Medicines Adverse Reactions Committee

Meeting date	**13 September 2018**	Agenda item	
Title	**Dabigatran and gout, gout aggravation or gout-like symptoms**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent Dabigatran	**Medicines** Pradaxa hard capsules 75 mg 110 mg 150 mg	**Sponsors** Boehringer Ingelheim (NZ) Ltd	
Funding	Pradaxa is funded in New Zealand.		
Previous MARC meetings	Gout, gout aggravation or gout-like symptoms in association with dabigatran have not been discussed previously.		
Prescriber Update	This topic has not been included in PU.		
Schedule	Prescription medicine		
Usage data	Number of Pradaxa prescriptions dispensed at a community pharmacy 2016: - 75 527 prescriptions of 110 mg tablets - 68 540 prescriptions of 150 mg tablets - 2 720 prescriptions of 75 mg tablets Source: MoH Pharmaceutical Collection, extracted 18 December 2017.		
Advice sought	**The Committee is asked to advise whether:** – The data sheet for dabigatran should be updated regarding the risk of gout, gout aggravation or gout-like symptoms – This topic requires further communication other than an update of the [redacted] communication and MARC's Remarks in *Prescriber Update*.		

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1.0 PURPOSE

In September 2017 a report of gout aggravation in association with dabigatran treatment was received by the Centre for Adverse Reactions Monitoring (CARM). The patient experienced a marked increase in episodes of gout after starting dabigatran and improved after treatment with dabigatran had been stopped, without other interventions. For further case details – see section 3.3.1.

A review of the World Health Organization (WHO) database Vigibase showed that 70 cases of gout or gout-like symptoms suspected to be associated with dabigatran use had been reported worldwide. This was a higher number than expected, making the association a safety signal.

To obtain more information, the safety concern was added to the medicines monitoring ([redacted]) scheme on 31 January 2018. The monitoring finished 31 July 2018. During the reporting period, eight more cases of gout, gout aggravation or gout-like symptoms were reported to CARM.

The purpose of this paper is to review the available information on the possible risk of drug induced gout, gout aggravation or gout-like symptoms with dabigatran.

2.0 BACKGROUND

2.1 Pradaxa (dabigatran)

Pradaxa contains dabigatran etexilate (as mesilate) which is a prodrug without any pharmacological activity. After oral administration however, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor.

Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

The therapeutic indications for Pradaxa as listed in the NZ data sheet are:

- Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with nonvalvular atrial fibrillation with one or more of the following risk factors:
  - Previous stroke, transient ischaemic attack, or systemic embolism
  - Left ventricular ejection fraction <40%
  - Symptomatic heart failure, ≥New York Heart Association Class 2
  - Age ≥75 years
  - Age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension.
- Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.
- Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death.
- Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death.

The normal dosing of dabigatran is 150 mg twice daily, except after orthopaedic surgery when the dose is 220 mg once daily. The recommended dose may be reduced, for example when renal function is impaired or for elderly patients.

The most common side effects with dabigatran are gastrointestinal symptoms (such as dyspepsia, gastritis-like symptoms) and bleeding. Dabigatran is contraindicated in patients with active bleeding or at significant risk of major bleeding, patients with prosthetic heart valve replacement, severe renal impairment, i.e. a creatinine clearance less than 30 mL/min, organ lesions at risk of clinically significant bleeding or if the patient receives concomitant treatment with systemic ketoconazole (1, 2).

2.2 Gout

2.2.1 Description and presentation

Gout results from a raised total body uric acid (urate) concentration with consequent deposition of crystals in joints and occasionally elsewhere. Uric acid is mostly excreted by the kidneys. Too much uric acid may build up in the blood either if it is not excreted quickly enough or if too much is being produced. Hyperuricaemia is defined as a serum uric acid more than 0.36 mmol/L in women and more than 0.42 mmol/L in men (3).

When urate levels in the blood reach the saturation point, monosodium urate crystals can form and accumulate in joint fluid, cartilage, bones, tendons and other tissues. The inflammatory response to these crystals results in gout flares which are characterised by painful, red, hot, swollen joints. The big toe is the most commonly affected joint (4).

Gout usually presents as a painful monoarthritis that spontaneously resolves over a few days to one to two weeks. Gout is characterised by recurrent flares of severe joint inflammation, but most patients are asymptomatic between attacks.

2.2.2 Phases of gout

There are three classic clinical stages of gout: gout flare, intercritical gout, and tophaceous gout (5). The clinical stages of gout can be regarded as emerging sequentially (but with some overlapping), with clinical severity that often parallels the frequency of gout flares and the eventual development of chronic gouty arthropathy and tophaceous gout.

