Medicines Adverse Reactions Committee

Meeting date	5 December 2019	Agenda item	3.2.4
Title	**Potential drug-drug interaction between capecitabine and proton pump inhibitors**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**	**Sponsor**	**PHARMAC funded?**
capecitabine	Brinov tablet	REX	Y
lansoprazole	Lanzol capsule	Mylan	Y
omeprazole	Dr Reddy's Omeprazole capsule	Dr Reddy's	
	Losec tablet	Bayer	
	Losec capsule, MUPS tablet	AstraZeneca	
	Omeprazole Actavis capsule	Teva Pharma	Y
	Omeprazole infusion, injection	Dr Reddy's	Y
	Omezol infusion	Mylan	
pantoprazole	Pantoprazole (Dr Reddy's)	Dr Reddy's	
	Panzop tablet	Mylan	Y
PHARMAC funding	Products funded in the community are shown above		
Previous MARC meetings	No previous discussion		
Prescriber Update	No previous articles		
Classification	As shown below. Please refer to the classification database for conditions: • capecitabine: prescription-only • lansoprazole: prescription-only, pharmacist-only • omeprazole: prescription-only, pharmacy-only • pantoprazole: prescription-only, pharmacy-only		
Usage data	Total of 2109 people received a dispensing of PHARMAC funded capecitabine at least once from a community pharmacy in 2018. Omeprazole was the second top prescription medicine by volume in PHARMAC's 2018 review.		
Advice sought	**The Committee is asked to advise on the following:** • Is there sufficient evidence on the interaction between capecitabine and proton pump inhibitors? • Does the capecitabine data sheet require updating? • Any further communication required other than MARC's Remarks in *Prescriber Update*?		

Table of Contents

1 PURPOSE

Capecitabine is an oral prodrug of 5-fluorouracil (5-FU) used in the treatment of the following cancers: breast, colon, colorectal and oesophagogastric [1].

Proton pump inhibitors (PPIs) inhibit gastric acid secretion by blocking the proton pump of the gastric parietal cell [2]. Their uses include treatment of gastric and duodenal ulcers, in combination for the eradication of *Helicobacter pylori,* and the treatment of dyspepsia and gastro-oesophageal reflux disease [2]. PHARMAC's 2018 year in review shows omeprazole was widely used (the second top prescription medicine by volume) [3].

The potential interaction between capecitabine and PPIs has been described by Chu et al (2017) and Sun et al (2016) [4, 5]. Both studies report this potential interaction could result in reduced efficacy of capecitabine. The proposed mechanism of the interaction is that PPIs increase gastric pH which may reduce the dissolution and absorption of capecitabine.

Information on this potential interaction in clinical texts is varied. The capecitabine data sheet and New Zealand Formulary (NZF) do not contain any information on this interaction; Lexicomp advises close monitoring for evidence of reduced capecitabine effectiveness if co-administered; Micromedex states concurrent use may result in reduction in capecitabine bioavailability.

The purpose of this paper is to review the potential interaction between capecitabine and PPIs.

2 BACKGROUND

2.1 Capecitabine

Capecitabine is an oral prodrug that is selectively tumour-activated to the pyrimidine analogue 5-fluorouracil (5-FU) [6]. Hepatic carboxylesterase metabolises capecitabine to 5'DFCR which is then converted by cytidine deaminase to 5'-DFUR [1]. Cytidine deaminase is principally located in the liver and tumour tissues. 5'-DFUR then undergoes further catalytic activation to 5-FU by thymidine phosphorylase [1]. Thymidine phosphorylase is found in both normal and tumour tissues but levels are higher in tumour tissues [1].

5-FU is further catabolised by dihydropyrimidine dehydrogenase to the much less toxic dihydro-5-fluorouracil (FUH2) [1]. Dihydropyrimidase cleaves the pyrimidine ring to yield 5-fluoro-ureidopropionic acid (FUPA) [1]. Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine [1]. Dihydropyrimidine dehydrogenase activity is the rate limiting step and deficiency of this enzyme may lead to increased toxicity of capecitabine [1].

Capecitabine is used in the treatment of breast cancer, colon cancer, colorectal cancer and oesophagogastric cancer [1]. It is generally administered orally twice daily for 2 weeks followed by a 1-week rest period every 3 weeks [1]. Please refer to the data sheet for full dosing information.

