efficacy. Unfortunately, no medicine is completely without risk. All medicines have the potential to cause side effects, and these are outlined in the product information for each medicine. The product information comprises of:

- Summary of Product Characteristics: (SmPC) a document describing the properties and the officially approved conditions of use of a medicine. SmPC forms the basis of information for healthcare professionals on how to use the medicine safely and effectively

- Patient Information Leaflet (PIL): The leaflet in every pack of medicine that contains information for patients on the medicine and its use.

The benefits and risks of all medicines, including nilotinib, are continually and rigorously assessed throughout the lifecycle of the product using a range of different sources of information. When necessary, the MHRA will take action to ensure the benefits of a product continue to outweigh the risk. This may include changing the product information to include warnings of additional side effects or other changes in how the medicine is used.

When assessing whether a drug may have caused a suspected side effect, it is also important to consider a number of other factors such as the full diagnosis, past medical history, previous treatments and concomitant medications.

I will address concerns that there was a lack of awareness of the side effect of interstitial lung disease among healthcare professionals and the provision of information to patients.

Nilotinib has been licenced for marketing in the UK since November 2007. The SmPC and the PIL include the known side effects of this cancer medicine. Interstitial lung disease is an uncommon side effect of nilotinib and currently there is information provided in the SmPC and the PIL.

The text is provided below:

- The SmPC for Tasigna (nilotinib)

Section 4.8 of the SmPC lists Adverse reactions from clinical studies and post-marketing reports (Table 3) - pneumonia is listed as a common side effect (estimated to affect between 1 in 100 and 1 in 10 patients). Interstitial lung disease is listed as an uncommon side effect (estimated to affect between 1 in 1000 and 1 in 100 patients)

- The PIL for nilotinib –

The PIL includes the following general information:
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist…
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet….

The PIL explains that like all medicines, nilotinib can cause side effects, although not everybody gets them. Section 4 of the PIL includes information about "Possible side effects". It also provides information about signs of lung disorders in general and interstitial lung disease as follows:

> ***Some side effects could be serious.***
> ***……***
> *signs of lung disorders: difficulty breathing or painful breathing, cough, wheezing with or without fever, swelling of the feet or legs*
> *……...*
> *Some side effects are common (may affect up to 1 in 10 people)*
> *- pneumonia*
> *……*
> ***Some side effects are uncommon (may affect up to 1 in 100 people)***
> *……...*
> *signs of interstitial lung disease: cough, difficulty breathing, painful breathing...*

The second concern raised relates to continuation of nilotinib therapy following remission.

The SmPC for Tasigna (nilotinib) includes detailed information about discontinuation of treatment with nilotinib in case of sustained deep molecular response in eligible patients, monitoring and measurement of molecular response, loss of remission and nilotinib reinitiation where appropriate. Health Care Professionals are also reminded in the SmPC that *Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs…."*

The MHRA recognises that as the medicines' regulator, it is not within our remit to comment on clinical practice issues. It is a healthcare professional's responsibility to prescribe a drug based on the information contained within the SmPC and to obtain appropriate consent after counselling the patient on their individual benefits and risks with use.

Overall, the MHRA considers that the information provided in the SmPC and PIL for nilotinib adequately reflects the current scientific evidence available and no updates are required. However, we note the concern raised about a lack of awareness of the side effect of interstitial lung disease.

The British National Formulary (BNF) is a valuable source of information for healthcare professionals and we have noted that the BNF drug monograph for nilotinib includes the term “respiratory disorders” as a side-effect, which covers a range of respiratory side-effects, including interstitial lung disease. The publishers of the BNF are a separate organisation to the MHRA. We have reached out to the BNF editorial team and have asked them to consider including interstitial lung disease as a separate side-effect term in the nilotinib drug monograph.

The BNF have informed us ‘interstitial lung disease’ will appear as a separate term in the side-effects sections of relevant BNF and BNF for Children (BNFC) monographs in the January 2025 online updates of BNF and BNFC and the BNF + BNFC app. This update will be included in the next print edition of BNF which will be published in March 2025.

The MHRA collects and monitors information about adverse effects of medicines through the Yellow Card Scheme. Patients, carers, parents and healthcare professionals in the UK are encouraged to report suspected side effects through the Yellow Card scheme using https://yellowcard.mhra.gov.uk/ website, the app or through some healthcare professional IT clinical systems. There is also guidance on what to report. I am grateful to you for bringing this report to our attention and I can confirm that the side effects experienced by Mrs Mclaughlin have now been included in the MHRA Yellow Card database (reference number is 34193346).

As with all medicines including nilotinib, the MHRA will continue to monitor the safety of them and where necessary, take action to ensure that a medicine continues to be used in a way which minimises risk and maximises benefits to the patient.

Once again, we thank you for bringing these important patient safety issues to our attention and should you have any further questions, please do not hesitate to contact me.

Yours sincerely,

[redacted]

[redacted]
Chief Executive
Medicines and Healthcare products Regulatory Agency
E: [redacted]