

Medicines Adverse Reactions Committee

Meeting date	8 June 2017	Agenda item	3.2.3
Title	The risk of haemorrhage from concomitant use of statins and dabigatran		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent	Medicines	Sponsors	
Dabigatran	Pradaxa capsule*	Boehringer Ingelheim	
Simvastatin	Arrow-Simva coated tablet*	Teva Pharma (New Zealand) Limited	
	Auro-Simvastatin film coated tablet	Aurobindo Pharma NZ Limited	
	Lipex film coated tablet	Merck Sharp & Dohme (NZ) Limited	
	SimStatin film coated tablet	AFT Pharmaceuticals Ltd	
	* these products are currently funded by PHARMAC		
Funding	Pradaxa and Arrow-Simva are funded in the community and hospital.		
Previous MARC meetings	<p>This specific issue has not been discussed at previous MARC meetings. Dabigatran has been discussed previously at the following meetings:</p> <ul style="list-style-type: none"> – 148th Meeting — 8 December 2011 Update on the safety profile of dabigatran (Pradaxa) – 147th Meeting — 8 September 2011 Dabigatran safety profile <p>Statins have been discussed previously at the following meetings:</p> <ul style="list-style-type: none"> – 163rd Meeting — 10 September 2015 Statins and interstitial lung disease – 162nd Meeting — 11 June 2015 Statin-associated autoimmune myopathy – 155th Meeting – 12 September 2013 Review of statins and the risk of acute kidney injury – 150th Meeting – 21 June 2012 Review of statins and the risk of new-onset diabetes mellitus – 149th Meeting – 8 March 2012 Review of the pharmacokinetic interaction between cyclosporine and individual statins – 141st Meeting – 11 March 2010 Statins, neuromuscular degenerative disease and amyotrophic lateral sclerosis-like syndrome – 136th Meeting – 11 December 2009 Statins, neuromuscular degenerative disease and amyotrophic lateral sclerosis-like syndrome – scheduled review – 131st Meeting – 13 September 2007 Statins, neuromuscular degenerative disease and amyotrophic lateral sclerosis-like syndrome – 110th Meeting – 20 June 2002 		

	Withdrawal of statins
<i>Prescriber Update</i>	<p><u>Dabigatran</u> Update: Oral Anticoagulants and Gastrointestinal Bleeding (June 2016) New Oral Anticoagulants - Interactions Still Important (June 2015) Dabigatran - New Contraindication (March 2013) Antithrombotic Medicines - Still Causing Bleeding (March 2012) Dabigatran etexilate (Pradaxa): Summary of reports to CARM (December 2011) Medicines interactions: the role of P-glycoprotein (September 2011)</p> <p><u>Simvastatin</u> Simvastatin Interactions and Fatal Reports (December 2014) Statins and CYP Interactions (March 2014)</p>
Schedule	Prescription medicine
Advice sought	<p>The Committee is asked to advise whether:</p> <ul style="list-style-type: none"> – the available evidence suggests that there is a clinically relevant interaction between simvastatin and dabigatran leading to an increased risk of haemorrhage <ul style="list-style-type: none"> ○ if yes, are data sheet updates required – the outcome of this review requires further communication or advice to healthcare professionals or consumers other than MARC's Remarks in <i>Prescriber Update</i> – any other regulatory actions are required.

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1.0 PURPOSE

Medsafe has become aware of an article recently published in the Canadian Medical Association Journal (CMAJ) by Antoniou et al titled 'Association between statin use and ischemic stroke or major haemorrhage in patients taking dabigatran for atrial fibrillation'. Considering the wide use of dabigatran and statins in New Zealand Medsafe considers that these safety concerns should be reviewed by the MARC.

2.0 BACKGROUND

2.1 Dabigatran

Dabigatran is indicated for the [1]:

- prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one risk factor (such as previous stroke, transient ischaemic attack, or systemic embolism, left ventricular ejection fraction <40%, symptomatic heart failure, age ≥75 years, age ≥65 years with coronary artery disease, hypertension, or diabetes)
- prophylaxis of venous thromboembolism following total hip replacement or total knee replacement surgery
- treatment of deep-vein thrombosis or pulmonary embolism
- prevention of recurrent deep-vein thrombosis or pulmonary embolism.

Pradaxa is the Medsafe approved and PHARMAC funded medicine containing dabigatran available in New Zealand at this time. Pradaxa contains the pro-drug dabigatran etexilate as dabigatran is poorly absorbed after an oral dose [2]. Dabigatran etexilate gets converted quickly to dabigatran. It is thought the conversion to active dabigatran is due to carboxylesterases [3].

Dabigatran is a reversible inhibitor of thrombin. As part of the coagulation process, thrombin enables the conversion of fibrinogen into fibrin and consequently the inhibition of thrombin by dabigatran prevents thrombus development [2]. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin induced platelet aggregation [2].

The bioavailability of dabigatran is approximately 6% and peak serum concentration is reached in 1.5-2.0 hours [4]. The half-life of dabigatran is between 12 and 17 hours in patients with normal renal function but because dabigatran is primarily excreted by the kidney, the drug accumulates in patients with severe renal impairment [4].

2.1.1 P-glycoprotein

P-glycoprotein (P-gp) is a drug transporter involved in the movement of dabigatran and other drugs [5]. P-gp uses ATP to actively pump substrates across the membrane to the extracellular space [6]. P-gp is primarily localised in the gastrointestinal tract and also in hepatic, renal and brain tissue [5, 6].

Dabigatran etexilate has been identified as a P-gp substrate [2, 7]. The active drug dabigatran is not a P-gp substrate [5]. P-gp is also known as multidrug resistance-1 [6].

Co-administration of P-gp inhibitors could result in increased exposure of P-gp substrates such as dabigatran etexilate [5].

Antoniou et al state it is possible that co-administration of dabigatran and other inhibitors of carboxylesterase or P-gp could increase the absorption of dabigatran etexilate and/or prevent its bioactivation to dabigatran [8]. This could increase the risk of haemorrhage or decrease the drug's effectiveness (see Figure 1) [8]. Inhibition of P-gp in the gastrointestinal tract results in enhanced drug bioavailability [6].

Dabigatran is not metabolised by cytochrome P450 isoenzymes but some studies have shown P-gp inhibitors raise dabigatran serum concentrations [9].

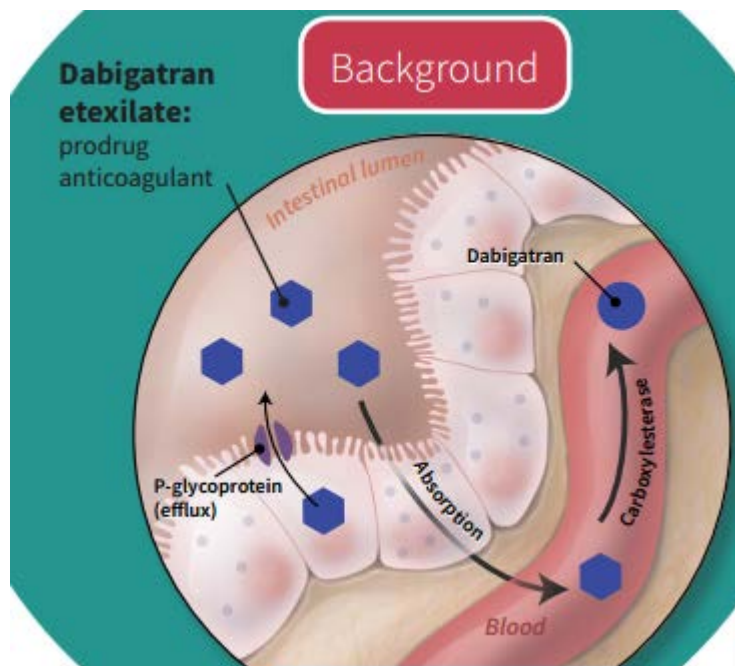


Figure 1 Diagram showing absorption of dabigatran etexilate. Taken from the Interaction of statins and dabigatran infographic in the 2016 CMAJ article by Antoniou et al [8].

2.2 Statins

2.2.1 Simvastatin

Antoniou et al conclude that in patients taking dabigatran, simvastatin and lovastatin are associated with a higher risk of major haemorrhage relative to other statins [8]. Lovastatin is not available in New Zealand so this paper focusses on simvastatin.