Initial gout flares usually involve a single joint. Over time, the flares can begin to involve multiple joints at once and may be accompanied by fever.

The time between gout flares is known as an intercritical period. A second gout flare typically occurs within two years, and additional gout flares may occur thereafter. If the gout is untreated over a period of several years, the time between gout flares may shorten and the flares may become increasingly severe and prolonged and involve multiple joints.

People who have repeated gout flares or persistent hyperuricemia for many years can develop tophaceous gout (accumulation of large numbers of urate crystals in masses called "tophi"). Tophi are usually not painful, although they can cause erosion of the bone, painful ulcers which are hard to heal, and eventually joint damage and deformity. Tophaceous gout used to be more common when treatment for hyperuricemia was unavailable.

2.2.3 Risk factors and prevalence

Long-term hyperuricaemia, often caused by declining kidney function, is the most important risk factor for development of gout. Additional factors that contribute to hyperuricaemia, and are associated with an increased risk of developing gout, include increasing age, genetic variation, male sex, hypertension, obesity, use of diuretics, antihypertensive medicines and low dose aspirin and excessive consumption of red meat, seafood, beer, spirits, sucrose or fructose-sweetened drinks.

About 10% of people with hyperuricaemia develop gout, but 80–90% of patients with gout are hyperuricaemic.

Gout is common in New Zealand. The prevalence and burden of gout is higher in Māori and Pacific patients than in other groups. In 2014, 7.6% of Māori and 12.7% of Pacific peoples aged over 20 years were identified as having gout, compared to 4% of people of New Zealand European or Asian descent (4).

2.2.4 Treatment

Non-steroidal anti-inflammatory drug (NSAID), corticosteroids or colchicine are used to treat gout flares.

Patients with hyperuricaemia and the following characteristics should start urate-lowering treatment:

- Two or more flares per year
- Tophi or erosions on X-ray
- Renal impairment
- Kidney stones

Allopurinol is the recommended first-line urate lowering medicine. Probenecid, benzbromarone and febuxostat are funded for patients who find allopurinol ineffective or intolerable (6).

2.2.5 Complications

Gout is associated with metabolic syndrome, nephrolithiasis, cardiovascular disease and chronic renal impairment. Hyperuricaemia and gout have been associated with increased risk of cardiovascular events in a variety of populations (7). Of interest for this report is a suggested link between gout/hyperuricemia and atrial fibrillation (AF), see section 3.1.

Comments:

The intermittent nature of gout makes it difficult to assess both cause of adverse effects and cause of improvement. Patients often have other diseases or risk factors increasing the risk to develop AF as well as gout.

2.3 Data sheets

2.3.1 New Zealand

No information on gout or gout related items is included in the dabigatran NZ data sheet.

2.3.2 Other countries

No information on gout or gout related items is included in the product information (PI) for dabigatran from the EMA, FDA or Health Canada. In Australia, as part of the Adverse effects section, the PI lists overviews of adverse events from certain clinical trials. Gout is listed as an adverse event reported in at least 2.0% of subjects in dabigatran etexilate arms and 2.7% in the warfarin arm in the clinical trial RE-LY (including more than 18 000 patients with AF) (8).

Comments:

The Australian PI is more detailed than the NZ data sheet and the EMA PI. All three list adverse effects in a table, but the Australian PI also list adverse effects affecting more than 2% of the patients in the dabigatran group from certain clinical trials as separate tables (such as the RE-LY clinical trial). Note that the NZ data sheet and the EMA PI were updated in January 2018 while the Australian PI was updated in February 2017.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

A literature search of PubMed did not result in any published material on dabigatran causing gout, gout aggravation or gout-like symptoms. Other aspects of gout/treatment of gout in association with atrial fibrillation/dabigatran have been published:

One publication suggests that colchicine, is a substrate of both cytochrome P450 3A4 and P-glycoprotein and may therefore interact with dabigatran (which is also a substrate of P-glycoprotein) (3).

There is published data regarding a potential association between gout/hyperuricemia and atrial fibrillation. A cohort study evaluated the risk of incident AF in patients with gout (n=70 015) versus osteoarthritis (n=210 045), using data from a US commercial insurance plan (9).

The mean age was 57 years and 81% were men. In a multivariable Cox regression adjusting for age, sex, comorbidities, medications and healthcare utilization, the HR of AF in gout was 1.13 (95%CI 1.04–1.23). When compared to non-gout, the multivariable HR of AF in gout was also increased (HR 1.21, 95%CI 1.11–1.33).

