Medicines Classification Committee

Meeting date	5 May 2015	Agenda item	5.4
Title	**Interactions with omeprazole**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For information
Proposal for reclassification to general sale medicine	In divided solid dosage forms for oral use containing 10 milligrams or less with a maximum daily dose of 20 milligrams for the short-term symptomatic relief of gastric reflux-like symptoms in sufferers aged 18 years and over when sold in the manufacturer's original pack containing not more than 14 dosage units.		
Reason for submission	This paper has been provided by the Medsafe pharmacovigilance team at the request of the Medicines Classification Committee. The Committee requested a report on whether there was any new evidence of interactions of omeprazole with other medicines.		
Relevant *Prescriber Update* articles	September 2014	Interaction between omeprazole and citalopram/escitalopram	
	September 2013	Interaction: Methotrexate and proton pump inhibitors	
	February 2010	Clopidogrel and omeprazole – interaction now confirmed	
	November 2009	Omeprazole and pantoprazole now pharmacist-only	
Worldwide exposure of OTC omeprazole	April 2013–April 2014	Approximately 1.2 million courses of treatment (20 mg per day for 14 days)	

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1.0 PURPOSE

At the 52nd Medicines Classification Committee (MCC) meeting, the committee recommended that Medsafe's pharmacovigilance team should be asked to produce a report for the next meeting on whether there was any new evidence of interactions of omeprazole with other medicines to support a reclassification to restricted medicine.

Therefore, the purpose of this paper is to review the information on interactions with omeprazole.

2.0 BACKGROUND

2.1 Classification

Omeprazole is currently classified as:

- prescription medicine; except when specified elsewhere in the Schedule
- pharmacy-only medicine; in divided solid dosage forms for oral use containing 20 milligrams or less with a maximum daily dose of 20 milligrams for the short-term symptomatic relief of gastric reflux-like symptoms in sufferers aged 18 years and over when sold in the manufacturer's original pack containing not more than 28 dosage units.

Omeprazole was classified as a prescription medicine at the 6th meeting of the Medicines Classification Committee on 10 March 1987.

At the 40th meeting on 25 November 2008, the Committee recommended that tablets or capsules containing 10 mg or less of omeprazole should be reclassified from prescription to restricted medicine when sold in packs which have received the consent of the Minister or the Director-General to their sale as restricted medicines and are sold in the manufacturer's original pack.

At the 42nd meeting on 3 November 2009, the Committee recommended that tablets containing 20 mg of omeprazole or less should be classified as a restricted medicine when sold in packs approved by the Minister or the Director-General for distribution as a restricted medicine.

At the 44th meeting on 2 November 2010, the Committee recommended that omeprazole, in tablets containing 20 mg or less of omeprazole, with a maximum daily dose of 20 mg of omeprazole in a pack size of up to 14 dosage units, should be reclassified from restricted medicine to pharmacy-only medicine for the short-term, symptomatic relief of gastric reflux-like symptoms in sufferers aged 18 years and over, when sold in a pack approved by the Minister or the Director-General for distribution as a pharmacy-only medicine.

At the 46th meeting on 15 November 2011, the Committee recommended that the current pharmacy-only classification of omeprazole should be amended to increase the maximum allowed pack size from 14 to 28 dosage units.

At the 50th meeting on 12 November 2013, the Committee recommended that omeprazole should not be reclassified from pharmacy-only medicine to general sale medicine, in solid dose form containing 10 mg or less and in packs containing not more than 14 dosage units, for the short-term symptomatic relief of gastric reflux-like symptoms in sufferers aged 18 years and older.

A reclassification to general sale medicine was discussed again at the 52nd meeting (http://www.medsafe.govt.nz/profs/class/mccMin21Octoberl2014.htm). At this meeting, the Committee recommended that a report should be prepared reviewing the information on interactions of omeprazole with other medicines.

2.2 Interactions[1]

Medicine interactions may be pharmacodynamic or pharmacokinetic.

2.2.1 Pharmacodynamic interactions

These occur between medicines which have similar or antagonistic pharmacological effects or adverse effects. They may be due to competition at receptor sites, or occur between medicines acting on the same physiological system. They are usually predictable from knowing the pharmacology of the interacting medicines. Some common examples are:

- serotonin syndrome with tramadol and an SSRI
- increased risk of confusion or sedation with benzodiazepines and antipsychotics
- exacerbated constipation with opioid analgesics and tricyclic antidepressants
- increased risk of hyponatraemia with co-administration of omeprazole and citalopram/escitalopram.

Medsafe comment:

Most pharmacodynamic interactions are relatively straightforward and predictable with a basic understanding of a medicine's mechanism of action and receptor effects. Therefore, these interactions can be anticipated, avoided or managed when the combination is required. Pharmacodynamic interactions are also generally considered to be less serious than pharmacokinetic interactions.

2.2.2 Pharmacokinetic interactions

These occur when one medicine alters the absorption, distribution, metabolism, or excretion of another medicine, therefore increasing or reducing the amount of medicine available to produce its pharmacological effects. Individual variation in metabolic capacity, genotype, organ function and other factors result in a degree of unpredictability and many pharmacokinetic interactions do not affect all patients taking the combination of medicines.

Pharmacokinetic interactions occurring with one medicine cannot be assumed to occur with related medicines unless their pharmacokinetic properties are known to be similar.

There are several types of pharmacokinetic interactions:

Affecting absorption: the rate of absorption or the total amount absorbed can both be altered by medicine interactions. Delayed absorption is rarely of clinical importance unless high peak plasma concentrations are required (eg, when giving a pain reliever). However, a reduction in the total amount absorbed may result in ineffective therapy. The mechanism for interactions affecting absorption is usually through transporter proteins (eg, P-glycoprotein).

Affecting metabolism: many medicines are metabolised in the liver and for some medicines significant metabolism occurs in other sites. The CYP450 family, especially CYP3A4, are of major importance. There are many isoenzymes of the hepatic CYP450 system. Medicines may be substrates, inducers or inhibitors of the different isoenzymes. There is extensive *in vitro* information available on the effect of medicines on these isoenzymes. However, since medicines are eliminated by a number of different metabolic routes as well as renal excretion, the clinical effects of interactions cannot be predicted accurately from laboratory data on the CYP450 isoenzymes. Glucuronidation is also involved in the metabolism of medicines and may therefore be important.

[1] New Zealand Formulary (NZF). NZF v31. 2015. *Drug interactions*. URL: nzf.org.nz/nzf_9751 (accessed 13 January 2015).

Due to changes in protein binding: to a variable extent most medicines are loosely bound to plasma proteins. A detectable increase in effect is produced only if a medicine is extensively bound (> 90%) and it is not widely distributed throughout the body. Drug displacement from plasma proteins is currently considered to have minor significance.