When the effects of an aluminium hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of capecitabine was investigated in 12 cancer patients, a small increase in plasma concentrations of capecitabine and one metabolite (5'DFCR) was reported; however, there was no effect on the concentrations of three major metabolites (FBAL, 5'DFUR and 5-FU) [1].

In vitro experiments conducted by Roche showed capecitabine tablets take longer to dissolve and disintegrate in a basic solution [7]. Tablet disintegration tests with pH of artificial gastric juice adjusted closer to neutral pH caused capecitabine tablets to dissolve more slowly (from 50 minutes to >100 minutes). There was also a delayed disintegration time from 20 to 40 minutes [7]. Results showed food has a profound effect on the AUC of capecitabine, a moderate effect on the AUC of 5'-DFCR and a minor influence on the AUC of other metabolites in plasma [7]. It is recommended capecitabine is administered within 30 minutes of a meal because absorption is decreased with food [1].

Comments:

The proposed mechanism for an interaction between capecitabine and PPIs is that PPIs increase gastric pH which may reduce the dissolution and absorption of capecitabine. However, the capecitabine data sheet notes that antacids containing aluminium hydroxide and magnesium hydroxide increase the concentrations of one metabolite (5'DFCR) with no effect on the three major metabolites (FBAL, 5'DFUR and 5-FU).

Antacids are thought to provide short-term symptomatic relief through acid neutralisation, whereas PPIs inhibit gastric acid secretion and are likely to have a longer duration of action. This could impart explain the differences in effect on the plasma concentrations of capecitabine and its metabolites.

2.2 Interaction with proton pump inhibitors (PPIs)

The effect of PPIs on chemotherapeutic agents was studied with tyrosine kinase inhibitors (TKIs) in 2015. A study of sunitinib and PPI use in patients with advanced or metastatic renal cell cancer demonstrated a reduction in progression-free survival and overall survival in patients who concurrently took PPIs throughout treatment compared with those who did not take PPIs [8]. In another study comparing use of PPIs and histamine 2 receptor antagonists in patients taking erlotinib for advanced non-small cell lung cancer, results showed better progression-free and overall survival in patients who did not take concomitant acid suppression therapy [9].

Clinical documentation of the potential interaction between capecitabine and PPIs has since been described. The Chu et al (2017) and Sun et al (2016) studies are most often quoted.

The Chu et al study involved patients with advanced gastroesophageal cancer who were treated with capecitabine and oxaliplatin (CapeOx) with or without lapatinib [4]. Lapatinib was first investigated in the TRIO-013 study which missed its primary and secondary endpoints of detecting statistically significant overall survival and progression-free survival improvements with lapatinib use. The post hoc analysis was conducted to see if capecitabine and/or lapatinib were affected by concomitant PPI administration. This study found that concurrent PPI use was associated with poorer progression-free survival and overall survival in the CapeOx arm, however this effect was not seen in the CapeOx + lapatinib arm. The PPI effects should be expected to be the same in both study arms because the primary outcomes in these groups were not statistically significant.

The second study by Sun et al (2016) involved patients with early stage colorectal cancer treated with adjuvant capecitabine [5]. This study found concurrent PPI use was associated with a decrease in five-year recurrence-free survival. However, this decrease was not statistically significant after multivariate analysis and adjusting for known prognostic factors.

Both these studies are described further in section 3 of this report. The authors had inadequate information on comorbidities that could affect overall survival and progression-free survival. PPIs are commonly used for the treatment or prevention of gastric bleeding which in itself can be a significant risk factor for long-term morbidity. PPI use is also common amongst patients taking antiplatelets and NSAIDs for chronic conditions, including cardiovascular diseases which could contribute to overall survival.

2.2.1 Lexicomp

Risk rating:	C (monitor therapy)
Severity:	Moderate
Reliability rating:	Fair (existing data/reports are inconsistent)
Management:	Consider the need for a PPI in patients receiving capecitabine. If combined, monitor closely for any evidence of reduced capecitabine effectiveness.

Discussion:

Chu et al (2017) found concurrent use of a PPI was associated with poorer progression-free survival (PFS) (4.2 months vs. 5.7 months, hazard ratio (HR) 1.55 (95% CI 1.29 to 1.81) and overall survival (9.2 months vs. 11.3 months, HR 1.34 (95% CI 1.06 to 1.62) among patients treated with capecitabine + oxaliplatin [4]. In the lapatinib arm of the study, PPI use was not associated with a significant difference in PFS or overall survival among patients treated with capecitabine and oxaliplatin + lapatinib. These differences were generally similar in a multivariate analysis with a significant difference in overall survival also emerging for patients treated with capecitabine and oxaliplatin + lapatinib who did not receive a PPI (HR 1.38).