In elderly (mean age 75 years) patients with gout, the risk of incident AF was almost doubled in a study using American Medicare data (10).

Colchicine has been discussed as a potential treatment for certain cardiovascular diseases (11) and lowering of hyperuricemia has been suggested as a way of preventing AF (12). The conclusion in the last of these publications is that hyperuricemia is an independent competing factor for AF. More studies are needed to prove whether lowering the level of serum uric acid is important for preventing AF or not.

Comments:

No published data has been found linking treatment with dabigatran to gout, gout aggravation or gout-like symptoms.

3.2 Company report

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]

[redacted]

[redacted]

3.3 CARM data

3.3.1 CARM cases

Apart from the original report of gout with dabigatran that triggered the [redacted], CARM has received 7 reports of gout or gout aggravation and one of pseudogout (chondrocalcinosis) during the monitoring time (31 January to 31 July 2018). The details of all the 9 reports are summarised below. Details and a summary from CARM is attached to this report as Annexe 2.

Case 125864 – September 2017

[redacted] 83 year old female who had been treated with pantoprazole, metoprolol, levothyroxine, candesartan and furosemide [redacted]

[redacted] presented with gout [redacted]

[redacted]

[redacted]

Case 127783 – March 2018

[redacted]80 year old female[redacted]
developed gout attacks[redacted]

Suspect medicines[redacted] were bendrofluazide and dabigatran,[redacted]

Case 127672 – March 2018

[redacted] 43 year old man[redacted] dabigatran[redacted]
[redacted] gout[redacted]
[redacted].

Case 127998 – April 2018

[redacted]82 year old man[redacted] paracetamol, bisoprolol and atorvastatin[redacted]
[redacted] Allopurinol[redacted].[redacted]dabigatran[redacted]
[redacted] gout[redacted]

Case 127999 – April 2018

[redacted]79 year old man[redacted] dabigatran, atorvastatin, finasteride and cilazaprin[redacted]
[redacted] and verapramil[redacted] gout[redacted]
gout aggravated.

Case 128243 – April 2018

[redacted] 67 year old male[redacted] dabigatran, metoprolol, felodipine
and omeprazole[redacted] cilazapril.[redacted]
[redacted] gout[redacted]

Case 128482 – May 2018

[redacted] 55 year old male [redacted] dabigatran [redacted] gout [redacted]

Case 128705 – May 2018

[redacted] 68 year old female [redacted] gout aggravation [redacted] dabigatran, [redacted]

Case 128379 – April 2018

[redacted] 76 year old male [redacted] pseudogout [redacted] dabigatran [redacted] sotalol. [redacted]

The table below shows a summary of the cases:

Details	**Number of patients**
Sex	6 males, 3 females
Age range	43 to 83 years, mean 70 and median 76 years
Diagnosis	Eight clinical diagnosis of gout One, chondrocalcinosis (pseudogout)
[redacted]	[redacted]
[redacted]	[redacted]
Dabigatran suspect medicine	All cases
[redacted]	[redacted]

The conclusion from the CARM evaluation was the following:

the intermittent nature of gout makes recovery on dechallenge, especially with treatment for gout, not necessarily supportive of a causal association. Conversely, recovery while continuing dabigatran may not be against a causal association especially if the patient is treated. [redacted]

[redacted] Also supportive is the reasonably consistent time to onset of gout after starting dabigatran. There is no clear dose association. The diagnosis is not completely sound [redacted] The reports do lend some additional support to a signal for dabigatran and gout.

Comments:

Eight new cases were reported to CARM during the reporting period, which suggests that some patients do experience gout, gout aggravation or gout-like symptoms, whether or not they are caused by dabigatran. Some of the cases (patients with new onset of gout or with frequent flares) do support a causality. However, there are also uncertainties such as comorbidities, common risk factors and especially regarding the intermittent nature of gout.

3.3.2 Vigibase

Before the start of the monitoring period, data from the database of the WHO Programme for International Drug Monitoring, VigiBase, regarding dabigatran in association with gout, gout aggravation or gout-like symptoms data was analysed by CARM. At that time, there were 70 reports with positive IC value in VigiBase. Of these, 16 had a completeness score of 0.60 or higher. In these 16 cases, symptoms typically occurred on the same date up until approximately seven months after intake, with the following distribution:

- 12/15 reports with TTO (time to onset) within two months
- 10/15 reports with TTO within one month
- 7/15 reports with TTO within one week
- 2/15 reports with TTO same date

The 16th case was a study report with TTO 2 yrs 4m.

About half of the patients were, or had been, treated with diuretics. Given the natural cycle of gout, it is difficult to draw conclusions from dechallenge data.

