Medicines & Healthcare products
Regulatory Agency

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Mr Stephen H G Covell
Assistant Coroner
Coroner for Cornwall & the Isles of Scilly
H.M Coroner's Office
[redacted]

28 May 2024

Dear Mr Covell,

Regulation 28 Report concerning Talia Evania Phillips, DOB 18/08/2000

Thank you for your Regulation 28 Report relating to the death of Talia Evania Phillips. I would like to offer my sincere condolences to Ms Phillip's' family on their tragic loss.

In the Matters of Concern section of the report relating to the tragic death of Talia Evania Phillips you request that guidance in relation to the prescribing of fluoxetine and management of patients on fluoxetine should be reviewed to consider in what circumstances a blood test to establish the level of fluoxetine in the patient's blood would be advisable.

We have reviewed the available evidence from the fluoxetine Summary of Product Characteristics (SmPC), data from the UK Yellow Card Scheme, literature[1-8] as well as the advice of our Expert Advisory Group (EAG) of the Commission on Human Medicines on the monitoring of blood levels of antidepressants in patients on fluoxetine treatment which was sought in May 2020 in response to a fatal case report and a Regulation 28 request.

The EAG previously advised that the evidence from the analyses of Yellow Card data and published information on antidepressant drug level monitoring was not sufficiently robust to advise clinicians to routinely monitor blood levels of antidepressants for all patients on treatment. The Group recommended however that blood level monitoring of antidepressants may be helpful in certain circumstances, for example in the event of symptoms suggestive of toxicity or when concomitant medicines may interact to increase antidepressant drug levels.

Circumstances which can have an impact on fluoxetine levels are described in the SmPC and the medications which are known to alter plasma levels of fluoxetine are detailed in the

fluoxetine SmPC section 4.5 on Interactions with other medicinal products and other forms of interactions. The use of fluoxetine concomitantly with a number of medicines requires caution, and these are listed in the attached Annex.

When fluoxetine drug level testing was previously discussed, the EAG commented that fluoxetine has a good safety margin in overdose with even a 10-fold increase in dose causing only low toxicity. The EAG acknowledged that fluoxetine has a wide therapeutic range and that currently there is no robust data regarding therapeutic plasma levels to support guidance. Overall, the EAG concluded that routine therapeutic drug level monitoring for fluoxetine would not be recommended unless clinically indicated based on risk factors for toxicity and QT prolongation in the patient.

In addition, the fluoxetine SmPC describes that steady state plasma concentrations are dependent on body weight. Fluoxetine is extensively metabolised by the liver and excreted by the kidneys. A lower dose, e.g., alternate day dosing, is recommended in patients with significant hepatic dysfunction. When given fluoxetine 20mg/day for 2 months, patients with severe renal failure (GFR <10ml/min) requiring dialysis showed no difference in plasma levels of fluoxetine or norfluoxetine compared to controls with normal renal function.

We note that the Deceased had a normal ECG during fluoxetine treatment in relation to an episode of palpitations. Palpitations at normal therapeutic doses are listed in the fluoxetine SmPC as commonly occurring in association with fluoxetine use and Electrocardiogram QT prolonged (QTcF≥450msec) is also listed as common.

The fluoxetine SmPC describes that signs of toxicity in overdose of fluoxetine alone usually have a mild course. Symptoms of overdose have included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias (including nodal rhythm and ventricular arrhythmias) or ECG changes indicative of QTc prolongation to cardiac arrest (including very rare cases of Torsade de Pointes), pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare.

The approved fluoxetine SmPC contains information reflecting the currently available data on known interactions and clinical circumstances which may predispose a person to fluoxetine toxicity and describes symptoms of toxicity in overdose. The fluoxetine SmPC does not make specific recommendations on when to perform blood tests to establish the level of fluoxetine as this is a clinical judgement depending on the unique individual patient circumstances and therefore would be a matter for clinical guidelines.

In order to complete our assessment of the adequacy of the current fluoxetine product information, we have sought details of any other medical indications in addition to anxiety, any concomitant medications the Deceased was prescribed, any information about the prescribed dose and duration of fluoxetine use in addition to the blood levels found and information on previous tests performed and a copy of the postmortem report via a response for further information to the registered Yellow Card.

If the follow up information indicates that additional guidance would be beneficial, a further review of the adequacy of the fluoxetine product information will be undertaken.

Finally, I take this opportunity to confirm that this case report has been added to the Yellow Card database (reference number ADR 28344736), which is the UK's system for collecting and monitoring information on suspected adverse drug reactions (ADRs) and medical device adverse incidents.

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
[redacted]

Annex: The use of fluoxetine concomitantly with a number of medicines requires caution

Phenytoin: Changes in blood levels have been observed when combined with fluoxetine. In some cases, manifestations of toxicity have occurred. Consideration should be given to using conservative titration schedules of the concomitant drug and to monitoring clinical status.

Serotoninergic drugs (lithium, tramadol, triptans, tryptophan, selegiline (MAOI-B), St. John's Wort (Hypericum perforatum)): There have been reports of mild serotonin syndrome when SSRIs were given with drugs also having a serotoninergic effect. Therefore, the concomitant use of fluoxetine with these drugs should be undertaken with caution, with closer and more frequent clinical monitoring.

QT interval prolongation: Pharmacokinetic and pharmacodynamic studies between fluoxetine and other medicinal products that prolong the QT interval have not been performed. An additive effect of fluoxetine and these medicinal products cannot be excluded. Therefore, co-administration of fluoxetine with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine), anti-malaria treatment particularly halofantrine, certain antihistamines (astemizole, mizolastine), should be used with caution.

Buprenorphine-containing medicinal products
Fluoxetine should be used cautiously when co-administered with Buprenorphine-containing medical products as the risk of serotonin syndrome, a potentially life-threatening condition, is increased.

Drugs affecting haemostasis (oral anticoagulants, whatever their mechanism, platelet anti-aggregants including aspirin and NSAIDs): risk of increased bleeding.
Clinical monitoring, and more frequent monitoring of INR with oral anticoagulants, should be made. A dose adjustment during the fluoxetine treatment and after its discontinuation may be suitable.

Cyproheptadine: There are individual case reports of reduced antidepressant activity of fluoxetine when used in combination with cyproheptadine.

Drugs inducing hyponatremia: Hyponatremia is an undesirable effect of fluoxetine. Use in combination with other agents associated with hyponatremia (e.g. diuretics, desmopressin, carbamazepine and oxcarbazepine) may lead to an increased risk.

Drugs lowering the epileptogenic threshold: Seizures are an undesirable effect of fluoxetine. Use in combination with other agents which may lower the seizure threshold (for example, TCAs, other SSRIs, phenothiazines, butyrophenones, mefloquine, chloroquine, bupropion, tramadol) may lead to an increased risk.

Other drugs metabolised by CYP2D6: Fluoxetine is a strong inhibitor of CYP2D6 enzyme, therefore concomitant therapy with drugs also metabolised by this enzyme system may lead to drug interactions, notably those having a narrow therapeutic index (such as flecainide,

propafenone and nebivolol) and those that are titrated, but also with atomoxetine, carbamazepine, tricyclic antidepressants, and risperidone. They should be initiated at or adjusted to the low end of their dose range. This may also apply if fluoxetine has been taken in the previous 5 weeks.

References

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