Simvastatin is indicated for the prevention of cardiovascular events in high risk patients and treatment of hypercholesterolemia [10].

Simvastatin is hydrolysed to a beta-hydroxy acid form after oral ingestion. This principal metabolite and an inhibitor of HMG-CoA reductase catalyses a step in the biosynthesis of cholesterol [11].

Most statins are administered in the orally active beta-hydroxy acid form however simvastatin and lovastatin are administered as inactive lactone prodrugs [12]. The lactone forms exhibit different inhibitory effects on P-gp-mediated transport of rhodamine 123; the lactone forms exhibited more potent P-gp inhibition than corresponding acid forms [12].

Antoniou et al state that statins administered in their lactone forms such as simvastatin and lovastatin are potent inhibitors of P-gp and carboxylesterase enzyme activity [8]. This effect is not included in simvastatin data sheets or international product information (see below).

2.3 Haemorrhage and stroke

Haemorrhage, or bleeding, is a major side effect of treatment with dabigatran etexilate and can be disabling, life-threatening or fatal [7]. Bleeding associated events can occur in different anatomical regions [7]. Intracranial haemorrhage, gastrointestinal haemorrhage, skin haemorrhage, urogenital haemorrhage, injection site haemorrhage, catheter site haemorrhage, traumatic haemorrhage, incision site haemorrhage, wound haemorrhage and post-procedural haemorrhage are all listed in the data sheet for Pradaxa [7].

The concomitant use of Pradaxa with medicines that affect coagulation such as vitamin K antagonists can markedly increase the risk of bleeding (see section 2.4 for more information on data sheet wording).

The Stroke Foundation of New Zealand defines stroke, or cerebrovascular accident, as 'a sudden interruption of blood flow to part of the brain causing it to stop working and eventually damaging brain cells' [13]. Approximately 7000 New Zealanders suffer from a stroke every year [14]. This can have a large physical, psychological and financial impact on patients, families, the healthcare system and society [13]. The use of anticoagulants such as dabigatran has important public health benefits. According to the 2010 New Zealand Clinical Guidelines for Stroke Management, stroke is the second most common cause of death worldwide and the third greatest cause of death in New Zealand (after all cancers combined and heart disease) [13].

2.4 Data sheets

2.4.1 Pradaxa (dabigatran)

Relevant wording from the New Zealand data sheet, the Australian product information and the UK Summary of Product Characteristics (SPC) for Pradaxa can be found in Appendix 1.

Australian product information is similar to New Zealand data sheet wording in that both contain extensive information on the possibility of increased dabigatran levels when P-gp inhibitors and dabigatran are concomitantly taken. The adverse effects section of both Australian and New Zealand product information includes many haemorrhage terms as adverse events.

Examples of P-gp inhibitors given in the Pradaxa product information do not include simvastatin, lovastatin, or any statin.

The UK Summary of Product Characteristics (SPC) is also similar to the New Zealand and Australian product information. The UK additionally distinguishes between mild to moderate and strong P-gp inhibitors. Statins are not mentioned in the SPC as a P-gp inhibitor.

2.4.2 Simvastatin

None of the simvastatin products available in New Zealand with published data sheets at 5 April 2017 mention an interaction with dabigatran or any effect on P-gp.

3.0 SCIENTIFIC INFORMATION

3.1 Guidance documents

3.1.1 Australian Prescriber, 2014 [15]

P-gp is a drug transporter that determines the uptake and efflux of a range of medicines by pumping its substrates from inside to outside the cell. Plasma and tissue concentrations, and ultimately the final effects, of medicines are affected by this process. P-gp inducers or inhibitors can interact with medicines that are handled by P-gp.

P-gp is therefore an important mediator of drug-drug interactions.

Dabigatran etexilate is a P-gp substrate and consequently there is potential for drug interactions to occur between dabigatran etexilate and drugs that act on P-gp. Inhibitors of P-gp may increase plasma concentrations of dabigatran leading to an increased risk of severe haemorrhage. Inhibitors of p-glycoprotein are ketoconazole, amiodarone, verapamil, ticagrelor and clarithromycin.

Comments:

This article does not mention simvastatin as a p-glycoprotein inhibitor.

3.1.2 Scientific Statement from the American Heart Association – Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients with Cardiovascular Disease

This document reviews drug-drug interactions, pharmacological differences in the various statins and the significance of statin drug-drug interactions with select medications used to treat patients with cardiovascular disease.

Competitive inhibition of P-gp is the most common mechanism by which substrates inhibit P-gp. Although reports vary, atorvastatin, lovastatin, pitavastatin and simvastatin are thought to be both P-gp substrates and inhibitors. The table below shows statin substrates, inhibitors and inducers for P-gp.

Table 1 Common P-gp substrates, inhibitors and inducers associated with the CYP 450 enzymes affecting statin metabolism

Enzyme	Statin Substrates	Inhibitors	Inducers
P-gp	Atorvastatin, lovastatin, pitavastatin, simvastatin	Amiodarone, atorvastatin, azithromycin, captopril, carvedilol, cimetidine, clarithromycin, colchicine, conivaptan, cyclosporine, diltiazem, dipyridamole, dronedarone, erythromycin, felodipine, grapefruit juice, itraconazole, ketoconazole, lovastatin, mefloquine, nicardipine, omeprazole, protease inhibitors, quinidine, ranolazine, reserpine, sertraline, simvastatin, tacrolimus, verapamil	Carbamazepine, phenytoin, rifampin, St. John's wort

This document provides recommendations for statin-warfarin drug-drug interactions. The authors state that there is no clinically significant increase in statin exposure with co-administration of warfarin and combination therapy is useful when clinically indicated. With regards to dabigatran use, no clinically significant drug interactions have been reported or are anticipated with statins and novel anticoagulants dabigatran, apixaban, rivaroxaban and edoxaban.

Comments:
The American Heart Association reports lovastatin and simvastatin to be P-gp inhibitors.

3.1.3 European Medicines Agency, 2012 – Guideline on the investigation of drug interactions [16]

The European Medicines Agency guideline states that dabigatran etexilate or fexofenadine seem to be more sensitive to intestinal P-gp inhibition than oral digoxin and therefore these drugs, particularly dabigatran etexilate due to the clinical relevance are recommended as probes for intestinal P-gp inhibition.

3.2 Published literature

3.2.1 Antoniou et al, 2016 (Annex 3) [8]

This article in the CMAJ was the trigger for this review. Two population-based, nested case-control studies were conducted using Ontario residents 66 years of age and older who started dabigatran etexilate between 1 May 2012 and 31 March 2014.

Comprehensive prescription drug records were obtained from the Ontario Drug Benefit Database and hospital admission and emergency department data was obtained from the Canadian Institute for Health Information’s Discharge Abstract database and National Ambulatory Care Reporting System respectively. The Ontario Health Insurance Plan database was used to identify claims for physician services, validated disease registries were used to ascertain the presence of comorbidities and the Registered Persons Database (for residents eligible for health insurance) was used to obtain basic demographic data.

Ongoing dabigatran use was defined as receipt of a prescription refill within 1.5 times the days covered by the previous prescription.

In the first study, cases were defined as patients taking dabigatran therapy who had a hospital admission or emergency department visit for ischaemic stroke within 60 days of receiving a prescription for one statin. Patients receiving prescriptions for multiple statins were excluded. Four age and sex matched controls were matched to each case. Cases that could not be matched to at least one control were excluded.

In the second study, cases were defined as patients taking dabigatran who had any haemorrhagic event resulting in hospital admission or a visit to an emergency department within 60 days of receiving a statin.

Controls were required to be event free at the index date (the date of hospital admission or emergency department visit) and have received a single statin within 60 days of the index date.

Multivariable conditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence intervals (CI) for the association between stroke or ischaemic attack and exposure to lovastatin or simvastatin relative to other statins. A similar analysis was conducted for the association between statins and major haemorrhage. Chronic kidney disease and warfarin could act as effect modifiers in the association between lovastatin or simvastatin and the study outcomes so these variables and the study group were tested for interactions in separate models.