Affecting renal excretion: medicines are eliminated through the kidney both by glomerular filtration and by active tubular secretion. Competition occurs between those which share active transport mechanisms in the proximal tubule.

2.2.3 Relative importance of interactions

Many medicine interactions are harmless and many of those which are potentially harmful may only occur in a small population of patients. In addition, the severity of an interaction varies between patients. Medicines with a narrow therapeutic index and those which require careful control of dosage are most often reported to cause clinically significant interactions.

Patients at increased risk from medicine interactions include the elderly and those with impaired renal or liver function.

3.0 OMEPRAZOLE & INTERACTIONS

In order to understand potential omeprazole interactions it is important to understand its pharmacokinetics.

3.1 Pharmacokinetics[2]

3.1.1 Absorption and distribution

Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules or MUPS tablets. Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1–2 hours after dose.

Absorption of omeprazole takes place in the small intestine and is usually completed within 3–6 hours. The time of administration and concomitant intake of food has no influence on the bioavailability. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 65%.

The mean volume of distribution in healthy subjects given 20 mg orally was reported to be approximately 0.3 L/kg body weight. Omeprazole is more than 95% plasma protein bound, principally albumin and α1-acid glycoprotein. It subsequently becomes preferentially concentrated within parietal cells of stomach mucosa.

Bioequivalence between Losec capsules and Losec MUPS tablets, based on both area under the omeprazole plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of omeprazole, has been demonstrated for all doses (10 mg and 20 mg).

It is important to note that the change in stomach pH may affect absorption of medicines.

3.1.2 Metabolism and excretion

Omeprazole is almost completely metabolised by the CYP450 system so that virtually no unchanged medicine is excreted. The major part of its metabolism is dependent on CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on CYP3A4, responsible for the formation of omeprazole sulphone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic medicine-

[2] Bayer New Zealand Limited. 2013. *Losec Data Sheet.* 25 June 2013. URL: www.medsafe.govt.nz/profs/datasheet/l/Losectab.pdf (accessed 23 December 2014).

medicine interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme (extensive metabolisers).

Total plasma clearance is about 30–40 L/h after a single dose. The plasma elimination half-life of omeprazole is usually shorter than one hour, both after single and repeated oral once-daily dosing. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time and dose dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (eg, the sulphone). Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

Poor metabolisers

Approximately 3% of the Caucasian population and 15–20% of the Asian population lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5–10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher by 3–5 times. This however, is unlikely to result in meaningful medicine accumulation with omeprazole 20 mg once daily and dose adjustment does not appear to be indicated.

3.1.3 Special populations

Impaired hepatic function: the metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once daily dosing.

Impaired renal function: the pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

Elderly: the metabolism rate of omeprazole is somewhat reduced in elderly subjects (75–79 years of age).

3.2 Interactions with omeprazole[3]

There are two main mechanisms involved in interactions with omeprazole:

- modulation of gastric pH
- CYP450 enzyme system.

Interactions with omeprazole can result in either:

- changes in the pharmacokinetics of other active substances, or
- changes in the pharmacokinetics of omeprazole.

[3] Bayer New Zealand Limited. 2013. *Losec Data Sheet.* 25 June 2013. URL: www.medsafe.govt.nz/profs/datasheet/l/Losectab.pdf (accessed 23 December 2014).

3.2.1 Modulation of gastric pH

By decreasing gastric acidity, omeprazole has the potential to modify the absorption of medicines with gastric pH dependent absorption (Table 1).

Table 1: Effects of omeprazole on the pharmacokinetics of active substances with pH dependent absorption

Medicine	Effect on medicine
digoxin	• ↑bioavailability by 10% (up to 30% in two out of ten subjects) with concomitant administration of omeprazole 20 mg daily
ketoconazole, itraconazole, erlotinib	• ↓absorption

3.2.2 CYP enzymes

3.2.2.1 CYP2C19

Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Therefore, the metabolism of concomitant active substances also metabolised by CYP2C19 may be decreased and the systemic exposure to these substances increased (Table 2).

Table 2: Effects of omeprazole on the pharmacokinetics of active substances metabolised by CYP2C19

Medicine (dose)	Effect on medicine	Additional information
clopidogrel (300 mg loading dose/75 mg maintenance dose)	• ↓exposure of active metabolite by 46% • ↓maximum inhibition of platelet aggregation by average of 16%.	• effect on clopidogrel observed with omeprazole 80 mg daily (ie, four times the recommended dose) • inconsistent data on the clinical implications of a PK/PD interaction of omeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies • clinical relevance of interaction is uncertain • concomitant use should be discouraged as a precaution.
cilostazol, warfarin (R-warfarin) and other vitamin K antagonists	• ↑systemic exposure	• monitoring of INR is recommended and a reduction of the warfarin (or other vitamin K antagonist) dose may be necessary • concomitant treatment with omeprazole 20 mg daily did not change coagulation time in patients on continuous treatment of warfarin.
diazepam	• ↑systemic exposure	
phenytoin	• ↑systemic exposure	• monitoring of phenytoin levels is recommended and a reduction of phenytoin dose may be necessary • concomitant treatment with omeprazole 20 mg daily did not change the blood concentration of phenytoin in patients on continuous treatment of phenytoin.

3.2.2.2 CYP3A4

Omeprazole does not inhibit CYP3A4. Therefore, it does not affect the metabolism of medicines metabolised by CYP3A4 such as ciclosporin, lidocaine, quinidine, estradiol, erythromycin, and budesonide.

3.2.2.3 Inhibitors of CYP2C19 and/or CYP3A4

Omeprazole is metabolised by CYP2C19 and CYP3A4. Active substances known to inhibit CYP2C19 and CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism (Table 3).

Table 3: Effects of medicines on pharmacokinetics of omeprazole by inhibiting CYP2C19 and/or CYP3A4

Medicine (dose)	Effect on omeprazole	Additional information
voriconazole	• ↑omeprazole exposure by more than double	• high doses of omeprazole have been well-tolerated so dose adjustment is not required during temporary concomitant use

3.2.2.4 Inducers of CYP2C19 and/or CYP3A4

Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

Medsafe comment:

These interactions are unlikely to be dangerous but may require an increase in the dose of omeprazole.

3.2.3 Unknown mechanism

There are interactions where the mechanism is not fully understood (Table 4).

