Domperidone for the prevention of chemotherapy-induced nausea and vomiting: Information following the MHRA alert (INTERIM)

May 2014

Purpose of the document

This summary has been produced to help clinicians consider the action to be taken regarding the prescribing of domperidone for the prevention of nausea and vomiting associated with chemotherapy, in light of the recent MHRA announcement. The various possible options appear to include:

- Continue as currently (no adoption of MHRA recommendations)
- Adopt a lower dose of domperidone (10mg TDS) as standard for all patients, or for those with the contraindications highlighted by the MHRA
- Use an alternative agent for all patients, or for those with the contraindications highlighted by the MHRA. It is however unclear if any of the listed possible alternatives would be ever be considered as appropriate to implement on a general basis due to their own side-effects and safety concerns.
- Adopt the antiemetic protocols recommended in guidance from ESMO/MASCC, ASCO or the NCCN [none of these include domperidone]. This would however have financial implications.

The MHRA recommendations also state that the maximum treatment duration should not usually exceed one week. There are some cases in which treatment would currently extend beyond this in this setting, where multiday chemotherapy is used. If domperidone is to remain in use then this will also need to be considered.
MHRA alert

On 25th April 2014, the MHRA issued an alert on domperidone advising of new contra-indications, a restricted indication, and reductions in the recommended dose and duration of use (1). This action was taken in response to a European review of the risks and benefits of domperidone, which confirmed a small increased risk of serious cardiac adverse drug reactions related to its use, including QTc prolongation, torsade de pointes (TdP), serious ventricular arrhythmia and sudden cardiac death. A higher risk was observed in patients older than 60 years, adults taking daily oral doses of more than 30mg, and those taking QT-prolonging medicines or CYP3A4 inhibitors concomitantly.

The MHRA alert announced the following (1):

- Domperidone is now restricted to use in the relief of symptoms of nausea and vomiting.
- It should be used at the lowest effective dose for the shortest possible time.
- Domperidone is contraindicated in people:
  - with conditions where the cardiac conduction is, or could be, impaired
  - with underlying cardiac diseases such as congestive heart failure
  - receiving other medications known to prolong QT or potent CYP3A4 inhibitors
  - with severe hepatic impairment

Patients with these conditions should have their treatment reviewed at their next routine appointment and be switched to an alternative treatment if required.

- For adults and adolescents over 12 years of age and weighing 35kg or more, the recommended maximum oral dose is 30mg in 24 hours (10mg up to three times a day)
- Non-prescription domperidone (adults and adolescents ≥16 years) should only be used at a dose of up to 10mg three times a day for a maximum period of 48 hours [pharmacists supplying domperidone without a prescription should advise people of this dosing, that it should be taken only for nausea and vomiting, and should ask questions to exclude supply for use by people for whom domperidone is contra-indicated (as above)]
- In children under 12 years of age and weighing less than 35kg, the recommended maximum oral dose is 0.75mg/kg body weight in 24 hours (0.25mg/kg body weight up to three times a day)
- Suppositories should only be used in adults and adolescents weighing 35kg or more, the recommended maximum daily dose in 24 hours is 60mg (30mg twice a day)
- The maximum treatment duration should not usually exceed one week. [The current MHRA advice does not include ‘usually’ but this has been clarified with the MHRA, and a Drug Safety article clarifying this recommendation will be published later this month.]
- Oral liquid formulations of domperidone should only be given via an appropriately designed, graduated oral syringe to ensure dose accuracy

The European Medicines Agency notes that the scope of the European review did not cover use outside of the licensed indications; however the principles behind these recommendations should be considered whenever domperidone is used (2).

Background

A possible association between use of domperidone and QT prolongation and cardiac adverse events was identified in the mid 1980s, when high and rapidly administered intravenous doses were administered to patients with cancer undergoing cytotoxic treatment. Upon recognition of this possible association, the Marketing Authorisation Holder voluntarily withdrew the IV formulation in 1985 and no such formulations have been produced since (3).

