Medicines & Healthcare products
Regulatory Agency

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20 June 2023

FOI 23/264

Dear [redacted]

Thank you for your information request, dated 05 April 2023.

In relation to the drug Pregabalin you ask for information regarding the following:

1. For each of the years from 2018 to 2022 the number of deaths where Pregabalin has been recorded as the only drug involved.

MHRA Reply 1:

From a search of MHRA Yellow Card database the following number of fatal cases were identified.

Year	**Number of reports where pregabalin was reported as the only suspect medication**
2018	5
2019	1
2020	1
2021	1
2022	4

2. For each of the years from 2018 to 2022 the number of deaths where Pregabalin has been recorded as a contributory drug involved.

MHRA Reply 2:

From a search of MHRA Yellow Card database the following number of cases were identified.

Year	Number of reports where pregabalin was reported as a suspect medication alongside another medication
2018	60
2019	11
2020	16
2021	31
2022	65

3. For each of the years from 2018 to 2022 the number of deaths where Pregabalin has been recorded as a contributory drug alongside an opioid based drug.

MHRA Reply 3

From a search of MHRA Yellow Card database the following number of cases were identified.

Year	Number of reports where pregabalin and an opioid were reported as a suspect medication
2018	48
2019	10
2020	15
2021	29
2022	60

The definition of opioid used in the case search was from the ATC code published by the WHO available at https://www.whocc.no/atc_ddd_index/?code=N02AX&showdescription=no And Annex A of the report from Public Health England available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/940255/PHE_PMR_report_Dec2020.pdf

4. Provide a detailed list of all concerns relating to the use of Pregabalin in relation to its prescribing with opioids.

MHRA Reply 4

The MHRA approved product information for pregabalin consists of the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) and contains details the known concerns relating to use of pregabalin with opioids. The SmPC is for healthcare professionals, the PIL reflects the information in the SmPC in a format suitable for most patients. It is important to note that the SmPC may include additional medical information and given the nature of the questions raised we have outlined the information provided in the SmPC. In the SmPC section on special

warnings and precautions for use (section 4.4) there is a subheading on concomitant use with opioids.

The SmPC states that caution is advised when prescribing pregabalin concomitantly (at the same time) with opioids due to risk of Central Nervous System (CNS) depression. In a case-control study of opioid users, those patients who took pregabalin concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone (adjusted odds ratio [aOR], 1.68 [95% CI, 1.19 – 2.36]). This increased risk was observed at low doses of pregabalin (≤ 300 mg, aOR 1.52 [95% CI, 1.04 – 2.22]) and there was a trend for a greater risk at high doses of pregabalin (> 300 mg, aOR 2.51 [95% CI 1.24 – 5.06]).

In the interaction section of the SmPC (section 4.5) it states that in the post marketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or other CNS depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

A warning in the SmPC relating to reduced lower gastrointestinal tract function states that, “there are post marketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).”

5. Provide a detailed list of all concerns relating to the use of Pregabalin in relation to its interactions with illegal opioids.

MHRA Reply 5

The MHRA does not hold a detailed list of concerns relating to the use of pregabalin with illicit products such as illegal opioids. However, twenty-two of the fatal cases for which figures are provided in response to question 2 and 3 involved use of heroin. The pregabalin SmPC does not list any known interactions with illicit substances.

6. Provide all information relating to the safety of Pregabalin in relation to its concomitant use with other Central Nervous System (CNS) drugs.

MHRA Reply 6

The MHRA approved pregabalin SmPC Interactions section (4.5) contains the following information:

Central nervous system influencing medical products

Pregabalin may potentiate the effects of ethanol and lorazepam. In the post marketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

7. Provide a short summary of information relating to the approval of Pregabalin for use as a treatment for Generalised Anxiety Disorder.

8. Provide a short summary of information relating to the approval of Pregabalin for use as a treatment for chronic neuropathic pain.

MHRA Reply 7 and 8

Further information on the authorisation of Lyrica (pregabalin) for Generalised Anxiety Disorder and chronic neuropathic pain is available from the European Medicines Agency. The Public Assessment Report contain the assessment of studies submitted for the authorisation of pregabalin for these indications. This is available at
https://www.ema.europa.eu/en/medicines/human/EPAR/lyrica

9. Provide a short summary of information relating to warnings by the manufacturer on its use as a treatment for Generalised Anxiety Disorder.

10. Provide a short summary of information relating to warnings by the manufacturer on its use as a treatment for chronic neuropathic pain.

MHRA Reply 9 and 10

Pregabalin is indicated in adults for the treatment of peripheral and central neuropathic pain, as adjunctive therapy in adults with partial seizures with or without secondary generalisation, and for generalised anxiety disorder in adults. The MHRA approved pregabalin SmPC contains warnings irrespective of which of the three licensed indications it is prescribed for as they relate to the totality of data available across the indications.

The MHRA approved warnings section (4.4) summarises the warnings on use of pregabalin:

Special warnings and precautions for use

Diabetic patients
In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicinal products.

Hypersensitivity reactions
There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported rarely in association with pregabalin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, pregabalin should be withdrawn immediately and an alternative treatment considered (as appropriate).

Dizziness, somnolence, loss of consciousness, confusion and mental impairment
Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

Vision-related effects
In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients

In the post-marketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient.

Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

Renal failure
Cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction.

Withdrawal of concomitant antiepileptic medicinal products
There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin.

Congestive heart failure
There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Treatment of central neuropathic pain due to spinal cord injury
In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, central nervous system adverse reactions and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medicinal products (e.g. anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.

Respiratory depression
There have been reports of severe respiratory depression in relation to pregabalin use. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly may be at higher risk of experiencing this severe adverse reaction. Dose adjustments may be necessary in these patients. (see section 4.2).