Table 4: Effects of omeprazole on the pharmacokinetics of active substances by an unknown mechanism

Medicine (dose)	Effect on medicine	Additional information
atazanavir, nelfinavir saquinavir	• ↓serum levels • ↑serum levels	• concomitant administration of omeprazole and atazanavir or nelfinavir is not recommended • clinical importance and mechanisms for interactions with antiretrovirals are not always known but include increased gastric pH by omeprazole and via CYP2C19 • there are also some antiretrovirals for which unchanged serum levels have been reported when given with omeprazole.
tacrolimus	• ↑serum levels	• reinforce monitoring of tacrolimus concentrations and renal function (creatinine clearance) • adjust dose of tacrolimus if needed.
methotrexate	• ↑levels have been reported in some patients	• in high-dose methotrexate administration, a temporary withdrawal of omeprazole may need to be considered

Medsafe comment:

The information provided in section 3.2 above is consistent with the UK summary of product characteristics (SPC) for Losec and the most recent periodic benefit-risk evaluation report (PBRER) covering the period 16 April 2013 to 15 April 2014 for OTC omeprazole.

The proposed outer packaging for Losec for sale as a general medicine includes "DO NOT USE LOSEC IF ANY OF THE FOLLOWING APPLY TO YOU, UNLESS A DOCTOR HAS TOLD YOU TO DO SO: if you are taking any other prescription medicines".

The pack insert section on medical interactions expands on this and includes all medicines for which there is a potential interaction.

4.0 FURTHER INFORMATION

Medsafe performed a review of recent literature. A summary of recent reviews of interactions with omeprazole is outlined below.

4.1 Published literature

4.1.1 Li et al, 2013[4]

The authors conducted a literature search to review and identify:

- factors determining the degree of drug-drug interactions (DDIs) between omeprazole and comedication
- pharmacokinetic DDI profile of omeprazole with adverse consequences
- corresponding clinical risk management.

Inclusion criteria included studies describing omeprazole DDI with potential adverse consequences or inconsistent conclusion on clinical relevance. Exclusion criteria included studies that described omeprazole DDIs with therapeutic benefits or insignificant clinical relevance and studies that only addressed DDI issues of other PPIs, instead of omeprazole. 63 articles were retrieved using these inclusion/exclusion criteria.

In addition, the authors conducted a further review of the literature indicating that other PPIs and histamine 2 antagonists could be alternatives to omeprazole when significant DDIs occurred between omeprazole and combined medicines.

The authors summarised the DDIs associated with omeprazole and clinical risk management as presented in Table 5.

[4] Li W, Zeng S, Yu L, et al. 2013. Pharmacokinetic drug interaction profile of omeprazole with adverse consequences and clinical risk management. *Therapeutics and Clinical Risk Management* 9: 259–71. DOI: 10.2147/TCRM.S43151 (accessed 5 January 2015).

Table 5: Drug-drug interactions associated with omeprazole and clinical risk management

Medicine	Mechanism	Clinical risk management
Effects of omeprazole on other medicines		
diazepam	omeprazole impairs CYP2C19-mediated demethylation of diazepam	• avoid combination in case of diazepam toxicity • pantoprazole and lansoprazole are alternative PPIs. Oxazepam and lorazepam are alternatives to use with omeprazole.
carbamazepine	omeprazole competitively inhibits CYP3A4-mediated carbamazepine metabolism	• therapeutic drug monitoring should be carried out when carbamazepine is coadministered with omeprazole • pantoprazole is an alternative PPI.
clozapine	omeprazole induces CYP1A2-mediated clozapine metabolism	• close monitoring of plasma clozapine levels is recommended • pantoprazole is an alternative PPI.
indinavir, nelfinavir, atazanavir, rilpivirine	Absorption of indinavir, nelfinavir, atazanavir and rilpivirine decreased due to increased gastric pH. Omeprazole competitively inhibits CYP2C19-mediated formation of nelfinavir's pharmacologically active metabolite.	• indinavir: concomitant 200 mg ritonavir therapy may overcome the significant DDI. Cimetidine is an alternative to omeprazole. • nelfinavir: combination use of nelfinavir and PPI may be acceptable for indications where the PPI is required for fewer than 30 days. • atazanavir: increasing the atazanavir/ritonavir dose to 400/100 mg can attenuate the effect of omeprazole and warrant enough antiviral effect against wild-type HIV. Or select alternative anti-HIV treatment that has minimal risk of DDI with omeprazole. • rilpivirine: famotidine may be an alternative if spaced appropriately (ie, famotidine administered 12 hours before or 4 hours after rilpivirine).
methotrexate	omeprazole blocks the active tubular secretion of MTX by the inhibition of renal elimination of hydrogen ion, as well as MTX efflux via the breast cancer-resistance protein in kidney proximal tubules	• close therapeutic drug monitoring should be performed for patients receiving high-dose MTX therapy • a histamine 2 antagonist is recommended to substitute for a PPI.
tacrolimus	omeprazole competitively inhibits CYP3A4-mediated tacrolimus metabolism especially in poor metabolisers for CYP2C19	• close therapeutic drug monitoring should be carried out when starting or switching a PPI • rabeprazole and pantoprazole are alternative PPIs

mycophenolate mofetil	PPIs reduce absorption by elevating gastric pH	• pay more attention to monitoring mycophenolate levels especially in the first week post-transplantation • intensified dosing of mycophenolate (1.5 g twice daily on days 1–5, then 1.0 g twice daily) instead of standard dosing (1.0 g twice daily).
clopidogrel	PPIs competitively impair the metabolic activation of clopidogrel via CYP2C19 inhibition	• pantoprazole and rabeprazole are alternative PPIs • clopidogrel spaced 10 hours apart from aspirin and omeprazole is a good strategy in comparison with synchronous administration of aspirin, clopidogrel and omeprazole.
digoxin	omeprazole induces the gastric permeability to digoxin and impairs the clearance by P-glycoprotein inhibition	• pantoprazole is an alternative PPI • monitor serum concentrations and toxicity symptoms of digoxin and adjust dose of digoxin as needed.
itraconazole, posaconazole	omeprazole suppresses gastric secretion and reduces the absorption of itraconazole and posaconazole	• avoid using PPIs • monitor serum levels of posaconazole or switch to an alternative antifungal therapy. Histamine 2 antagonists have less interaction with poscaonazole than PPIs • coadministration of an acidic solution can counteract the adverse effect of gastric acid suppressants on the bioavailability of itraconazole.
oral iron supplementation	omeprazole decreases the absorption	• may need high-dose iron therapy for a longer duration or with intravenous iron therapy
Effects of other medicines on omeprazole		
efavirenz, herbal medicines (St John's wort, Ginkgo biloba)	Efavirenz and St John's wort induce CYP2C19 and CYP3A activity which accelerates omeprazole elimination. Ginkgo biloba can induce CYP2C19-mediated hydroxylation of omeprazole.	• rabeprazole is an alternative PPI

The degree to which DDIs are associated with omeprazole and clinical outcomes depends on many factors such as genotype status of CYP2C19 and CYP1A2, ethnicity, dose, and treatment course of omeprazole, pharmaceutical formulation of the object medicine, other concomitant medicines, and administration schedule.