Sun et al (2016) conducted a retrospective analysis of patients treated with capecitabine for early-stage colorectal cancer aimed to determine if PPI use reduced capecitabine efficacy [5]. Among the 298 analysed patients, 77 patients received a PPI during capecitabine therapy and 221 patients did not. Univariate analysis found PPI use was associated with a decrease in 5-year recurrence-free survival (HR 1.89, 95% CI 1.07 to 3.35). Although the authors concluded a significant drug interaction exists, after multivariate analysis and adjustment for gender, cancer stage, age and ECOG performance scores, PPI use was no longer associated with a decrease in 5-year recurrence-free survival (HR 1.65, 95% CI 0.93 to 2.94). Overall survival was unaffected by PPI use in both analyses.

The mechanism of this potential interaction is unknown. Chu et al (2017) and Sun et al (2016) hypothesise that the elevated gastric pH caused by PPI use may impair capecitabine tablet dissolution and/or reduce absorption [4, 5]. In contrast, no significant pharmacokinetic interaction was observed when capecitabine was combined with a magnesium hydroxide and aluminium hydroxide containing antacid, with modest increases in capecitabine AUC and maximum serum concentration reported in a study by Reigner et al (1999) [10].

2.2.2 Micromedex

Interaction effect:	Reduction in capecitabine bioavailability
Summary and Clinical management:	Coadministration of capecitabine with PPIs may lower the anti-tumour efficacy of capecitabine based on reduced overall survival and progression-free survival in an ad hoc evaluation of a capecitabine efficacy trial in patients with metastatic oesophagogastric cancer [4] and reduced recurrence-free survival in a retrospective review of patients with early stage colorectal cancer [5]. Consider discontinuing the PPI or adjusting oral capecitabine to parenteral fluorouracil regimens to avoid this interaction.
Severity:	Major
Onset:	Unspecified
Substantiation:	Probable
Probable mechanism:	Decreased solubility and absorption of capecitabine due to increased pH of the upper gastrointestinal tract caused by PPIs.
Literature reports:	a) Coadministration of capecitabine with a PPI significantly reduced capecitabine efficacy in an ad hoc analysis of the TRIO-013/LOGiC trial in patients with metastatic oesophagogastric cancer randomised to capecitabine/oxaliplatin with or without lapatinib (n=545). PPI use was identified by medication records, with 20% or more overlap for the duration of study treatment, and was evenly distributed across treatment arms. Among patients treated with capecitabine/oxaliplatin (n=117), those without a concurrent PPI had a significantly prolonged median progression-free survival (5.7 vs. 4.2 months) and median overall survival (11.3 vs. 9.2 months) compared with PPI-treated patients. Patients treated with lapatinib did not have a difference progression-free survival or overall survival between concurrent PPI or

not. Neither pharmacokinetics nor drug levels were assessed during the original trial [4].

b) Coadministration of capecitabine monotherapy with a PPI at any point was associated with an increased recurrence risk in a retrospective review of patients with early stage colorectal cancer (n=298). Patients who took a concurrent PPI while on capecitabine treatment (n=77) had a significant decrease in 5-year recurrence-free survival rate compared with patients who did not take a PPI (n=221; 74% vs. 83%), but overall survival was not affected. Recurrence-free survival was not different between the 2 groups when adjusting for male gender, stage III, advanced age, and poorer Eastern Cooperative Oncology Group performance status. Neither pharmacokinetics nor drug levels were assessed during capecitabine treatment in the patients included in this review [5].

2.3 Data sheets

There is no information on the potential interaction between capecitabine and PPIs in the New Zealand data sheets. However, there is information relating to the use of antacids with capecitabine. This is the same as in the UK, Australia, Canada and US. Relevant wording is shown in Table 1 but please refer to the data sheet for full information.