Out of 45991 patients taking dabigatran, 397 patients were treated with dabigatran, diagnosed with an ischemic stroke or transient ischemic attack and received a statin preceding the index date. 1117 patients were treated with dabigatran, diagnosed with major haemorrhage and received a statin in the 60 days before the index date.

After multivariable adjustment, use of simvastatin or lovastatin was not associated with an increased risk of stroke relative to other statins (adjusted OR 1.33, 95% CI 0.88 to 2.01). In contrast, use of simvastatin and lovastatin was associated with a higher risk of major haemorrhage (adjusted OR 1.46, 95% CI 1.17 to 1.82). In sensitivity analyses, the presence of chronic kidney disease (CKD) (p for interaction = 0.09) or prior warfarin use (p for interaction = 0.83) did not influence the association between statin group and major haemorrhage.

Table 2 Association between statin use and stroke or transient ischaemic attack

Statin	No. (%)		OR (95% CI)	Adjusted OR* (95% CI)
	Cases n = 397	Controls n = 1588		
Atorvastatin, pravastatin, fluvastatin or rosuvastatin (ref)	358 (90.2)	1438 (90.6)	1.00	1.00
Simvastatin or lovastatin	39 (9.8)	150 (9.4)	1.04 (0.72–1.51)	1.33 (0.88–2.01)

Note: CI = confidence Interval, OR = odds ratio, ref = reference category.

*Adjusted for history of stroke or transient Ischemic attack in preceding 5 years, Charlson Comorbidity Index score, diabetes, hypertension, myocardial infarction, congestive heart failure, chronic kidney disease, number of prescription drugs in previous year, medications (β -adrenergic receptor blockers, nitrates, acetylsalicylic acid and dipyridamole, antiarrhythmics, clopidogrel, warfarin, nonsteroidal anti-inflammatory drugs, P-glycoprotein inhibitors, cytochrome P450 3A4 inhibitors), carotid Doppler ultrasonography, pacemaker insertion and duration of statin use.

Table 3 Association between statin use and major haemorrhage

Statin	No. (%)		OR (95% CI)	Adjusted OR* (95% CI)
	Cases n = 1117	Controls n = 4465		
Atorvastatin, pravastatin, fluvastatin or rosuvastatin (ref)	984 (88.1)	4069 (91.1)	1.00	1.00
Simvastatin or lovastatin	133 (11.9)	396 (8.9)	1.39 (1.13–1.71)	1.46 (1.17–1.82)

Note: CI = confidence interval, OR = odds ratio, ref = reference category.
*Adjusted for history of major hemorrhage, Charlson Comorbidity Index score, myocardial infarction, angina, congestive heart failure, chronic kidney disease, chronic liver disease, residence in long-term care facility, number of prescription drugs in previous year, medications (β -adrenergic receptor blockers, nitrates, clopidogrel, warfarin, nonsteroidal anti-inflammatory drugs, P-glycoprotein inhibitors, P-glycoprotein inducers, cytochrome P450 3A4 inhibitors), angiography and percutaneous coronary angioplasty.

The authors identified limitations of the study. These included a lack of access to laboratory data and information on renal function, smoking, non-prescription use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) and the adequacy of blood pressure and diabetes control, medication adherence was unknown, possible misclassification of outcomes and there was some imbalance in baseline characteristics of cases and controls. It was unknown whether doses of dabigatran were adjusted in patients with CKD but CKD was not found to be an effect modifier for statin use and haemorrhage. The power of the study may not have been sufficient to detect an association between lovastatin and simvastatin as the number of cases receiving these statins was small (stroke: lovastatin 12 (0.6%), simvastatin 177 (8.9%), haemorrhage: lovastatin 27 (0.5%), simvastatin 502 (9.0%)). These findings may not be generalisable to younger patients who are likely to have fewer risk factors for stroke or major haemorrhage.

The authors concluded simvastatin and lovastatin were associated with an increased risk of major haemorrhage in older patients taking dabigatran and this may reflect increased dabigatran absorption as a result of p-glycoprotein inhibition. The authors consider that statins other than simvastatin and lovastatin should be given preferentially in older patients receiving dabigatran etexilate who require statin therapy.

Comment:

A number of limitations are associated with this study such as the potential for residual confounding and differences between the cases and control groups. There is limited evidence that simvastatin is a clinically significant inhibitor of P-gp in humans.

3.2.2 Thomsen et al, 2014 [17]

Carboxylesterase 1 is involved in the metabolism of several therapeutic agents and activates ester-containing prodrugs including dabigatran etexilate. The authors consider polypharmacy is common in the treatment of hypertension, diabetes, congestive heart failure and other diseases and several of the drugs that may be prescribed are substrates of carboxylesterase 1. There is the potential therefore for clinically relevant drug interactions involving carboxylesterase 1. The authors screened a panel of cardiovascular, antiplatelet and anticoagulant drugs; drugs of abuse; and immunosuppressive agents for their inhibitory potential against carboxylesterase 1.

The screening assay showed simvastatin and atorvastatin both inhibited carboxylesterase 1 with 0.2% and 44.1% residual activity respectively (Figure 2).

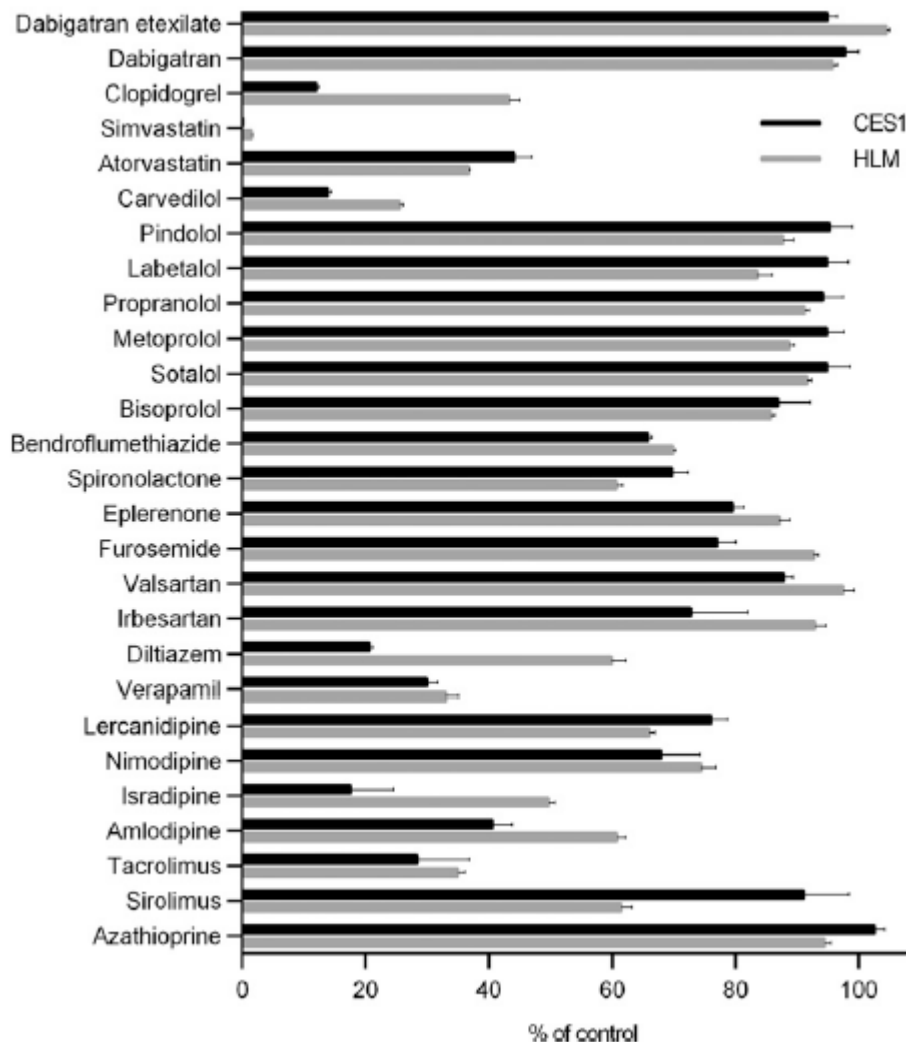


Figure 2 Inhibition of carboxylesterase 1 by therapeutic drugs. Inhibitory effects of drugs on the hydrolysis of 50 µM p-nitrophenyl acetate in recombinant human carboxylesterase or human liver microsomes. Concentrations of tested compounds were 100 µM. Values represent mean ± SEM (n=3). Control activity was 382 nmol/min/mg protein for carboxylesterase and 838 nmol/min/mg protein for human liver microsomes.