The authors state that drug toxicity and treatment failure resulting from inappropriate combination therapy with omeprazole have been reported sporadically and conclude that adequately powered randomised controlled trials with pharmacodynamic evaluation are still needed to confirm the persisting doubts about the DDIs associated with omeprazole. In addition, investigations into factors determining the degree of DDIs as well as outcomes of clinical risk management and clinical pharmacy interventions should be strengthened.

4.1.2 Blume et al, 2006[5]

The aim of the authors was to review and highlight similarities and differences among the proton pump inhibitors (PPIs) in terms of likelihood, relevance and mechanisms of drug-drug interactions (DDIs). Although this was not a systematic analysis, the review was based on a search of the literature using MEDLINE with additional articles obtained from manual searches of the reference lists of relevant reviews and papers.

The authors noted that the interaction profiles of omeprazole and pantoprazole have been extensively studied, whereas those for esomeprazole, lansoprazole and rabeprazole are less well defined. The major findings of these studies are summarised in Table 6.

The effects of omeprazole on the pharmacokinetics of antacids, metoprolol, NSAIDs, iron and theophylline have also been investigated and these studies have not noted any clinically significant findings.

Compounds exhibiting a high affinity for CYP3A4, such as ketoconazole, clarithromycin and moclobemide, may affect the bioavailability of omeprazole by increasing its serum concentrations. However, this is only thought to be of clinical relevance in patients with CYP2C19 deficiency (ie, poor metabolisers) who rely on the CYP3A4 metabolic pathway for the metabolism of omeprazole.

Table 6: Pharmacokinetic interaction profiles of proton pump inhibitors

Concomitant drug	Effect of proton pump inhibitor on concomitant drug				
	esomeprazole	lansoprazole	omeprazole	pantoprazole	rabeprazole
Antacid	Unknown	Conflicting results	None	None	None
Phenazone (antipyrine)	Unknown	↑ Clearance	↓ Clearance	None	Unknown
Caffeine	Unknown	None	Conflicting results	None	Unknown
Carbamazepine	Unknown	Unknown	↓ Clearance	None	Unknown
Oral contraceptives	Unknown	Conflicting results	Unknown	None	Unknown
Ciclosporin	Unknown	Unknown	Conflicting results	None	Unknown
Cinacalcet	Unknown	Unknown	Unknown	None	Unknown
Diazepam	↓ Clearance	None	↓ Clearance	None	None[a]
Diclofenac	Unknown	Unknown	None	None	Unknown
Digoxin	Unknown	Unknown	↑ Absorption	None[b]	↑ Absorption
Ethanol	Unknown	None	None	None	Unknown
Glibenclamide	Unknown	Unknown	Unknown	None	Unknown
Levothyroxine	Unknown	Unknown	Unknown	None	Unknown
Metoprolol	Unknown	Unknown	None	None	Unknown
Naproxen	Unknown	Unknown	None	None	Unknown
Nifedipine	Unknown	Unknown	↑ Absorption ↓ Clearance	None[c]	Unknown
Phenprocoumon	Unknown	Unknown	↓ Clearance	None	Unknown
Phenytoin	↓ Clearance	None	↓ Clearance	None	None
Piroxicam	Unknown	Unknown	None	None	Unknown
Tacrolimus	Unknown	↓ Clearance	Unknown	None	None
Theophylline	Unknown	Conflicting results	None	None	None
Warfarin	↓ Clearance[d]	None	↓ Clearance[d]	None	None

a Effects were seen with the desmethyl metabolite of diazepam but were significant only in CYP2C19-deficient individuals.
b β-Acetyldigoxin.
c Only for nifedipine sustained-release.
d Only for *R*-warfarin.
↓ indicates decreases; ↑ indicates increases.

The authors conclude that although there have been a number of omeprazole-related drug interactions reported, not all of them are considered clinically significant. However, the potential for drug interactions should be taken into account when choosing a therapy for gastric acid-related disorders, especially for elderly patients in whom polypharmacy is common, or in those receiving a concomitant medicine with a narrow therapeutic index. In addition, omeprazole is the PPI that has been available the longest and this may be the reason why there appear to be more drug interactions associated with it than with other PPIs.

[5] Blume H, Donath F, Warnke A, et al. 2006. Pharmacokinetic drug interaction profiles of proton pump inhibitors. *Drug Safety* 29(9): 769–784.

4.1.3 Wedemeyer and Blume, 2014[6]

This is an updated review of the article published by Blume et al in 2006 (see 4.1.2 above). Much of the review remains relevant but as the current knowledge is likely to have advanced, the authors conducted a thorough review of the literature published since 2006. Forty new references were identified and used in this updated review. The authors' findings are summarised as follows.

Since 2006, new data are available for the interaction of PPIs and mycophenolate mofetil. Administration of PPIs increases intragastric pH which slows down the hydrolysis of mycophenolate mofetil resulting in decreased maximum exposure and availability of mycophenolic acid, at least at early time points.

Data are also now available outlining the altered pharmacokinetics of protease inhibitors with concomitant PPI exposure by modulation of gastric pH. The authors state that this is a group effect with clear clinical implications assumed for several protease inhibitors that can have significantly altered bioavailability if coadministered with PPIs.

There have been extensive discussions in recent reviews and meta-analyses on the drug interactions between certain PPIs and clopidogrel. The authors state that these interactions appear to be mediated by CYP2C19 and are clinically relevant.

Case reports and population pharmacokinetic studies suggest that coadministration of PPIs and methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, although the mechanism for this interaction is not clearly understood.

Major findings of studies on the interaction profiles of PPIs are summarised in Table 7.

The authors conclude that overall, the conclusions from the 2006 review still remain relevant. Lansoprazole, pantoprazole and rabeprazole appear to be associated with lower incidences of drug interactions than omeprazole and esomeprazole resulting either from their lower affinity for specific CYP isoenzymes or the involvement of additional elimination processes. With little difference among the PPIs in terms of clinical efficacy at equivalent doses, differences in drug interaction propensities become important factors in prescribing decisions, particularly in patients who are taking multiple concomitant medicines (such as the elderly) or those on medicines with a narrow therapeutic window.

[6] Wedemeyer R, Blume H. 2014. Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. *Drug Safety* 37(4): 201–211. DOI: 10.1007/s40264-014-0144-0 (accessed 5 January 2015).