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known. Cases of suicidal ideation and behaviour have been observed in patients treated with pregabalin in the postmarketing experience. An epidemiological study using a self-controlled study design (comparing treatment periods with non-treatment periods within an individual) showed evidence of an increased risk of new onset of suicidal behaviour and death by suicide in patients treated with pregabalin.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. Patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Discontinuation of pregabalin treatment should be considered in case of suicidal ideation and behaviour.

Reduced lower gastrointestinal tract function

There are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).

Concomitant use with opioids
Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression. In a case-control study of opioid users, those patients who took pregabalin concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone (adjusted odds ratio [aOR], 1.68 [95% CI, 1.19 – 2.36]). This increased risk was observed at low doses of pregabalin (≤ 300 mg, aOR 1.52 [95% CI, 1.04 – 2.22]) and there was a trend for a greater risk at high doses of pregabalin (> 300 mg, aOR 2.51 [95% CI 1.24 – 5.06]).

Misuse, abuse potential or dependence
Pregabalin can cause drug dependence, which may occur at therapeutic doses. Cases of abuse and misuse have been reported. Patients with a history of substance abuse may be at higher risk for pregabalin misuse, abuse and dependence, and pregabalin should be used with caution in such patients. Before prescribing pregabalin, the patient's risk of misuse, abuse or dependence should be carefully evaluated.

Patients treated with pregabalin should be monitored for symptoms of pregabalin misuse, abuse or dependence, such as development of tolerance, dose escalation and drug-seeking behaviour.

Withdrawal symptoms
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness. The occurrence of withdrawal symptoms following discontinuation of pregabalin may indicate drug dependence. The patient should be informed about this at the start of the treatment. If pregabalin should be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see section 4.2).

Convulsions, including status epilepticus and grand mal convulsions, may occur during pregabalin use or shortly after discontinuing pregabalin.
Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

Encephalopathy

Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.

Women of childbearing potential/Contraception
Pregabalin use in the first-trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment (see section 4.6).

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per each capsule, that is to say essentially 'sodium-free'.

11. It is documented and indeed the subject of a Drug Safety Update that Pregabalin has been responsible for deaths due to respiratory depression/failure. Can you please provide details of the mechanism of death that have been observed in these cases.

MHRA Reply 11

The MHRA Drug Safety Update [1]Article dated 18 February 2021 summarises the recent European review of safety data considering reports of severe respiratory depression thought to be related to the action of pregabalin alone on the central nervous system. Given the available data on this risk, including spontaneous reports, and the plausible mechanism of action, the product information for medicines available in the UK will be amended to include new warnings for respiratory depression.

The review identified a small number of worldwide cases of respiratory depression without an alternative cause or underlying medical conditions. In these cases, respiratory depression had a temporal relationship with the initiation of pregabalin or dose increase. Other cases were noted in patients with risk factors or underlying medical history. The majority of cases reviewed were reported in elderly patients.

12. It is documented and included in the Specific Product Characteristics of Pregabalin by the manufacturer that the drug can result in deaths from use with opioids by potentiating the adverse effects of opioids. Can you please provide details of the mechanism by which Pregabalin potentiates opioids specifically to result in death from opioid overdose.

MHRA Reply 12

[1] Pregabalin (Lyrica): reports of severe respiratory depression - GOV.UK (www.gov.uk)

Opioid medications and pregabalin are both known to suppress the central nervous system function. The MHRA approved SmPC for pregabalin describes the additive effects of a combination of central nervous system depressants in the Interactions section (4.5):

Central nervous system influencing medical products
Pregabalin may potentiate the effects of ethanol and lorazepam. In the postmarketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

13. Can you please confirm if there are any ongoing investigations into the safety of the drug Pregabalin in relation to its use when prescribed to patients concomitantly with other CNS depressant drugs.

MHRA Reply 13

The MHRA continually monitors the safety of use of all medicines, including pregabalin. Safety monitoring includes the multidisciplinary review of Yellow Card reports at weekly signal meetings and review of interactions with other CNS depressant drugs in periodic safety update reports which summarise both spontaneously reported adverse events and the wider scientific literature. Information from all available sources including other regulatory authorities are taken into consideration when monitoring the safety of medicines.

14. Can you please confirm if there are any ongoing investigations into the safety of the drug Pregabalin when it is prescribed to patients with a known history of or current usage of illegal opioids.

MHRA reply 14

Although there are currently no ongoing specific investigations of this nature for pregabalin, the safety of pregabalin when prescribed to patients with a known history or current usage of illegal opioids is monitored by review of Yellow Card reports and review of periodic safety updates for pregabalin which will contain reports of all reported adverse events associated with pregabalin and other concomitant drugs including illegal opioids. The MHRA will carefully consider any emerging data.

The MHRA approved SmPC in the warning section (4.4) states that:

Pregabalin can cause drug dependence, which may occur at therapeutic doses. Cases of abuse and misuse have been reported. Patients with a history of substance abuse may be at higher risk for pregabalin misuse, abuse and dependence, and pregabalin should be used with caution in such patients. Before prescribing pregabalin, the patient's risk of misuse, abuse or dependence should be carefully evaluated.

Patients treated with pregabalin should be monitored for symptoms of pregabalin misuse, abuse or dependence, such as development of tolerance, dose escalation and drug-seeking behaviour.

MHRA is aware that Guidance from the General Medical Council states that, together with the patient, healthcare professionals should make an assessment of the patient's condition before deciding to prescribe a medicine. The professional must have, or take, an adequate history, which considers recent use of other medicines—including non-prescription medicines, herbal medicines, illegal drugs, and medicines purchased online.

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Yours sincerely,

Safety and Surveillance