This study demonstrated simvastatin to be a potent inhibitor of carboxylesterase 1 and atorvastatin moderately inhibited the enzyme. This study supports the findings of Fukami et al which found lactone-containing statins (simvastatin and lovastatin) are more potent inhibitors of carboxylesterase 1 than statins existing as hydroxyl acids (eg atorvastatin) (section 3.2.5).

Comment:

Inhibition of carboxylesterase-1 would be expected to reduce the efficacy of dabigatran as it will not be metabolised from the pro-drug. It therefore seems possible that we would expect see thrombosis rather than bleeding.

3.2.3 Fukami et al, 2010 [18]

This study examined the inhibitory effects of various antidiabetic or antihyperlipidemic drugs on carboxylesterase 1A1 enzyme activity and compared this with the inhibitory effect on carboxylesterase 2 enzyme activity.

The activity by recombinant carboxylesterase 1A1 was inhibited by simvastatin and lovastatin (both 0.6% of control). Simvastatin and lovastatin are hydrolysed to simvastatin hydroxyl acid and

lovastatin hydroxyl acid (the active *in vivo* metabolites). The acid forms did not show the same inhibitory effects as the parent drugs (Figure 3).

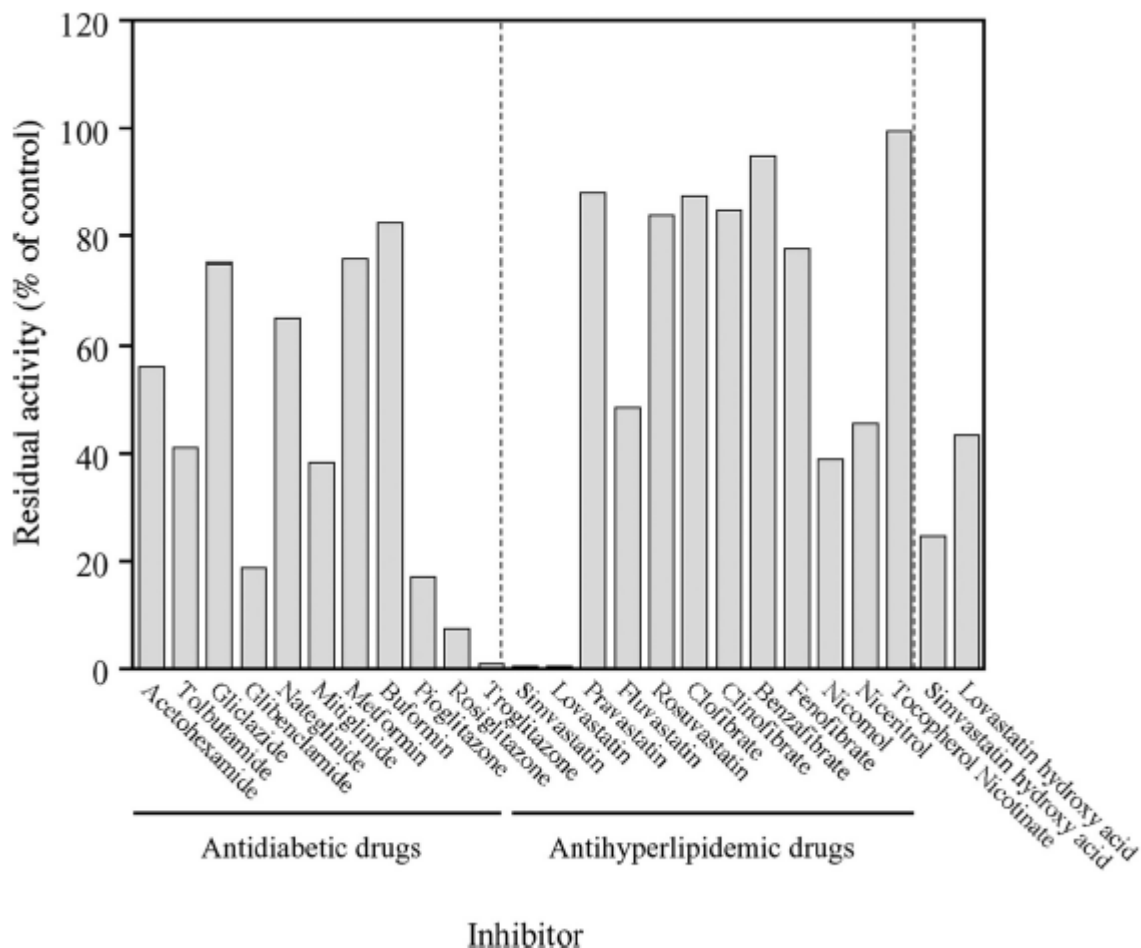


Figure 3 Inhibitory effects of 12 antidiabetic and 11 antihyperlipidemic drugs plus simvastatin acid and lovastatin acid on imidapril hydrolase activity by recombinant carboxylesterase 1A1. The concentration of imidapril was 100 µM. The concentrations of 25 drugs and metabolites were 200 µM except for (±)-α-tocopherol nicotinate (100 µM). Each column represents the mean of duplicate determinations. The control activity by recombinant carboxylesterase 1A1 was 1.73 nmol/min/mg.

Lineweaver-Burk plots showing inhibition constant (K_i) values and inhibition patterns of simvastatin are shown in Figure 4. The K_i values and inhibition patterns of simvastatin for recombinant carboxylesterase 1A1 were $0.11 \pm 0.01 \mu\text{M}$ (Figure 4).

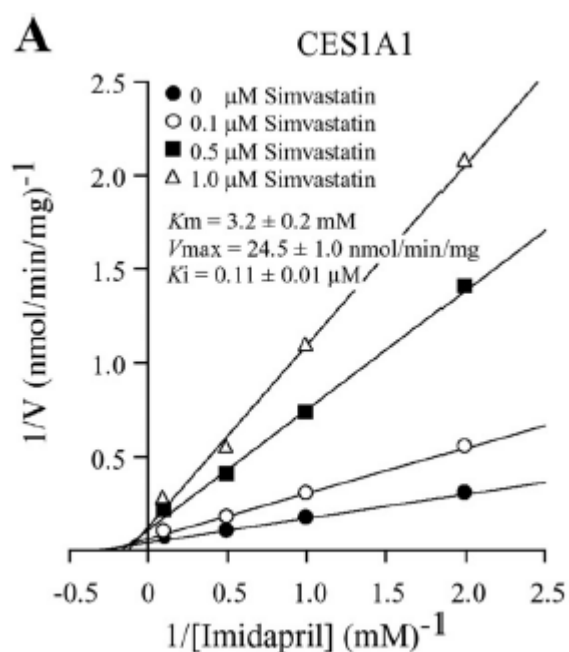


Figure 4 Inhibitory effects of simvastatin on the imidapril hydrolase activities by recombinant carboxylesterase 1A1. Each data point represents the mean of duplicate determinations. The K_m , V_{max} and K_i values represent the mean \pm S.E.

The study found that lactone-ring containing statins such as simvastatin and lovastatin strongly inhibited carboxylesterase 1A1 enzyme activity whereas statins with an open acid form such as pravastatin and fluvastatin did not show strong inhibition of carboxylesterase 1A1 enzyme activity.

The authors quantitatively predicted *in vivo* drug-drug interactions by comparing the maximum value of the unbound concentration at the inlet to the liver ($I_{inlet, u, max}$) estimated using pharmacokinetic data and the value of K_i obtained *in vitro*. They found the $I_{inlet, u, max}$ value of simvastatin to be lower than the K_i value for the imidapril hydrolase activity in human liver microsomes ($0.76 \pm 0.06 \mu\text{M}$) and therefore simvastatin may have a low inhibitory potential on the imidapril hydrolase activity *in vivo* in human.