Table 7: Pharmacokinetic interaction profiles of proton pump inhibitors

Concomitant drug	Effect of PPI on concomitant drug				
	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole-Na	Rabeprazole
Antacid	Unknown	Conflicting results	None	None	None
Phenazone (antipyrine)	Unknown	↑ Clearance	↓ Clearance	None	Unknown
Bortezomib	Unknown	Unknown	None	Unknown	Unknown
Caffeine	Unknown	None	Conflicting results	None	Unknown
Carbamazepine	Unknown	Unknown	↓ Clearance	None	Unknown
Oral contraceptives	Unknown	Conflicting results	Unknown	None	Unknown
Ciclosporin	Unknown	Unknown	Conflicting results	None	Unknown
Cinacalcet	Unknown	Unknown	Unknown	None	Unknown
Ciprofloxacin ER	Unknown	Unknown	None	Unknown	Unknown
Citalopram	Unknown	Unknown	↓ Clearance[a]	Unknown	Unknown
Clarithromycin	Unknown	Unknown	None	None	Unknown
Clopidogrel	↓ Absorption	None	↓ Absorption	None	Unknown
Diazepam	↓ Clearance	None	↓ Clearance	None	None[b]
Diclofenac	Unknown	Unknown	None	None	Unknown
Digoxin	Unknown	Unknown	↑ Absorption	None[c]	↑ Absorption
Ethanol	Unknown	None	None	None	Unknown
Etravirine	Unknown	Unknown	↓ Clearance	Unknown	Unknown
Gemifloxacin	Unknown	Unknown	None	Unknown	Unknown
Glibenclamide	Unknown	Unknown	Unknown	None	Unknown
Ivabradine	Unknown	None	None	Unknown	Unknown
Levothyroxine	Unknown	Unknown	Unknown	None	Unknown
Metoprolol	Unknown	Unknown	None	None	Unknown
Naproxen	Unknown	Unknown	None	None	Unknown
Nifedipine	Unknown	Unknown	↑ Absorption ↓ Clearance	None[d]	Unknown
Phenprocoumon	Unknown	Unknown	↓ Clearance	None	Unknown
Phenytoin	↓ Clearance	None	↓ Clearance	None	None
Piroxicam	Unknown	Unknown	None	None	Unknown
Tacrolimus	Unknown	↓ Clearance	Unknown	None	None
Theophylline	Unknown	Conflicting results	None	None	None
Warfarin	↓ Clearance[e]	None	↓ Clearance[e]	None	None

Table modified from Blume et al. Reprinted with permission (with additions for bortezomib, ciprofloxacin ER, citalopram, clarithromycin, clopidogrel, etravirine, gemifloxacin and ivabradine)

↓ decreases, ↑ increases, *ER* extended release

[a] (+)-(*S*) enantiomer only

[b] Effects were seen with the desmethyl metabolite of diazepam but were significant only in CYP2C19-deficient individuals

[c] β-Acetyldigoxin

[d] Only for nifedipine sustained-release

[e] Only for *R*-warfarin; present in homozygous extensive metabolisers

4.1.4 Ogawa and Echizen, 2010[7]

The authors undertook a comprehensive review of DDIs attributable to PPIs using a systematic review method. 144 articles were included in this review.

Table 8 lists the medicines in which oral absorption was shown to be altered by coadministration of PPIs. The authors tentatively considered that the mechanism of altered intestinal absorption of medicines with coadministration of PPIs could be attributable to changes in the solubility of affected medicines when their solubility is known to be pH sensitive, and this was also evident with coadministration of H2 receptor antagonists.

[7] Ogawa R, Echizen H. 2010. Drug-drug interaction profiles of proton pump inhibitors. *Clin Pharmacokinet* 49(8): 509–533. DOI: 10.2165/11531320-000000000-00000 (accessed 14 January 2015).

Table 8: Effects of PPIs on AUC values (fold increases) of orally administered concomitant medicines

Concomitant drug	Subjects (n)	PPIs studied	Range of mean AUC ratio	Pooled AUC ratio	Dose adjustment [a]
Bismuths					
Bismuth biskalcitrate	18	OME	2.91*	NA	↓
Tripotassium dicitrato bismuthate	6	OME	3.74*	NA	↓
	35	OME	1.21 [b]	NA	↔
Digitalis					
Digoxin	75	OME, PAN, RAB	1.10–1.13	NA [c]	TDM may be required
	48	OME, RAB	1.01 [d]–3.55 [d]	NA	
Fluoroquinolones					
Ciprofloxacin	39	OME	0.84–0.96	0.94	↔
Gemifloxacin	13	OME	1.08	NA	↔
Lomefloxacin	12	OME	1.05	NA	↔
Macrolides					
Clarithromycin	43	OME, LAN	1.00–1.28	1.13	↔
Roxithromycin	24	OME, LAN	1.07–1.16	1.11	↔
Non-steroidal anti-inflammatory drugs					
Diclofenac	37	OME	1.04–1.08	1.06	↔
	24	PAN	1.01	NA [c]	↔
Naproxen	24	OME	0.99	NA	↔
Piroxicam	24	OME	0.99	NA	↔
HIV protease inhibitors					
Atazanavir	9	LAN	0.06*	NA	↑
Atazanavir/ritonavir	10	OME	0.38*	NA [c]	↑
Darunavir	17	OME	1.04	NA	↔
Fosamprenavir	25	OME	0.98	NA	↔
Fosamprenavir/ritonavir	23	OME	0.91	NA	↔
Indinavir	32	OME	0.53–0.66	0.59*	↔
Lopinavir/ritonavir	23	OME	0.92–1.07	NA [c]	↔
Nelfinavir	19	OME	0.64*	NA	↔
Raltegravir	14	OME	3.11*	NA	↓
Ritonavir	30	OME	1.03–1.14	1.10	↔
Saquinavir/ritonavir	30	OME	1.54–1.82	1.71*	↔
Triazole antifungals					
Fluconazole	12	OME	0.98	NA	↔
Itraconazole	31	OME	0.35*–0.85	NA [c]	↑
Ketoconazole	Unknown	RAB	0.70	NA	↔
Posaconazole	12	ESO	0.66	NA	↔
Others					
Amoxicillin	36	OME	0.95–1.00	0.98	↔
Cephalexin	21	OME	0.93–1.05	NA	↔
Domperidone	10	OME	0.94–1.06	NA	↔
Furazolidone	18	OME	0.82	NA	↔
Imatinib	12	OME	0.97	NA	↔
Mycophenolate mofetil	45	PAN	0.70 [f]–0.90 [f]	0.78*	↔
Mesalazine	20	OME	0.83 [g]–1.00 [g]	NA	↔
Oxybutynin	44	OME	1.13	NA	↔
Paricalcitol	26	OME	1.03	NA	↔
Tolterodine	44	OME	0.95	NA	↔

a We tentatively considered that a pharmacokinetic DDI may be clinically insignificant if the changes in the AUCs are within a range of –50% to +200%. This criterion assumes that the pharmacodynamic profiles of the victim drugs of DDIs remain unaltered.

b $C_{min,ss}/D$.

c The data retrieved from the original articles were unsuitable for pooled analysis.

d C_{ss}/D.

e Contained two adoptable datasets in a study.

f The data were provided for mycophenolate mofetil.

g Ratio of the 24-hour urinary recoveries of 5-aminosalicylic acid plus *N*-acetyl-5-aminosalicylic acid excreted after oral administration of mesalazine.

