Guy's and St Thomas' NHS
NHS Foundation Trust

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Your Ref: 01269 - 2013

Mr John Thompson
Clerk to Senior Coroner
Southwark Coroner's Court
1 Tennis Street
Southwark, London
SE1 1YD

06 May 2014

Dear Mr John Thompson

Re: **MR MICHAEL ANTHONY (DECEASED)** Date of Birth: **15-05-1948**
[redacted]
NHS No: [redacted]
Address: [redacted]

Many thanks for your letter of 10th April last sent to both myself and [redacted] in relation to the above deceased. We note and acknowledge receipt of the Regulation 28 report to prevent future deaths on the above addressed to myself and [redacted] I have asked for full disclosure by email to the coroner's office of the toxicologists report. In the meantime, we have asked for a review from the regional drug information service at Guy's. This is attached below and forms part of our reflection, learning and response.

We have spoken to [redacted] Clinical Lead for Diabetes and Endocrinology at Guy's and St. Thomas' and Clinical Director for the Clinical Academic Grouping of Diabetes and Endocrinology in King's Health Partner, who does not recognise this particular risk and in his own extensive experience , has not seen it.

[redacted] and I have conferred. We have used this drug over many years. It is licensed for the use of the treatment of pain syndrome in diabetics. We have never had any problems such as described in the case. We both note the comments by the Toxicologist.

We have made the necessary changes by building this review into our day to day practice. If there is any further comments to be added on receipt of the disclosure requested above, we will reply but at present we would ask that this letter serves as our conclusion and formal reply to the letter received from you on behalf of the Chief Coroner.

Yours sincerely

Electronically checked and authorised by

[redacted]
Consultant Physician

[redacted]
GP

[redacted]
General Practitioner

TALK If for an older person you require Outpatient Rapid Assessment same or next-day or advice from a Geriatrician - Phone 020 7188 1465

Patient Name: MICHAEL ANTHONY [redacted]

Princess Street Group Practice
2 Princess Street, Elephant And Castle
London
SE1 6JP

Patient Name: MICHAEL ANTHONY [redacted]

Drug Information Search South London DI Service

Dear [redacted]

Thank you for your enquiry in to gabapentin and the potential association with diabetic coma. We have looked in to the possibility of this side-effect and in particular as a toxic effect.

The understanding is that gabapentin was prescribed for a patient with type 2 diabetes for neuropathic pain. The most recent information available to us states that he was on a dose of 600mg three times a day. No information provided as to how long he has been on it for.

The following are the key outcomes of our research in to this enquiry. Details are provided further in the response.

1. Diabetic ketoacidosis is not a recognised adverse effect of gabapentin at both therapeutic and toxic doses.[1,2,6]
2. We disagree with the statement that gabapentin should not be used in diabetics as it is a licensed medicine in patients with diabetes to controlled symptoms of painful neuropathy. Licensed doses for this indication can go *up to* 3600 mg/day.[1,2]
3. The patient in question was renally impaired. Doses of gabapentin in renal impairment should be lowered [1, 2]. The named patient was within the referenced licensed doses for his level of impairment on 14/12/2012, which was the most recent date blood results that were available to us. We are unsure if after this time his kidney function deteriorated. Gabapentin is eliminated unchanged solely by renal excretion, [2] therefore an impaired renal function will impair clearance of the drug leading to the possibility of toxic effects from accumulation.
4. Within both licensed and toxic doses, reports of diabetic ketoacidotic complications or fatalities were not found, apart from one report that was submitted to the MHRA.[3] Furthermore, toxicology data does not suggest any information on gabapentin causing diabetic ketoacidosis.[4]
5. A literature search found one paper which claimed that due to *high doses* of gabapentin the patient developed ketoacidosis. It is however, not clear if this is the case reported to the MHRA and details of the case are not available as the full paper to ascertain how the conclusions were made.