Comment:

This study is consistent with comments made by Antoniou et al (section 3.2.1) stating that statins administered in their lactone forms such as simvastatin and lovastatin are potent inhibitors of carboxylesterase enzyme activity however the authors note simvastatin may have a low inhibitory potential *in vivo*.

3.2.4 Bernsdorf et al, 2006 [19]

The aim of this study was to evaluate whether simvastatin influences the intestinal expression of P-gp and multidrug resistance-related protein 2 (MRP2) and the disposition of the β_1 -selective blocker talinolol, a substrate of these transporter proteins.

The disposition of talinolol after intravenous (30 mg) and single or repeated oral administration (100 mg daily) was monitored before and after chronic treatment with simvastatin (40 mg daily) in 18 healthy subjects (10 males, eight females, body mass index $19.0\text{--}27.0 \text{ kg m}^2$) genotyped for ABCB1, ABCC2 and SLCO1B1 polymorphisms. The steady state pharmacokinetics of simvastatin was evaluated before and after repeated oral talinolol administration. The duodenal expression of ABCB1 and ABCC2 mRNA before and after simvastatin treatment was quantified.

Simvastatin did not influence the expression of duodenal ABCB1 and ABCC2. The study concluded that there was no significant pharmacokinetic interaction between simvastatin and talinolol during

their chronic co-administration to healthy subjects and simvastatin does not influence the intestinal expression of P-gp and MRP2 in man with ABCB1 and ABCC2 polymorphisms.

Comment:

These results suggest there is likely to be no interaction due to increased amount of intestinal P-gp.

3.2.5 Holtzman, 2006 [20]

This article reviews *in vitro* studies examining the role of P-gp in statin drug interactions. Simvastatin is often studied in its prodrug lactone form as well as the acid form (the active metabolite). Results of several studies with *in vitro* models have shown that lovastatin, simvastatin and atorvastatin are inhibitors for P-gp in a concentration-dependent manner. Simvastatin acid did not show significant inhibition of substrate transport. Concentrations of statins required in many of the studies reviewed exceeded systemic exposure after oral administration and no direct correlation between these models and clinical drug interactions has been proved.

Published studies suggest atorvastatin, lovastatin and simvastatin inhibit P-gp-mediated drug transport. Clinically, co-administration of lovastatin, simvastatin or atorvastatin with other P-gp substrates or inhibitors may result in statin drug interactions. Statins may increase or decrease the bioavailability of other drugs through P-gp modulation and increased concentrations of statins may increase the risk of adverse drug reactions when used concomitantly with drugs that are known P-gp substrates or inhibitors.

The authors conclude that clinically, co-administration of lovastatin, simvastatin or atorvastatin with other P-gp substrates or inhibitors may result in statin drug interactions.

Comment:

It is not clear why the authors consider co-administration of lovastatin, simvastatin or atorvastatin with other P-gp inhibitors may result in clinical drug interactions given that the *in vitro* studies outlined in the first paragraph show the interaction is not likely to be clinically relevant.

3.2.6 Sakaeda et al, 2006 [21]

This study investigated inhibitory effects of acid and lactone forms of eight statins on cytochrome P450 and multidrug resistance protein 1 (MDR1; p-glycoprotein) activity because studies have shown that conversion between the acid and lactone form of statins occurs in the body and drug-drug interactions on both forms should be considered. There is a growing clinical use of statins. Lovastatin and simvastatin are of a lactone form whereas others are an acid form.

The inhibitory effects of statins on MDR1 activity was investigated using MDR1-overexpressing LLC-GA5-COL150 cells.

Table 4 shows IC₅₀ values for MDR1 transporting activity as assessed using the MDR1-overexpressing cell line LLC-GA5-COL150 and a typical MDR1 substrate [³H]digoxin. MDR1-mediated transport of [³H]digoxin was inhibited only by lactone forms in the rank order of atorvastatin (15.1 μM), cerivastatin (28.2 μM), pitavastatin (34.9 μM), lovastatin (44.5 μM), and simvastatin (59.6 μM). Fluvastatin, pravastatin, and rosuvastatin showed no inhibition even at 100 μM.

Table 4 IC₅₀ values for CYP-mediated metabolic activities and MDR1-mediated transporting activity for eight statins

Statins	Model substrates	IC ₅₀ values (µM)					
		Paclitaxel 6α-hydroxylation, CYP2C8	Tolbutamide 4-hydroxylation, CYP2C9	S-Mephenytoin 4-hydroxylation, CYP2C19	Testosterone 6β-hydroxylation, CYP3A4/5	Paclitaxel 3-hydroxylation, CYP3A4/5	Digoxin net B-to-A transport, MDR1
Atorvastatin	Acid form ^a	38.4	>100	>100	>100	74.6	>100
	Lactone form	28.8	61.0	>100	9.7	5.6	15.1
Cerivastatin	Acid form ^a	29.8 ^b	>100	>100	>100	>100 ^b	>100
	Lactone form	44.3 ^b	42.9	>100	80.7	8.1 ^b	28.2
Fluvastatin	Acid form ^a	70.2	1.7 ^b	>100	>100	>100	>100
	Lactone form	55.4	81.8 ^b	>100	48.1	14.9	>100
Lovastatin	Acid form	74.6	>100	>100	>100	>100	>100
	Lactone form ^a	79.9	>100	>100	26.9	24.1	44.5 ^c
Pitavastatin	Acid form ^a	57.0	>100 ^b	>100	>100	>100	>100
	Lactone form	50.5	>100 ^b	>100	>100	67.2	34.9
Pravastatin	Acid form ^a	>100	>100	>100	>100	>100	>100 ^c
	Lactone form	99.3	>100	>100	>100	73.7	>100
Rosuvastatin	Acid form ^a	>100 ^b	>100 ^b	>100	>100	>100 ^b	>100
	Lactone form	32.5 ^b	20.5 ^b	>100	82.7	20.7 ^b	>100
Simvastatin	Acid form	51.5	>100	>100	79.0	12.0	>100
	Lactone form ^a	44.1	>100	>100	76.8	15.2	59.6 ^c

CYP, cytochrome P450.

^aThe form contained in oral prescriptions.^bAlready reported in (32).^cAlready reported in (20).

The authors noted the inhibitory effects on MDR1 activity were explained by lipophilicity (Figure 5, $p = -0.546$, $p = 0.004$).

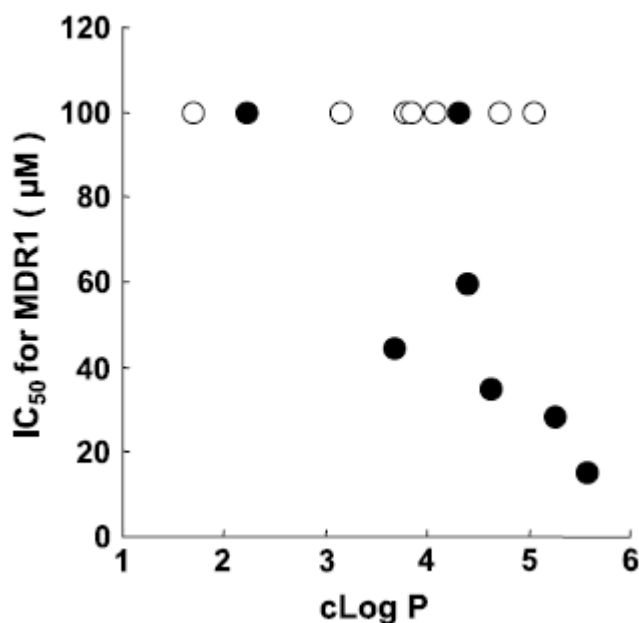


Figure 5 Relationship between the values of cLog P and IC₅₀ for MDR1 of eight statins. Closed and open circles represent lactone and acid forms respectively. A significant correlation was found with $p = -0.546$ and $p = 0.044$

This study concluded that there is a difference between the acid and lactone forms of statins in terms of drug interaction with CYPs and MDR1 and lipophilicity could be an important factor for inhibitory effects. In the case of statins it is important to examine the effects of both forms to understand events found in clinical settings.

Comment:

Hochman et al (see section 3.2.8 below) reported that for a 40mg/day dose, systemic steady state simvastatin levels were <100nM (well below concentrations that would inhibit P-gp).