$C_{min,ss}/D$ = dose-normalized steady-state minimum plasma concentration; **C_{ss}/D** = dose-normalized steady-state plasma concentration; **DDI** = drug-drug interaction; **ESO** = esomeprazole; **LAN** = lansoprazole; **NA** = not applicable; **OME** = omeprazole; **PAN** = pantoprazole; **RAB** = rabeprazole; **TDM** = therapeutic drug monitoring; ↑ indicates that the dose of the concomitant drug may be increased to ensure its efficacy; ↓ indicates that the dose of the concomitant drug may be reduced to avoid unexpected adverse drug reactions; ↔ indicates that dose adjustment may not be required; * $p < 0.05$.

Medsafe comment:

Table 8 shows some changes in the pooled AUC ratio for certain medicines. However, many of these are not considered to be clinically significant.

Table 9 summarises the studies where metabolic DDIs associated with omeprazole were assessed in healthy subjects and in patients. The authors state that collectively, the inhibitory effects of omeprazole on the metabolism of CYP2C19 substrates exist but their clinical implications would largely be insignificant except for a few medicines.

Table 9: Effects of omeprazole on AUC values (fold increases) of concomitant medicines

Concomitant drug	Major CYP enzymes	Subjects (n)	Concomitant drug dosing regimen	Omeprazole daily dose (mg)	Range of mean AUC ratio	Pooled AUC ratio	Dose adjustment [a]
S-acenocoumarol	2C9	8	Single PO	40	0.94	NA	↔
R-acenocoumarol	1A2, 2C9, 2C19	8	Single PO	40	0.97	NA	↔
Antipyrine (phenazone)	1A2, 2B, 2C, 3A4	13	Single PO	30–60	1.03–1.16	NA	↔
Bortezomib	3A4, 2C19	27	Multiple IV	40	0.96	NA	↔
Carbamazepine	2C8, 3A4	10	Multiple PO	40	1.89*	NA	↔
Cilostazol	1A2, 2C19, 2D6, 3A4	20	Single PO	40	1.22	NA	↔
Ciclosporin	3A4	13	Multiple IV, multiple PO	20–40	0.32 [b]–2.72 [b]	NA	TDM may be required
Citalopram	2C19, 2D6, 3A4	9	Single PO	20	0.57* [c], 0.86 [d]	NA	↔
Diazepam	2C19	60	Single IV, single PO	20–40	0.90–1.10 [e], 1.26–1.36 [f], 1.31–2.22 [g]	0.95 [e], 1.27* [f], 1.53* [g]	↔
Etravirine	2C9, 2C19, 3A4	18	Single PO	40	1.41*	NA	↔
Ivabradine	3A4	12	Single PO	40	0.98	NA	↔
Lidocaine (lignocaine)	3A4	10	Single IV	40	1.09	NA	↔
Methotrexate	NA [h]	1	Single IV	40	3.99 [i]–11.33 [i]	NA	TDM may be required
S-metoprolol	2D6	7	Multiple PO	40	1.02	NA	↔
R-metoprolol	2D6	7	Multiple PO	40	1.01	NA	↔
Metronidazole	2C9, 3A4	14	Single PO	20	0.94	NA	↔
Moclobemide	2C19	16	Single PO	40	0.80 [j], 2.21* [k]	NA	↔ [j], ↓ [k]
Nifedipine	3A4	7	Single PO	20	1.25*	NA	↔
Phenytoin	2C9	36	Single IV, single PO	40	1.00–1.25	1.12	↔
		8	Multiple PO	20	0.93 [i]–1.13 [i]	NA	↔
Prednisone	Unknown	18	Single PO	40	0.99	NA	↔
Proguanil	2C19, 3A4	12	Single PO	40	1.47*	NA	↔
Propranolol	2D6 + others	8	Multiple PO	20	1.02	NA	↔
Quinidine	3A4	8	Single PO	40	1.09	NA	↔
Tacrolimus	3A4	85	Multiple PO	20–40	0.85 [b]–2.8 [b], 1.83 [k]–2.11 [k], 2.11 [m]–2.31 [m], 3.27 [j]–6.38 [j]	NA	TDM may be required
Theophylline	1A2	26	Single IV, multiple PO	20–80	0.92–1.03	0.96	↔
Voriconazole	2C19, 2C9, 3A4	18	Multiple PO	40	1.41*	NA	↔
S-warfarin	2C9	17	Single PO	20	0.93 [n], 1.07 [k]	NA	↔
		56	Multiple PO	20	0.98 [i]–1.01 [i]	NA	↔
R-warfarin	1A2, 3A4	17	Single PO	20	0.91 [n], 1.20* [k]	NA	↔
		56	Multiple PO	20	1.10 [i]–1.12 [i]	NA	↔

a We tentatively considered that a pharmacokinetic DDI may be clinically insignificant if the changes in the AUCs are within a range of −50% to +200%. This criterion assumes that the pharmacodynamic profiles of the victim drugs of DDIs remain unaltered.

b $C_{b,min,ss}/D$.

c (+)-(*S*)-citalopram.

d (−)-(*R*)-citalopram.

e PMs of CYP2C19 substrates determined according to urinary excretion of 4′-hydroxylated *S*-mephenytoin (n = 6) or the $t_{½}$ of OME of >1.5 hours (n = 4).

f EMs of CYP2C19 determined according to urinary excretion of 4′-hydroxylated *S*-mephenytoin (n = 9) or the $t_{½}$ of OME of <1.5 hours (n = 6).

g Values obtained from subjects whose *CYP2C19* phenotypes were undetermined (n = 35).

h OME was considered to delay renal elimination of methotrexate.

i C_{min}/D at 18 hours after the end of methotrexate infusion.

j PM with *CYP2C19**2/*2, *2/*3 or *3/*3.

k EM with *CYP2C19**1/*1.

l C_{ss}/D.

m IMs with *CYP2C19**1/*2, *1/*3.

n *CYP2C19**1/*2, *1/*3, *2/*2, *2/*3 or *3/*3 (n = 7).