Six new reports have been added to VigiBase since the start of the monitoring period and three of them from New Zealand.

The conclusion from the CARM evaluation is that the signal has strengthened a little largely due to the NZ reports. The main limitations are the fluctuating nature of symptomatic gout and the limited information on how the diagnosis of gout was made.

Comments:

The data from Vigibase is uncertain. The total completeness score is relatively low and information as to how the diagnosis of gout was made is lacking. About half of the 16 cases are reported to have occurred within the first month after starting dabigatran therapy.

3.4 National collections data

Using National Collections data, we were able to determine the number of patients during the period 1 July 2013 to 30 June 2016 who had been dispensed both dabigatran and one of the medicines allopurinol, colchicine or probenecid (anti-gout medicines) from a community pharmacy. Using start

and stop dates for dispensing, we could assess if dabigatran or the anti-gout medicine was dispensed first. The results are summarised below:

- There were a total of 4059 patients who had got both dabigatran and one or more of the anti-gout medicines allopurinol, colchicine, probenecid, febuxostat or benzbromarone dispensed at the same time.
- Of these, 1452 patients had been dispensed dabigatran first and then the anti-gout medicine.
- A total of 1193 of these 1452 patients had started treatment with dabigatran and were later prescribed an anti-gout medicine while still on dabigatran (stop date for dabigatran later than start date for anti-gout medicine).
- 188 patients of the 1193 were dispensed an anti-gout medicine less than 31 days after dabigatran was dispensed.
- 453 patients of the 1193 were dispensed an anti-gout medicine less than 91 days after dabigatran was dispensed.
- Of the 4059 patients, 2607 had got an anti-gout medicine dispensed first and then dabigatran.

Comments:

It is not known if any of these cases were new onset of gout, as most patients are likely to be prescribed a non-steroidal anti-inflammatory drug (NSAID) as a first medicine against gout. In addition, it is not known if any of the patients were treated with a NSAID against gout before another anti-gout medicine was prescribed but after the starting date of dabigatran. We do not know how these findings correlate with the natural course of gout as a disease characterised by relapses. Even with these limitations, National Collections data is a source that can be used to gain more knowledge regarding patients who have got dabigatran and anti-gout medicine dispensed during a certain time period.

Due to the limitations of the first analysis described above, a similar analysis was performed that included NSAIDs:

- A total of 1850 patients who had dabigatran dispensed also had a NSAID and one of the anti-gout medicines dispensed during the time period of interest.
- Of these, 717 patients had NSAID dispensed after dabigatran.
- The NSAID was dispensed less than 31 days after the dispensing of dabigatran for 52 patients.
- The NSAID was dispensed less than 91 days after the dispensing of dabigatran for 159 patients.

Comments:

If a patient was dispensed both a NSAID and an anti-gout medicine it is likely that the condition treated was in fact gout, as compared to patients who only had an NSAID dispensed. However, it is still hard to draw conclusions from this data as NSAIDs are used in so many different indications.

4.0 DISCUSSION AND CONCLUSIONS

Treatment with dabigatran was associated with a marked increase in episodes of gout in a case reported to CARM. During the [redacted] reporting period eight additional cases of gout, gout aggravation or gout like symptoms were reported to CARM. In VigiBase there are 76 reports of gout associated with dabigatran use.

Gout, gout aggravation or gout like symptoms are currently not listed in the NZ data sheet or in EMA, US or Canada PI for dabigatran.

There are factors in the reported cases that point to a relationship between dabigatran and gout, such as onset of new gout after commencing dabigatran. [redacted]

However, the intermittent nature of gout makes it difficult to assess the cause of development of the disease as well as cause of improvement at a certain time. Patients may have had other disease or risk factors that increase the risk to develop AF as well as gout. In addition there is uncertainty regarding how gout was diagnosed in the case reports.

National Collections data shows that there are a number of patients in NZ who are dispensed both an anti-gout medicine and dabigatran, and who got the dabigatran dispensed before the anti-gout medicine. Note that a limitation is that it is rather likely that the first anti-gout medicine prescribed was an NSAID.

No publication regarding a link between dabigatran and gout has been found. [redacted]

Currently, there is insufficient data to confirm that dabigatran is associated with gout. However, the issue will continue to be monitored by Medsafe through routine pharmacovigilance.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The data sheet for dabigatran should be updated regarding the risk of gout, gout aggravation or gout-like symptoms
- This topic requires further communication other than an update of the [redacted] communication and MARC's Remarks in *Prescriber Update*.

6.0 ANNEXES

1. [redacted]
2. CARM report

7.0 REFERENCES

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