3.2.7 Chen et al, 2005 [12]

This study examined the interaction of four statins (atorvastatin, lovastatin and simvastatin in acid and lactone forms, and pravastatin in acid form only with multidrug resistance gene 1 (MDR1), P-gp, multidrug resistance-associated protein-2 (MRP2) and organic anion-transporting polypeptide 1B1 (OATP1B1). In the inhibition assays (MDR1, MRP2 (human), Mrp2 (rat) and OATP1B1), the IC₅₀ values for efflux transporters (MDR1, MRP2 and Mrp2) were >100 µM for all statins in acid form except lovastatin acid (>33 µM) and the IC₅₀ values were up to 10-fold lower for the corresponding lactone forms.

The authors state their data demonstrates that lactone and acid forms of statins exhibit differential substrate and inhibitor activities toward efflux and uptake transporters. Lactone and acid forms of most statins convert between the two in the body and this can potentially influence drug-transporter interactions. The lactone forms of all three statins exhibited more potent P-gp inhibition compared with their corresponding acid forms.

An earlier study by Bogman et al, 2001, confirmed simvastatin, lovastatin and atorvastatin were P-gp inhibitors and pravastatin was not. The authors consider a certain lipophilicity may be necessary for interaction with P-gp as pravastatin is more hydrophilic than all other statins.

3.2.8 Hochman et al, 2004 [22]

The inhibition of P-gp by simvastatin, simvastatin acid and atorvastatin was evaluated to assess the role of P-gp in drug interactions.

Inhibition of P-gp was evaluated by studying the vinblastine efflux in Caco-2 cells and in P-gp overexpressing KBV1 cells at concentrations of simvastatin, simvastatin acid and atorvastatin up to 50µM. Two P-gp assays were used. One studied the impact of statins on P-gp restricted drug accumulation in cells and the second evaluated inhibition of P-gp mediated directional transport.

Results from this inhibition study were consistent with previous P-gp inhibition studies. Simvastatin inhibited P-gp at relatively high concentrations (IC₅₀ 25-50 µM). In contrast simvastatin acid did not significantly inhibit P-gp mediated vinblastine transport at concentrations as high as 50 µM.

The authors consider that given their studies, it is unlikely that P-gp plays a significant role in observed clinical drug interactions for simvastatin. For a 40mg/day dose, systemic steady state simvastatin levels were <100nM (well below concentrations that would inhibit P-gp). Simvastatin is highly plasma protein bound (96%) and it is unlikely that circulating levels of simvastatin would impact P-gp transport of other drugs. In addition, simvastatin co-administration results in pharmacologically irrelevant elevations in systemic levels of other P-gp substrates (eg digoxin).

The study concludes that the moderate level of P-gp mediated transport and low-affinity of simvastatin, simvastatin acid and atorvastatin for P-gp inhibition compared to systemic drug levels suggest that drug interactions due to competition for P-gp transport is unlikely to be a significant factor in adverse drug reactions.

Table 5 Inhibition of p-glycoprotein mediates transport of vinblastine by simvastatin, simvastatin acid and atorvastatin: Effect on Directional Transport and KBV1 Cellular Accumulation

Cell line (substrate) Inhibitor	% Inhibition directional transport		Cellular accumulation	
	L-MDR1 cells (ritonavir)	Caco-2 cells (vinblastine)	L-MDR1/LLC PK-1 (vinblastine)	KBV1/KB-3-1 (vinblastine)
Control	0%	0%	8%	12%
SV 1 µM	ND	26%	5%	14%
SV 10 µM	ND	44%	9%	18%
SV 25 µM	30%	60%	33%	47%
SV 50 µM	100%	71%	34%	128%
SVA 1 µM	ND	14%	ND	12%
SVA 10 µM	ND	13%	ND	14%
SVA 50 µM	15%	9%	6%	17%
AVA 50 µM	9%	43%	5%	15%
CsA 10 µM	ND	94%	68%	114%

ND, not determined.

* No directional transport of ritonavir detected in control LLC-PK1 cells.

Comment:

The authors conclude it is unlikely that P-gp plays a significant role in observed clinical drug interactions for simvastatin.

The above studies do not provide strong evidence that the impact of P-gp inhibition on an interaction with dabigatran is clinically relevant.

Comment:

The last Periodic Benefit Risk Evaluation Report (PBRER) received by Medsafe for Pradaxa was for the period 19 March 2015 to 18 September 2015. This PBRER does not include any information relating to a possible interaction with simvastatin.

3.3 International

[Redacted content]

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3.5 CARM data

CARM have received 211 reports reporting dabigatran as the suspect medicine and a statin reported as either suspect or concomitant medicine. Out of these 211 reports, 87 cases reported at least one haemorrhage-related term (107 haemorrhage terms in total were reported for these 87 cases). A statin was not reported as suspect medicine in any of these 87 cases. 4 cases reported both dabigatran and a statin as suspect medicines however the reported reactions were not haemorrhage related terms.

For these 87 cases involving dabigatran, a statin and a haemorrhage, 64% (n=56) concerned simvastatin and 36% (n=31) concerned atorvastatin. In these cases, all reports concerned patients who were at least 50 years of age. A breakdown of the age distribution can be found on page 2 of Annex 4. A line listing of the 87 cases can also be found in Annex 4.

4.0 DISCUSSION AND CONCLUSIONS

Dabigatran is an oral anticoagulant and simvastatin is a cholesterol and triglyceride lowering medicine. Most statins are administered in the orally active beta-hydroxy acid form however simvastatin and lovastatin are administered as inactive lactone prodrugs. Statins administered in their lactone forms are thought to be stronger inhibitors of P-gp. P-gp is a drug transporter involved in the movement of dabigatran etexilate, a P-gp substrate. Co-administration of P-gp inhibitors could result in increased exposure of dabigatran.

The current safety concern relates to simvastatin and lovastatin use in patients taking dabigatran and the risk of major haemorrhage. A case-control study conducted by Antoniou et al and published in the Canadian Medical Association Journal in 2016 concluded that in patients taking dabigatran etexilate, simvastatin and lovastatin were associated with a higher risk of major haemorrhage relative to other statins.

A literature review has been carried out, the recent CMAJ article has been discussed by international regulators as part of the International Post-Market Surveillance Teleconference and Boehringer-Ingelheim (sponsor of the dabigatran product Pradaxa) and Merck Sharp & Dohme (sponsor of the simvastatin product Lipex) have also carried out reviews of this topic.

A number of limitations of the Antoniou et al study were noted. The authors lacked information on some important factors including renal function, smoking, non-prescription use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), there was possibly misclassification of outcomes and some differences between baseline characteristics of cases and controls. The study design, possible lack of power, risk of residual confounding remaining and a risk of bias makes interpretation of the study results difficult. In addition, the odds ratio for the risk of major haemorrhage with simvastatin and lovastatin in patients taking dabigatran was relatively small (1.46).

There is some evidence that simvastatin inhibits P-gp however the literature reviewed does not provide strong evidence that simvastatin is a clinically significant inhibitor of P-gp in humans. The

company reviews do not support the Antoniou et al findings that co-administration of dabigatran etexilate and statins, including simvastatin and lovastatin, results in an interaction between these medicines increasing dabigatran exposure or bleeding rates.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- the available evidence suggests that there is a clinically relevant interaction between simvastatin and dabigatran leading to an increased risk of haemorrhage
 - if yes, are data sheet updates required
- the outcome of this review requires further communication or advice to healthcare professionals or consumers other than MARC's Remarks in *Prescriber Update*
- any other regulatory actions are required.

6.0 ANNEXES

1. Boehringer Ingelheim Signal Assessment Report
2. Merck, Sharp & Dohme Signal Evaluation
3. Antoniou, T., et al., *Association between statin use and ischemic stroke or major haemorrhage in patients taking dabigatran for atrial fibrillation*. Canadian Medical Association Journal, 2016.
4. Overview of CARM cases

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8.0 APPENDIX ONE

Relevant wording from the New Zealand data sheet, the Australian product information and the UK Summary of Product Characteristics (SPC) for Pradaxa.

8.1 New Zealand

The Pradaxa data sheet discusses p-glycoprotein interactions in the interactions and warnings and precautions sections of the data sheet and relevant wording is copied below [7]:

Contraindications

Concomitant treatment with systemic ketoconazole (see Interactions).