$C_{b,min,ss}/D$ = dose-normalized steady-state minimum blood concentration; **C_{min}/D** = dose-normalized minimum plasma concentration; **C_{ss}/D** = dose-normalized steady-state plasma concentration; **CYP** = cytochrome P450; **DDI** = drug-drug interaction; **EM** = extensive metabolizer; **IM** = intermediate metabolizer; **IV** = intravenous; **NA** = not applicable; **OME** = omeprazole; **PM** = poor metabolizer; **PO** = oral; **$t_{½}$** = elimination half-life; **TDM** = therapeutic drug monitoring; ↓ indicates that the dose of the concomitant drug may be reduced to avoid unexpected adverse drug reactions; ↔ indicates that dose adjustment may not be required; * $p < 0.05$.

At present no medicines have been shown to alter the absorption of omeprazole. There is a possibility that concomitant administration of medicines with strong inhibitory effects on either CYP2C19 or CYP3A4 may alter the systemic exposure of omeprazole. Table 10 summarises relevant *in vivo* data retrieved from the literature.

Table 10: Effects of concomitant medicines on AUC values (fold increases) of omeprazole and esomeprazole

Concomitant drug	Subjects (n)	PPI regimen	Changes in mean AUC ratio	Dose adjustment [a]	References
Omeprazole					
Absorption					
Alginate	24	20 mg/day multiple PO	1.01	↔	161
Diclofenac	24	20 mg/day multiple PO	0.98	↔	26
Fexofenadine	8	40 mg single PO	0.96 [b]	↔	162
Maalox®	11 [c]	20–30 mg single PO	1.12 [c]	↔	163,164
Naproxen	24	20 mg/day multiple PO	1.00	↔	26
Piroxicam	24	20 mg/day multiple PO	1.05	↔	26
Metabolism					
Artemisinin	9	20 mg single PO	0.52*	↔	165
Clarithromycin	29 [c]	40 mg/day multiple PO	1.96* [c]	↔	22,166
Clopidogrel	12	40 mg single PO	1.28* [d], 1.02 [e]	↔	167
Fluconazole	18	20 mg single PO	6.29*	↓	168
Fluvoxamine	18	40 mg single PO	5.62* [d], 2.38* [f], 1.15 [e]	↓ [d], ↔ [e,f]	169
Ginkgo biloba	18	40 mg single PO	0.59* [d], 0.75* [f], 0.63* [e]	↔	170
Ketoconazole	10	20 mg single PO	1.36 [g], 1.99* [h]	↔	171
Moclobemide	16	40 mg single PO	2.07* [d], 1.17 [i]	↔	172
Ranitidine	14	40 mg single PO	1.20*	↔	173
Roxithromycin	12	20 mg/day multiple PO	1.31	↔	24
St John's wort (hypericum)	12	20 mg single PO	0.51* [d], 0.59* [e]	↔	174
Yin zhi huang	18	20 mg single PO	0.56* [d], 0.59* [f], 0.83* [e]	↔	175
Esomeprazole					
Fosamprenavir	24	20 mg/day multiple PO	1.56* [d]	↔	31
Fosamprenavir/ritonavir	24	20 mg/day multiple PO	1.06 [d]	↔	31

a Based on a criterion in which a pharmacokinetic DDI with a PPI is not considered critical if the changes in the AUCs are within a range of –50% to +300%.
b AUC_∞.
c Pooled data.
d *CYP2C19**1/*1.
e *CYP2C19**2/*2 or *2/*3.
f *CYP2C19**1/*2 or *1/*3.
g EMs of CYP2C19 assessed by urinary excretion of 4′-hydroxylated *S*-mephenytoin.
h PMs of CYP2C19 assessed by urinary excretion of 4′-hydroxylated *S*-mephenytoin.
i *CYP2C19**1/*2, *1/*3, *2/*2, *2/*3 or *3/*3.

AUC_∞ = AUC from 0 to 8 hours; **CYP** = cytochrome P450; **DDI** = drug-drug interaction; **EM** = extensive metabolizer; **PM** = poor metabolizer; **PO** = oral; **PPI** = proton pump inhibitor; ↓ indicates that the dose of omeprazole or esomeprazole may be reduced; ↔ indicates that dose adjustment of the drugs may not be required; * $p < 0.05$.

Previous studies have demonstrated that strong inhibitors of CYP3A4 (eg, clarithromycin, ketoconazole, fluconazole) and CYP1A2 (eg, fluvoxamine) significantly increased the AUCs of omeprazole by 20–50%. In addition moclobemide, a CYP2C19 substrate, increased the AUCs of omeprazole on average by 2-fold. However, the authors state that it remains unclear whether the augmented systemic exposure of omeprazole by other medicines may be associated with any detrimental effects.

Medsafe comment:

Table 9 includes doses of omeprazole used. The majority of doses were 20 mg or 40 mg daily. It is not certain if the same effects on the AUC of medicines would be exerted by omeprazole when used at lower doses.

The authors noted that previous studies have demonstrated that some medicines significantly increased the AUCs of omeprazole by up to 2-fold. The Losec data sheet includes a section on overdose which states that in the literature, doses of up to 560 mg have been described and occasional reports have been received when single oral doses have reached up to 2400 mg. The symptoms described in omeprazole overdose have been transient and no serious outcome has been reported.

4.1.5 Fendrick et al, 2004[8]

The authors conducted a 3-month observational study in an OTC setting to determine whether consumers could:

- appropriately self-select to use omeprazole according to the 6 specific criteria (heartburn symptoms ≥2 days/week, ≥18 years old, not pregnant/breastfeeding, not allergic to omeprazole, no contraindicated symptoms that have not been reported to a healthcare provider, not taking the contraindicated medicines phenytoin, diazepam, warfarin, clarithromycin, itraconazole, ketoconazole that have not been reported to a healthcare provider) on the outer packaging
- comply with directions on the outer packaging that states to use for 14 consecutive days of once-daily dosing
- use more than 14 doses of omeprazole only under the advice of a healthcare provider.

Consumers were interviewed at 5 shopping malls in geographically distinct areas of the US and asked whether they had heartburn. Study personnel (who were not in the healthcare field) were explicitly instructed not to use any cues (eg, age, gender, body size) to aid in the selection of potential study candidates.

Consumers who self-reported to have heartburn were invited to participate in the study. Each potential consumer was then shown the OTC omeprazole outer packaging and only on the basis of their understanding of the packaging, they determined whether the medicine was appropriate for them to use. Those who believed that OTC omeprazole was an appropriate treatment option purchased the product.

A diary was provided to measure patterns of OTC omeprazole use during the 3-month study period. A phone interview was conducted three months after study initiation to assess heartburn symptoms and related treatment.

Of the 1999 self-reported heartburn sufferers, 866 determined the product was appropriate for their condition and purchased the product. Of these, 758 (88%) returned diaries documenting product usage and physician contact.