Table 1: Summary of information in capecitabine data sheets from New Zealand and other jurisdictions

Country (product name)	Information in data sheet
New Zealand (Brinov)	Interactions section: When the effects of an aluminium hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of capecitabine was investigated in 12 cancer patients, a small increase in plasma concentrations of capecitabine and one metabolite (5'DFCR) was reported; however, there was no effect on the concentrations of three major metabolites (FBAL, 5'DFUR and 5-FU).
United Kingdom (Xeloda)	Interactions section: The effect of an aluminium hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of capecitabine was investigated. There was a small increase in plasma concentrations of capecitabine and one metabolite (5'DFCR) was reported; here was no effect on the 3 major metabolites (5'-DFUR, 5-FU and FBAL).
Australia (various products)	Interactions section: The effect of an aluminium hydroxide (220mg/5 mL) and magnesium hydroxide (195 mg/5 mL) containing anatacid on the pharmacokinetics of capecitabine was investigated in 12 cancer patients. There was a small increase in plasma concentrations of capecitabine and one metabolite (5'DFCR); there was no effect on the 3 major metabolites (5'DFUR,5-FU and FBAL).
Canada (Xeloda)	Interactions section: The effect of an aluminium hydroxide and magnesium hydroxide-containing antacid (Maalox®) on the pharmacokinetics of capecitabine was investigated in 12 cancer patients. There was a small increase in plasma concentrations of capecitabine and one metabolite (5'DFCR); there was no effect on the 3 major metabolites (5'DFUR, 5-FU and FBAL).

United States (Xeloda)	Pharmacokinetics section: When Maalox® (20 mL), an aluminium hydroxide- and magnesium hydroxide-containing antacid, was administered immediately after Xeloda (1250 mg/m^2, n=12 cancer patients), AUC and C_{max} increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for 5'-DFCR. No effect was observed on the other three major metabolites (5'-DFUR, 5-FU, FBAL) of Xeloda.

2.4 Usage

Usage data for capecitabine is shown in Table 2. Note this is likely to be an underestimate as capecitabine is funded by PHARMAC in both community and hospital settings, whereas the table only displays community pharmacy dispensing.

Table 2: Number of people who received a dispensing of PHARMAC funded capecitabine from a community pharmacy at least once during the year, 2014-2018 (extracted 12 November 2019)

Year	Number of people
2014	2114
2015	2009
2016	1976
2017	2018
2018	2109

Source: Pharmaceutical data web tool

Proton pump inhibitors are available on prescription and over-the-counter (OTC). PHARMAC's 2018 year in review shows there were 1,370,000 prescriptions for omeprazole making it the second top prescription medicine by volume [3].

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Chu et al 2017 – Association of proton pump inhibitors and capecitabine efficacy in advanced gastroesophageal cancer: Secondary analysis of the TRIO-013/LOGiC randomised clinical trial (Annex 1) [4]

This was a secondary (post hoc) analysis of TRIO-013, a phase III randomised trial, comparing capecitabine and oxaliplatin (CapeOx) with or without lapatinib in 545 patients with ERBB2/HER2-positive metastatic gastroesophageal cancer (GEC) [11]. Patients were randomised 1:1 between CapeOx with or without lapatinib.

Proton pump inhibitor (PPI) use was identified by medicine records. Coadministration of PPIs was defined by 20% or more overlap between PPI prescription and trial treatment duration. Progression-free survival and overall survival were compared between patients treated with PPIs vs. patients who were not. Specific subgroups were accounted for such as younger age (<60 years), Asian ethnicity, female sex, and disease stage (metastatic/advanced) in multivariate Cox proportional hazards modelling.

The TRIO-013 trial accrued and randomised patients between June 2008 and January 2012 and this analysis took place in January 2014.

Of the 545 patients with GEC included in the study, 229 received PPIs (42%) and were evenly distributed between arms. Figures 1 and 2 show progression-free survival and overall survival, respectively. In the placebo arm, PPI-treated patients had poorer median progression-free survival, overall survival and disease

control rate vs. patients not treated with PPIs. In multivariate analysis considering age, race, disease stage and sex, PPI-treated patients had poorer progression-free survival and overall survival. In patients treated with CapeOx and lapatinib, PPIs had less effect on progression-free survival and overall survival.

The authors conclude PPIs negatively affected capecitabine efficacy possibly by raising gastric pH levels leading to altered dissolution and absorption. These results are consistent with previous erlotinib and sunitinib studies. Whether PPIs affected lapatinib is unclear given concurrent capecitabine.

[redacted]

[redacted]

Comments:

This study was designed to compare the efficacy of CapeOx with or without lapatinib and was not designed to study the effect of PPIs on these exposures.