Warnings and Precautions

Haemorrhagic risk:

Factors increasing dabigatran plasma levels – p-glycoprotein inhibitor co-medication.

Factors, such as decreased renal function (30 - 50ml/min CrCl), age ≥ 75 years, or strong P-gp-inhibitor comedication are associated with increased dabigatran plasma levels. The presence of one or more than one of these factors may increase the risk of bleeding (see Dosage and Administration).

The concomitant use of PRADAXA with the following treatments has not been studied and may increase the risk of bleeding: and the P-gp inhibitors, itraconazole, tacrolimus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir.

The concomitant use of dronedarone increases exposure of dabigatran and is not recommended (see Pharmacokinetics - Special Populations).

The concomitant use of ticagrelor increases the exposure to dabigatran and may show pharmacodynamic interaction, which may result in an increased risk of bleeding.

Interactions

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and had no effects *in vitro* on human cytochrome P450 enzymes. Therefore related drug-drug interactions are not expected with dabigatran etexilate or dabigatran (see special populations).

P-glycoprotein interactions

P-glycoprotein inhibitors:

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, systemic ketoconazole, dronedarone, ticagrelor and clarithromycin) is expected to result in increased dabigatran plasma concentrations.

Concomitant administration of systemic ketoconazole is contraindicated.

For the other P-gp inhibitors listed above no dose adjustments are required for PRADAXA in the indications “prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation”, “treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death” or “prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death”.

Amiodarone: Dabigatran exposure in healthy subjects was increased by 1.6 fold (+60%) in the presence of amiodarone (see Pharmacokinetics - Special Populations).

In patients in the RE-LY trial concentrations were increased by no more than 14% and no increased risk of bleeding was observed.

Verapamil: When PRADAXA (150 mg) was co-administered with oral verapamil, the C_{max} and AUC of dabigatran were increased but magnitude of this change differs depending on timing of administration and formulation of verapamil (see Pharmacokinetics - Special Populations).

In patients in the RE-LY trial concentrations were increased by no more than 21% and no increased risk of bleeding was observed.

Quinidine: Dabigatran exposure in healthy subjects was increased by 1.5-fold (+53%) in the presence of quinidine (see Pharmacokinetics - Special Populations).

Clarithromycin: Dabigatran exposure in healthy subjects was increased by 19% in the presence of clarithromycin without any clinical safety concern (see Pharmacokinetics - Special Populations).

Ketoconazole: Dabigatran exposure was increased by 2.5 fold (+150%) after single and multiple doses of systemic ketoconazole (see Contraindications and Pharmacokinetics - Special Populations).

Dronedarone: Dabigatran exposure was increased by 2.1 fold (+114%) after single or 2.4 fold (+136%) after multiple doses of dronedarone, respectively (see Pharmacokinetics – Special Populations).

Ticagrelor: Dabigatran exposure in healthy subjects was increased by 1.46 fold (+46%) in the presence of ticagrelor at steady state or by 1.73 fold (+73%) when a loading dose of ticagrelor was administered simultaneously with a single dose of 75 mg dabigatran etexilate.

Dabigatran steady state exposure in healthy subjects was increased by 1.26 fold (+ 26 %) in the presence of ticagrelor at steady state or by 1.49 fold (+49%) when a loading dose of ticagrelor was administered simultaneously with 110 mg dabigatran etexilate. The increase in exposure was less pronounced when the 180 mg ticagrelor loading dose was given two hours after dabigatran intake (+27%).

8.2 Australia

Relevant wording from the Australian product information is presented below.

Contraindications

Concomitant treatment with systemic ketoconazole, cyclosporin, itraconazole or dronedarone (see Precautions).

- Simultaneous initiation of treatment with dabigatran etexilate and oral verapamil.
- Treatment initiation with oral verapamil in patients following major orthopaedic surgery who are already treated with dabigatran etexilate.

Precautions

Haemorrhagic risk

Factors, such as decreased renal function (30–50 mL/min CrCL), age ≥ 75 years or P-glycoprotein (P-gp) inhibitor co-medication are associated with increased dabigatran plasma levels. The presence of one or more of these factors may increase the risk of bleeding, especially if combined (see Dosage and Administration).

The concomitant use of PRADAXA with the following treatments has not been studied and may increase the risk of bleeding: and the P-gp inhibitors itraconazole, tacrolimus, cyclosporin, ritonavir, tipranavir, nelfinavir and saquinavir (see Interactions with other medicines, Anticoagulants and platelet aggregation agents).

The concomitant use of dronedarone increases exposure of dabigatran and is not recommended (see Interactions with other medicines).

The concomitant use of ticagrelor increases the exposure to dabigatran and may show pharmacodynamic interaction, which may result in an increased risk of bleeding (see Effect on laboratory tests and Interactions with other medicines, Co-medication with P-glycoprotein inhibitors)

Factors increasing dabigatran plasma levels – p-glycoprotein inhibitor co-medication (some P-gp inhibitors are contraindicated – see contraindications section).

Interaction with P-glycoprotein inhibitors

Coadministration of dabigatran etexilate with strong P-gp inhibitors (amiodarone, clarithromycin, nelfinavir, ritonavir, saquinavir, and verapamil) should be used with caution and close clinical surveillance (looking for signs of active bleeding or anaemia) is required, due to a potential risk of higher plasma levels of dabigatran and consequent potentially exaggerated pharmacodynamic effect of dabigatran etexilate (notably bleeding risk) (see Precautions, Interactions with other medicines). The concomitant use of dabigatran etexilate with tacrolimus is not recommended. Concomitant use of dabigatran etexilate with cyclosporin, itraconazole, ketoconazole or dronedarone is contraindicated.

Interactions with other medicines

P-glycoprotein inhibitors/inducers

The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-gp.

Therefore, co-administration of dabigatran etexilate and a P-gp inhibitor or inducer may alter the plasma dabigatran concentration. Co-medications with P-gp transporter inhibitors and inducers have been investigated.

Co-medication with P-glycoprotein inhibitors

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, systemic ketoconazole, dronedarone, ticagrelor and clarithromycin) is expected to result in increased dabigatran plasma concentrations.

Amiodarone: When dabigatran etexilate was coadministered with a single dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 1.6-fold and 1.5-fold (+60% and 50%), respectively. In the population pharmacokinetics study from RELY, no important changes in dabigatran trough levels were observed in patients who received amiodarone.

In patients in the RE-LY study concentrations were increased by no more than 14%.

The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone.

Dronedarone: When dabigatran etexilate and dronedarone were given at the same time total dabigatran AUC_{0-∞} and C_{max} values increased by about 2.4-fold and 2.3-fold (+136 % and 125%), respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold (+114% and 87%), respectively, after a single dose of 400 mg. The terminal half-life and renal clearance of dabigatran were not affected by dronedarone. When single and multiple doses of dronedarone were given 2 hours after dabigatran etexilate, the increases in dabigatran AUC_{0-∞} were 1.3-fold and 1.6 fold, respectively.

Verapamil: When dabigatran etexilate was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased depending on timing of administration and formulation of verapamil.

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of C_{max} by about 2.8-fold (+180%) and AUC by about 2.5-fold (+150%)). The effect was

progressively decreased with administration of an extended release formulation (increase of C_{max} by about 1.9-fold (+90%) and AUC by about 1.7-fold (+70%)) or administration of multiple doses of verapamil (increase of C_{max} by about 1.6-fold (+60%) and AUC by about 1.5-fold (+50%)). This can be explained by the induction of P-gp in the gut by chronic verapamil treatment.

There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 10% and AUC by about 20%). This is explained by completed dabigatran absorption after 2 hours.

No data are available for the parenteral application of verapamil; based on the mechanism of the interaction, no meaningful interaction is expected.

In the RE-LY study, patients treated concomitantly with verapamil had on average a 16% higher trough dabigatran plasma concentration and a 20% higher 2 hours post-dose dabigatran plasma concentration only, compared to patients who were not on concomitant verapamil. Accordingly, the annualised bleeding rates in patients who had used verapamil at least once together with warfarin, dabigatran etexilate 110 mg twice daily or 150 mg twice daily were 3.33%, 3.09% and 3.92%, respectively.