Of the 866 self-selected purchasers of OTC omeprazole 81% met all 6 pre-specified criteria required for appropriate self-selection. For each individual criterion, 90–100% of the subjects correctly determined the appropriate study medicine.

Overall, 75% of subjects had contact with a physician about heartburn before, during, or soon after the study (26% contacted a physician during the 3-month study). Of the 758 subjects, only one took more than 14 tablets without consulting a physician and had recurrence of heartburn. 79% were compliant with the directions on the package.

15 subjects reported taking one out of the six contraindicated medicines as listed on the product label. 13 (87%) consulted a physician about their heartburn during or soon after the trial. Two reported taking phenytoin, but answered “no” when asked if they took phenytoin, which may suggest they did not recognise the generic name. Six reported taking diazepam during the study of which 3 were under the care of a physician. Six took warfarin during the trial all of which contacted a physician during or after the study. The remaining subject was prescribed clarithromycin for a sinus infection during the study and had informed the physician that they were taking omeprazole.

The authors conclude that actual use data support that consumers accurately self-select if an OTC proton pump inhibitor is appropriate for use, comply with a 14-day regimen in the OTC setting, and appropriately seek physician involvement for longer-term management of frequent heartburn.

[8] Fendrick AM, Shaw M, Schachtel B, et al. 2004. Self-selection and use patterns of over-the-counter omeprazole for frequent heartburn. *Clinical gastroenterology and hepatology* 2(1): 17–21.

Medsafe comment:

This study was conducted in the US where omeprazole is available for purchase without the pharmacist present (equivalent to general sale classification in NZ). It is not clear whether omeprazole 10 mg or 20 mg was used in this study. However, it appears that only the 20 mg strength of omeprazole is available over-the-counter in the US.

4.2 Spontaneous reports in New Zealand

From 1 January 2000 to 30 November 2014, the Centre for Adverse Reactions Monitoring (CARM) has received 1324 cases involving omeprazole of which three describe an interaction. These three reports are summarised in Table 11.

Table 11: Summary of CARM cases

ID/year	Age/ sex	Medicines	Omeprazole dose	Reported reactions, additional info
58528/ 2003	9/F	carbamazepine (i), omeprazole (i)	10 mg daily	drug interaction, drug level increased not serious report from pharmaceutical company
85145/ 2009	64/M	omeprazole (i), warfarin (i), enalapril, simvastatin, metformin	20 mg daily	brand switch, drug interaction, INR increased not serious report from pharmaceutical company
108858/ 2013	59/F	warfarin (i), amoxicillin, omeprazole (i), naproxen, alendronate+colecalciferol	20 mg daily	INR increased, drug interaction life threatening report from pharmacist

i = interacting medicine

Medsafe comment:

Case 108858 is a report of a patient who was on warfarin therapy at a usual dose of 4 mg. The patient was subsequently prescribed naproxen; omeprazole was also prescribed on the same date for gastroprotection. Therefore, this interaction was not due to incorrect self-selection by a patient.

4.3 Esomeprazole

Esomeprazole is the S-isomer of omeprazole. The two ingredients are closely related chemically and converted in the body to the same active substance. Therefore, they demonstrate very similar efficacy and safety profiles in clinical use.

In July 2014, Pfizer Consumer Healthcare Ltd submitted a request to reclassify esomeprazole (Nexium Control) from pharmacy-only to general-sale in the UK. Pfizer's proposal for reclassification was published on the Medicines and Healthcare Products Regulatory Agency's (MHRA) website for consultation[9]. In this consultation document, it was noted that US data provided on omeprazole used

[9] Medicines and Healthcare Products Regulatory Agency. 2014. Consultation document: ARM 88; Nexium Control 20 mg Gastro-resistant Tablets. *Request to classify a product as GSL.* 2 July 2014. URL:

in the general-sale setting showed a low number of drug interactions and the likelihood of clinical significance was low. The data did not show any specific safety issues relating to misuse or accidental overdose as a result of the sale and supply of a proton pump inhibitor in a general-sale environment.

In January 2015, the request to reclassify esomeprazole to general-sale was approved by the MHRA. The MHRA's public assessment report[10] for this reclassification states that clinically important interactions of esomeprazole with commonly used medicines are considered rare.

The MHRA noted that the company (Pfizer) presented an in depth analysis of the interaction profile for both esomeprazole and OTC omeprazole focusing on important identified interactions with the following eight medicines: warfarin, phenytoin, atazanavir, nelfinavir, digoxin, methotrexate, tacrolimus, and clopidogrel. The evidence indicates that for the above medicines there is a low potential for interactions with esomeprazole and the likelihood for clinically significant effects is minimal. The MHRA considered that the interaction profile is acceptable for a general-sale product which is intended for a short duration of use and in a small pack.

Medsafe comment:

The terms of reclassification for esomeprazole in the UK includes a maximum strength of 20 mg tablets, maximum daily dose of 20 mg, maximum pack size of 14 tablets, maximum duration of treatment not exceeding 2 weeks without consulting a doctor, in adults aged 18 years and over for the treatment of reflux symptoms.

5.0 DISCUSSION AND CONCLUSIONS

Modulation of gastric pH and the CYP450 enzyme system (CYP2C19, CYP3A4) are the two main mechanisms involved in interactions with omeprazole.

Although there have been a number of interactions reported with omeprazole, only the following are considered to have potential clinical significance:

- diazepam
- carbamazepine
- clozapine
- nelfinavir, atazanavir
- methotrexate
- tacrolimus
- clopidogrel
- digoxin
- itraconazole.

Toxicity and treatment failure resulting from inappropriate combination therapy with omeprazole have only been reported sporadically.

Some interactions such as with clopidogrel have been the subject of intense debate. However, it now appears that this interaction is unlikely to be clinically significant but concomitant use should be discouraged as a precaution.

www.gov.uk/government/uploads/system/uploads/attachment_data/file/326255/ARM_88_Consultation_Final_Document.pdf (accessed 5 February 2015).

[10] Medicines and Healthcare Products Regulatory Agency. 2015. Nexium Control 20 mg Gastro-Resistant Tablets. *Public Assessment Report* January 2015. URL: www.mhra.gov.uk/home/groups/s-par/documents/websiteresources/con504924.pdf (accessed 5 February 2015).

There is no evidence that interactions resulting in increased levels of omeprazole are harmful. Interactions decreasing the availability of omeprazole can be managed by increasing the omeprazole dose.

Medsafe was unable to identify information as to whether lower doses of omeprazole (eg, 10 mg daily) have a different interaction potential to 20 mg or 40 mg doses. Information reported from the scientific literature does not indicate a safety concern regarding omeprazole interactions. Data from CARM does not indicate any change in risk of harm due to omeprazole interactions following previous classification changes.