3.1.2 Sun et al 2016 – Concomitant administration of proton pump inhibitors and capecitabine is associated with increased recurrence risk in early stage colorectal cancer patients (Annex 2) [5]

The authors conducted a retrospective analysis of early stage (stage I-III) colorectal cancer patients treated with adjuvant monotherapy capecitabine in a Canadian Cancer Institute between 1 January 2008 and 31 December 2012. Data was collected from electronic medical records, paper charts and electronic pharmacy dispensing records. Eligible patients were divided into PPI and non-PPI groups. Inclusion into the PPI group required patients to be on PPIs identified through prescription refill data at any point in time during capecitabine treatment. All other patients were assigned to the non-PPI group.

Of 298 identified patients who met inclusion criteria, 25.8% (n=77) received concurrent PPIs. The majority of patients in the PPI group took PPIs for the entire duration of capecitabine treatment. The two groups were balanced for gender, Eastern Cooperative Oncology Group performance status, stage and location of primary (colon vs. rectal). Of the 298 patients included in the study, 217 patients experienced toxicity related to capecitabine, most commonly hand-foot-skin reaction and diarrhoea.

Five-year recurrence-free survival was 74% vs. 83% (HR 1.89, 95% CI 1.07 to 3.35) in PPI vs. non-PPI patients, respectively (Figure 3). Overall survival was 81% vs. 78%, respectively (HR 1.13, 95% CI 0.60 to 2.14) (Figure 4). After accounting for gender, stage, age and performance status, PPI patients tended toward decreased recurrence-free survival (HR 1.65, 95% CI 0.93 to 2.94). Findings were no longer statistically significant after multivariate analysis (Table 3).

The authors conclude PPIs appear to impact recurrence-free survival. This may be due to PPIs preventing capecitabine tablet dissolution and absorption. Patients with dose reductions or who stopped treatment had worse outcomes than patients who continued with treatment at starting doses.

Comments:

Results from this study are consistent with Chu et al's post hoc analysis with a statistically significant improvement in progression-free survival between patients who did not take PPIs compared with PPI patients. However, this finding was not statistically significant after multivariate analysis and adjusting for known prognostic factors.

3.1.3 Cheng et al 2019 – Concomitant use of capecitabine and proton pump inhibitors – Is it safe? [12]

The Canadian authors evaluated the supportive evidence for the probability of occurrence and potential seriousness of the drug interaction between capecitabine and proton pump inhibitors (PPIs).

The probability of occurrence was evaluated based on the clinical, pharmacokinetic and in vitro evidence using the Drug Interaction Probability Scale. The possibility of seriousness was assessed based on the potential impact on the therapeutic intent of capecitabine therapy.

The probability of the occurrence is doubtful. Clinical findings from two retrospective post hoc analyses (Chu et al and Sun et al) showed inconsistent trends towards reduced survival. Pharmacokinetic studies found no significant decrease in systemic capecitabine level with concurrent gastric acid suppression with antacid or food intake. In vitro data do not support the proposed mechanism of reduced capecitabine absorption due to increased gastric pH. The possibility of seriousness varies depending on the treatment intent of capecitabine therapy. The most and least serious possible outcome would be reduced possibility of cure or survival and symptom control, respectively.

The authors conclude although the possible outcome may be serious, the probability of interaction between capecitabine and PPIs is doubtful. Therefore, they suggest that intervention should be limited to minimal change to existing therapy plan. This may include routinely ascertaining the need for PPI use. Alternate acid suppressing agents may be considered based on the therapeutic intent of capecitabine therapy.

3.1.4 Rhinehart et al 2018 – Evaluation of the clinical impact of concomitant acid suppression therapy in colorectal cancer patients treated with capecitabine monotherapy [13]

This was a single-centre retrospective cohort study investigating if there is a clinical impact of the concomitant use of capecitabine and acid suppression therapy in adult patients with local and metastatic colorectal cancer. Patients with colorectal cancer on capecitabine monotherapy between 2011 and 2017 were identified from the Rochester Medical Center, United States. Progression-free survival and overall survival were compared between those on acid suppression therapy (either a PPI or histamine 2 receptor antagonist for at least 20% of the duration of capecitabine treatment) and those not on acid suppression therapy. In addition to concomitant acid suppression therapy, the use of acid suppression therapy at the initiation of capecitabine was examined.

A total of 70 patients were included. PPI use was much more common (88%) and only two patients (11%) were on a histamine 2 receptor antagonist.