In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received verapamil.

Clarithromycin: When clarithromycin 500 mg bid was administered together with dabigatran etexilate no clinically relevant PK-interaction was observed (increase of C_{max} by about 15% and AUC by about 19%).

Ketoconazole: Systemic ketoconazole increased total dabigatran AUC_{0-∞} and C_{max} values by about 2.4-fold (+138% and 135%), respectively, after a single dose of 400 mg, and about 2.5-fold (+153% and 149%), respectively, after multiple dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole. Concomitant administration of systemic ketoconazole is contraindicated.

Quinidine: Quinidine was given as 200 mg dose every 2nd hour up to a dose of 1000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day with or without quinidine. Dabigatran AUC_{t,ss} and C_{max,ss} were increased on average by about 1.5-fold (+53% and 56%), respectively with concomitant quinidine.

Ticagrelor: When a single dose of 75 mg dabigatran etexilate was co-administered simultaneously with a loading dose of 180 mg ticagrelor, the total dabigatran AUC and C_{max} were increased by 1.73-fold and 1.95-fold (+73% and 95%), respectively. After multiple doses of ticagrelor 90 mg twice daily, and following a single dose of 75 mg dabigatran etexilate, the increase of total dabigatran exposure was reduced to 1.56-fold and 1.46-fold (+56% and 46%) for C_{max} and AUC, respectively.

Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran AUC_{t,ss} and C_{max,ss} by 1.49-fold and 1.65-fold (+49% and 65%), respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran AUC_{t,ss} and C_{max,ss} was reduced to 1.27-fold and 1.23-fold (+27% and 23%), respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose. Concomitant administration of 90 mg ticagrelor BID (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran AUC_{t,ss} and C_{max,ss} 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.

8.3 United Kingdom

Section 4.3 – Contraindications

Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone (see section 4.5).

Section 4.4 - Special warnings and precautions for use

Haemorrhagic risk

Factors, such as decreased renal function (30-50 mL/min CrCL), age \geq 75 years, low body weight < 50 kg, or mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, quinidine or verapamil) are associated with increased dabigatran plasma levels (see sections 4.2, 4.5 and 5.2).

Factors increasing dabigatran plasma levels – P-gp inhibitor co-medication (some P-gp inhibitors are contraindicated, see section 4.3 and 4.5).

Section 4.5 – Interaction with other medicinal products and other forms of interaction

Transporter interactions

P-gp inhibitors

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, ketoconazole, dronedarone, clarithromycin and ticagrelor) is expected to result in increased dabigatran plasma concentrations.

If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with strong P-gp inhibitors. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure (see sections 4.2, 4.4 and 5.1).

The following strong P-gp inhibitors are contraindicated: systemic ketoconazole, cyclosporine, itraconazole and dronedarone (see section 4.3). Concomitant treatment with tacrolimus is not recommended. Caution should be exercised with mild to moderate P-gp inhibitors (e.g. amiodarone, posaconazole, quinidine, verapamil and ticagrelor) (see sections 4.2 and 4.4).

Ketoconazole: Ketoconazole increased total dabigatran AUC_{0-∞} and C_{max} values by 138 % and 135 %, respectively, after a single oral dose of 400 mg, and 153 % and 149 %, respectively, after multiple oral dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole (see section 4.4). Concomitant treatment with systemic ketoconazole is contraindicated (see section 4.3).

Dronedarone: When dabigatran etexilate and dronedarone were given at the same time total dabigatran AUC_{0-∞} and C_{max} values increased by about 2.4-fold and 2.3-fold (+136 % and 125 %), respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold (+114 % and 87 %), respectively, after a single dose of 400 mg. The terminal half-life and renal clearance of dabigatran were not affected by dronedarone. When single and multiple doses of dronedarone were given 2 h after dabigatran etexilate, the increases in dabigatran AUC_{0-∞} were 1.3-fold and 1.6-fold, respectively. Concomitant treatment with dronedarone is contraindicated.

Amiodarone: When Pradaxa was co-administered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 60 % and 50 %, respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone (see sections 4.2 and 4.4).

Patients treated for prevention of VTEs after hip or knee replacement surgery, dosing should be reduced to 150 mg taken once daily as 2 capsules of 75 mg Pradaxa if they receive concomitantly dabigatran etexilate and amiodarone (see section 4.2). Close clinical surveillance is recommended

when dabigatran etexilate is combined with amiodarone and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

Quinidine: Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1,000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day either with or without quinidine. Dabigatran AUC_{ss} and C_{max,ss} were increased on average by 53 % and 56 %, respectively with concomitant quinidine (see sections 4.2 and 4.4).

Patients treated for prevention of VTEs after hip or knee replacement surgery, dosing should be reduced to 150 mg taken once daily as 2 capsules of 75 mg Pradaxa if they receive concomitantly dabigatran etexilate and quinidine (see section 4.2). Close clinical surveillance is recommended when dabigatran etexilate is combined with quinidine and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

Verapamil: When dabigatran etexilate (150 mg) was co-administered with oral verapamil, the C_{max} and AUC of dabigatran were increased but magnitude of this change differs depending on timing of administration and formulation of verapamil (see sections 4.2 and 4.4).

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of C_{max} by about 180 % and AUC by about 150 %). The effect was progressively decreased with administration of an extended release formulation (increased of C_{max} by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increased of C_{max} by about 60 % and AUC by about 50 %).

Therefore, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with verapamil. In patients with normal renal function after hip or knee replacement surgery, receiving dabigatran etexilate and verapamil concomitantly, the dose of Pradaxa should be reduced to 150 mg taken once daily as 2 capsules of 75 mg. In patients with moderate renal impairment and concomitantly treated with dabigatran etexilate and verapamil, a dose reduction of Pradaxa to 75 mg daily should be considered (see sections 4.2 and 4.4).

For patients with NVAf treated for prevention of stroke and SEE and for DVT/PE patients, concomitantly receiving dabigatran etexilate and verapamil, the dose of Pradaxa should be reduced to 220 mg taken as one 110 mg capsule twice daily (see section 4.2).

Close clinical surveillance is recommended when dabigatran etexilate is combined with verapamil and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increased of C_{max} by about 10 % and AUC by about 20 %). This is explained by completed dabigatran absorption after 2 hours (see section 4.4).

Clarithromycin: When clarithromycin (500 mg twice daily) was administered together with dabigatran etexilate in healthy volunteers, increase of AUC by about 19 % and C_{max} by about 15 % was observed without any clinical safety concern. However, in patients receiving dabigatran, a clinically relevant interaction cannot be excluded when combined with clarithromycin. Therefore, a close monitoring should be exercised when dabigatran etexilate is combined with clarithromycin and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

Ticagrelor: When a single dose of 75mg dabigatran etexilate was coadministered simultaneously with a loading dose of 180 mg ticagrelor, the dabigatran AUC and C_{max} were increased by 1.73-fold and 1.95-fold (+73% and 95 %), respectively. After multiple doses of ticagrelor 90 mg b.i.d. the increase of dabigatran exposure is 1.56-fold and 1.46-fold (+56% and 46%) for C_{max} and AUC, respectively.

Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran AUC_{ss} and C_{max,ss} by 1.49-fold and 1.65-fold (+49% and 65%), respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran AUC_{ss} and C_{max,ss} was reduced to 1.27-fold and 1.23-fold (+27% and 23%), respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose.

Concomitant administration of 90 mg ticagrelor BID (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran AUC_{ss} and C_{max,ss} 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.

The following potent P-gp inhibitors have not been clinically studied but from *in vitro* results a similar effect as with ketoconazole may be expected:

Itraconazole and cyclosporine, which are contra-indicated (see section 4.3).

Tacrolimus has been found *in vitro* to have a similar level of inhibitory effect on P-gp as that seen with itraconazole and cyclosporine. Dabigatran etexilate has not been clinically studied together with tacrolimus. However, limited clinical data with another P-gp substrate (everolimus) suggest that the inhibition of P-gp with tacrolimus is weaker than that observed with strong P-gp inhibitors. Based on these data concomitant treatment with tacrolimus is not recommended.

Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when Pradaxa is co-administered with posaconazole.