We understand that said patient had chronic kidney disease. From the data available, we were able to work out the level of impairment. The last set of renal data we have (14/12/2012) suggests that the patient's creatinine clearance was approximately 56.7ml/min, which means that he had moderate (stage 3) renal impairment. Doses of gabapentin according to the summary of product characteristics should see gabapentin up to a total daily dose of 1800mg in renal impairment.[2] This patient was within this limit. It cannot be determined whether this was an appropriate dose at the time of the patient's death as an up to date renal profile was not available. Gabapentin toxicity in patients with impaired renal function can manifest as coma.[5]

Within licensed doses we found the most common adverse effects are sedation, ataxia, dizziness, fatigue, nystagmus, changes in blood pressure.[6] Toxic effects found signs such as those above and slurred speech, movement disorders, and gastrointestinal upset. In more severe cases, patients may present with mild hypotension and profound central nervous system depression requiring intubation. Usually withdrawal of the drug leads to reversal of these effects. [1,2,6]

One *non-fatal* report was found by the MHRA yellow card adverse reporting system for the development of diabetic ketoacidosis.[3] Please note that the likelihood of experiencing an adverse drug reaction when taking a medicine cannot be estimated from the information provided in these reports. This is due to limited information about how many people have taken the medicine *without* experiencing a reaction.[3]

An extensive literature search was done using Medline and Embase databases.[7,8] One paper found a patient on haemodialysis was found to have potential gabapentin toxicity which caused admission to hospital after a series of seizures. A review of her medicines found high doses of gabapentin, which was then discontinued. She showed improvement after stopping drug. The admission was complicated with diabetic ketoacidosis. The paper concluded this to be caused by gabapentin. It is however, unclear whether this is linked to the report found with the MHRA. Full text of paper not currently available. [9]

Toxicology data shows that toxicity is "probably" low with gabapentin. Adult patients have ingested up to 30g with only mild symptoms seen. Furthermore, ingestion of up to 90g caused transient drowsiness, dizziness and ataxia. Nil information found about diabetic ketoacidosis. [4]

It is a possibility that high levels of gabapentin contributed to the fatality of named patient. However, it cannot be exclusive that this was the main cause. The licensing information states that in the treatment of peripheral neuropathic pain such as painful diabetic neuropathy, *efficacy and safety* have *not* been examined in clinical studies for treatment periods *longer than 5 months*. This may have been a contributing factor, in particular because the patient was renally impaired.

This case has been reported via the MHRA yellow card reporting system.

I hope this information has been useful for you. Please feel free to contact us if any further information is required.

Kind Regards,

[redacted] STEP Pharmacist
Medicines Information | Pharmacy department
Guy's and St Thomas' NHS Foundation Trust | Great Maze Pond | London | SE1 9RT

Telephone: 02071888750 | Fax. 0207 188 3857

References:

1) BNF.org. *British National formulary*. http://www.medicinescomplete.com/mc/bnf/current/ Last accessed 09/05/2014

2) Summary of product characteristics for Gabapentin. *Electronic medicines compendium.* www.medicines.org.uk/emc/. Last accessed: 25/04/2014

3) Yellow card data (CHM Drug Analysis Prints)-Gabapentin. *MHRA* www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/TheYellowCardScheme/YellowCarddata/Druganalysisprints/index.htm. Accessed: 29/04/2014

4) Gabapentin monograph. *Toxbase.* www.toxbase.org. Last accessed 25/04/2014

5) Pierce D.A. Holt S.R. Reeves-Daniel. 2008. A Probable case of hearing loss in patient with acute renal failure. *Clinical Therapeutics.* Vol./is. 30/9 Pages:1681-1684

6) Micromedex. www.micromedexsolutions.com/home/dispatch. Last accessed 25/04/2014

7) Medline. www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases. Last accessed: 09/05/14

8) Embase. www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases Last accessed: 09/05/14

9) Patel S., Malhotra R. 2013. Gabapentin related neurotoxicity in hemodialysis patient. *Journal of General Internal Medicine.* vol./is. 28/(S330). Pages: 0884-8734

10)Stockleys Drug Interactions. http://www.medicinescomplete.com. Last accessed: 06/05/2014