In patients on any concomitant acid suppression therapy (n=18, 25%), there was a decreased rate of progression-free survival (HR 6.21, 95% CI 2.56 to 14.32) but not overall survival (HR 1.64, 95% CI 0.68 to 3.54) vs. those without concomitant acid suppression therapy after adjusting for age and disease severity (Table 4).

[redacted]

Patients on acid suppression therapy at capecitabine initiation (n=15, 21%) had decreased progression-free survival vs. those not on acid suppression therapy (HR 2.24, 95% CI 1.06 to 4.41) after adjusting for disease severity and age. Acid suppression therapy use was associated with a numerical decrease in overall survival (HR 1.86, 95% CI 0.81 to 3.91).

The authors conclude concurrent use of acid suppression therapy and capecitabine was associated with decreased progression-free survival and there was a trend towards decreased overall survival. Due to the demonstrated potential of decreased efficacy, concurrent use of PPIs or histamine 2 receptor antagonists should be avoided in colorectal cancer patients on treatment with capecitabine monotherapy.

Comments:
Previous studies by Chu et al and Sun et al only looked at PPI use whereas this study sought to also include histamine 2 receptor antagonists. However, only 2 patients used histamine 2 receptor antagonists. The sample size was small resulting in wide confidence intervals and imprecise findings.

3.1.5 Sekido et al 2019 – Rabeprazole intake does not affect systemic exposure to capecitabine and its metabolites, 5′deoxy-5-fluorocytidine, 5′-deoxy-5-fluorouridine, and 5-fluorouracil [14]

This Japanese study prospectively examined the effects of rabeprazole on the pharmacokinetics of capecitabine and its metabolites.

Patients administered adjuvant capecitabine plus oxaliplatin (CapeOx) for postoperative colorectal cancer and metastatic colorectal cancer patients receiving CapeOx ± bevacizumab were enrolled. Patients receiving a PPI before registration were allocated to the rabeprazole group and the PPI changed to rabeprazole 20 mg/day at least 1 week before initiation of capecitabine treatment. On day-1 oral capecitabine was administered 1 hour after rabeprazole intake. Oxaliplatin (and bevacizumab) administration on day-1 was shifted to day-2 for pharmacokinetic analysis of the first capecitabine dose. Plasma concentrations of capecitabine, 5′deoxy-5-fluorocytidine, 5′-deoxy-5-fluorouridine and 5-fluorouracil were analysed by high-performance liquid chromatography. Effects of rabeprazole on inhibition of cell proliferation by each capecitabine metabolite were examined with colon cancer cells.

A total of 5 patients were allocated to the rabeprazole group and 9 patients to the control group. Patients were enrolled between September 2017 and July 2018. No significant effects of rabeprazole on area under the plasma concentration-time curve divided by capecitabine dose for capecitabine and its 3 metabolites were observed (Figure 5, Table 5). Rabeprazole did not affect the proliferation inhibition of colon cancer cells by the respective capecitabine metabolites (Figure 6).

The authors conclude rabeprazole does not affect capecitabine pharmacokinetics.

Comments:

This is the only pharmacokinetic study of this potential interaction that was retrieved.

The authors selected rabeprazole as the PPI in this study because it is the PPI that is least affected by CYP2C19 polymorphism. There are no rabeprazole-containing products currently approved and available in New Zealand (approval lapsed).

3.1.6 Wong et al 2018 – Effects of proton pump inhibitors on FOLFOX and CapeOx regimens in colorectal cancer [15]

This Canadian study investigated PPI effects on effectiveness of CapeOx (capecitabine + IV oxaliplatin) vs. FOLFOX (IV 5-fluorouracil, leucovorin, oxaliplatin) chemotherapy.

The authors conducted a retrospective chart review of 389 patients with stage II-III colorectal cancer who received adjuvant CapeOx or FOLFOX from 2004 to 2013. Information on PPIs, chemotherapy and patient outcomes from medical records were analysed. PPI recipients were defined as individuals who received PPIs at any time during their CapeOx or FOLFOX treatment as determined from prescription fill data.

A total of 389 patients (CapeOx n=214, FOLFOX n=175) were included in the study. Stage of disease, and concurrent PPI use was comparable between the CapeOx and FOLFOX groups (23.4% and 28.0%, respectively). 3-year recurrence-free survival was significantly lower in CapeOx-treated PPI recipients than non-PPI recipients (69.5 vs. 82.6%). Unadjusted analysis showed CapeOx-treated PPI recipients were twice as likely to experience cancer recurrence or death as CapeOx-treated non-PPI recipients (HR 2.03, 95% CI 1.06 to 3.88) (Table 6). FOLFOX-treated PPI recipients had a non-statistically significant difference in 3-year recurrence-free survival vs. non-PPI recipients (82.9 vs. 61.7%) and a non-statistically significant difference in recurrence/death (HR 0.51, 95% CI 0.25 to 1.06). No significant differences were seen in overall survival between groups (Table 7).

The authors conclude their results suggest PPIs negatively affected recurrence-free survival in Cape-Ox-treated colorectal cancer patients and yielded no significant effects among FOLFOX-treated patients, potentially implicating a pharmacokinetic interaction between PPIs and capecitabine. No overall survival effects were seen.

3.2 Case reports

3.2.1 New Zealand – CARM (Annex 3)

CARM has received 6 cases up to 30 September 2019. Of these 6 cases, 1 case reported capecitabine and omeprazole as co-suspects, and the remaining 5 cases reported capecitabine as suspect and omeprazole as concomitant. All 6 cases are summarised in Table 8.

Table 8: Summary of cases reported to CARM where capecitabine and omeprazole were reported either as suspects or concomitant, up to 30 September 2019

Report	Date	Age M/F	Medicine(s)	Reaction(s)	[redacted]
073670	Oct 06	67 M	capecitabine*, flucloxacillin*, omeprazole*, oxaliplatin, bevacizumab	diarrhoea, colitis, renal failure acute, creatine phosphokinase increased, dehydration	
082446	Jan 09	66 F	capecitabine*, bevacizumab*, omeprazole, paracetamol	abdominal pain, chest tightness, diarrhoea	
085642	Jul 09	72 M	capecitabine*, diltiazem, thyroxine, atorvastatin, omeprazole	peripheral ischaemia	
085648	Jul 09	67 F	capecitabine*, atorvastatin, diltiazem, acetylsalicylic acid, omeprazole	diarrhoea, intestinal obstruction	
102983	Jul 12	62 M	capecitabine*, epirubicin, cisplatin, simvastatin, omeprazole	dermatitis lichenoid, neutropenia, fever	
115500	Mar 15	38 F	capecitabine*, pamidronate*, omeprazole, domperidone, zopiclone	progression of disease, vomiting, nausea, C-reactive protein positive, hepatic enzymes increased	

* = reported as suspect medicine(s)

3.2.2 International – WHO Vigibase

[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

The potential interaction between capecitabine and PPIs has been described mainly by Chu et al and Sun et al. Both these studies found concomitant administration of PPIs with capecitabine resulted in reduced progression-free survival. Since these studies were published, there is one pharmacokinetic study by Sekido et al using rabeprazole as the PPI, which concluded rabeprazole does not affect capecitabine pharmacokinetics.

The mechanism proposed for this potential interaction is increased gastric pH by PPIs resulting in reduced capecitabine dissolution and absorption. Interestingly, antacids were found to have no significant effect on capecitabine pharmacokinetics, but this could be due to their acid neutralising effect vs. acid suppression effect of PPIs, and a shorter duration of action compared to PPIs.

Information on this potential interaction in clinical texts varies. The capecitabine data sheet and NZF do not contain any information on this interaction – this is in line with data sheets from other jurisdictions such as the UK, Australia, Canada and US. However, Lexicomp advises close monitoring for evidence of reduced capecitabine effectiveness and Micromedex states concurrent use may result in reduced capecitabine bioavailability – both use the Chu et al and Sun et al studies as references.

Prescribers and pharmacists will need to be informed if a clinically meaningful interaction between capecitabine and PPIs exists. Options for managing the interaction could include monitoring for reduced capecitabine effectiveness as suggested by Lexicomp, changing to an intravenous formulation of 5-FU to bypass the gastrointestinal tract, or using an alternative gastric acid suppressant (eg, antacids).

5 ADVICE SOUGHT

The Committee is asked to advise on the following:

- Is there sufficient evidence on the interaction between capecitabine and proton pump inhibitors?
- Does the capecitabine data sheet require updating?
- Any further communication required other than MARC's Remarks in *Prescriber Update*?

6 ANNEXES

1. Chu et al 2017
2. Sun et al 2016
3. CARM data (confidential)

7 REFERENCES

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