The European Medicines Agency’s former Pharmacovigilance Working Party (PhVWP) previously reviewed the risk of serious cardiac events associated with domperidone in 2011, given new information from a published study. The review found that domperidone may be associated with a small increased risk of serious ventricular arrhythmia or sudden cardiac death, especially in those aged >60 years and in patients receiving daily oral doses of more than 30mg. The product information for domperidone-containing products authorised in the EU was modified to include information on these risks, and to emphasise that domperidone should be used at the lowest effective dose in adults and children (4). The Commission on Human Medicines advised that non-prescription domperidone products are not recommended for use in patients with underlying cardiac disease, without medical supervision (5). A Drug Safety Update article from the MHRA contains a summary of the recommendations and changes to prescribing following this initial review (5).
New cases of cardiotoxicity relating to domperidone however continued to be reported, and the Belgian medicines authority requested a further review (initiated on 1 March 2013) (3). This was conducted by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) and their recommendations to further restrict the use of domperidone-containing medicines, issued in March 2014, were endorsed by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) on 25th April 2014 (2). The MHRA alert was issued on the same day. The CMDh position has been sent to the European Commission, and an EU-wide legally binding decision is awaited.

The MHRA recommendations are in agreement with those of the European Medicines Agency.

Evidence considered by the EMA

Limited information on the data considered by the PRAC during its review is currently available; it is summarised in the press release confirming the CMDh endorsement of its recommendations (2).

According to this, the PRAC considered non-clinical and clinical data (published and unpublished) on the safety and efficacy of domperidone from various sources, including a thorough QT study, cumulative review of case reports of cardiac disorders and vascular investigations from the safety databases for domperidone products, pharmacoepidemiological studies, and published and unpublished efficacy studies.

The Committee considered there to be sufficient evidence to support the use of oral domperidone 10mg up to three times a day in a general indication of treatment of nausea and vomiting in adults. They noted that although well established, data to support paediatric use in this indication were limited; further data to support efficacy in this population have therefore been requested. The available data to support the efficacy of domperidone in other indications (e.g. dyspepsia and gastro-oesophageal reflux disorder) were deemed to be extremely limited, and the Committee therefore concluded that the benefits of domperidone do not outweigh its possible risks in these indications.

The recommendations do not discuss the use of domperidone in the prevention of chemotherapy-induced nausea and vomiting.

The results of the QT study indicated that domperidone does not significantly prolong the QTc interval when administered to healthy subjects at doses of 10mg and 20mg four times daily. The Committee however noted that the limitations in the study restrict the conclusions that can be made.

The safety database of the originator product was reviewed; this included 342 serious reports of cardiac events or vascular investigations, and a high frequency of associated cardiovascular risk factors, cardiovascular history and use of concomitant medicines associated with cardiac arrhythmias was noted in the affected patients. Of 57 reported cardiovascular fatalities, 27 had other risk factors, while 13 had either an implausible relationship to domperidone administration or an alternative aetiology. In general, safety reviews indicate that about 40% of such reports are in patients over 60 years of age.

The significant number of reported cases involving concomitant or co-suspect medication known to prolong QT interval, CYP3A4 inhibitors, or potassium-wasting diuretics is in agreement with data from drug-drug interaction studies, and from spontaneous reporting.

Epidemiological studies mostly suggest that domperidone exposure was associated with an increase in risk for sudden cardiac death or ventricular arrhythmia. Some of these studies also supported a greater risk in patients over 60 years of age or who were taking high doses (over 30mg/day).

The MHRA have confirmed that an assessment report giving more detail of the data considered in the review will be published on the EMA website once the European Commission has made the final, legally-binding decision on the European review, which is expected in June or July (6). It is unclear what further information will be made available at this time [and it is unlikely that it will allow the evaluation of risk in a particular patient group, receiving treatment for a specific indication].

Published data on cardiac safety risks with domperidone

Four epidemiological studies have reported on the relation between domperidone and either sudden cardiac death (SCD) alone, or serious ventricular arrhythmia (VA) and SCD as a combined endpoint (7-10). The two earlier studies focused on the broader category of QT-prolonging medications; cases and controls were not matched according to the individual medications and no special adjustment was made to address for confounding that may affect the estimates for individual medications (7, 8). Only the later two studies, which focused specifically on domperidone, are therefore discussed here.

Van Noord et al conducted an epidemiological study in the Netherlands to evaluate the association between use of domperidone and the risk of serious idiopathic VA (ventricular fibrillation or Torsades de
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Pointes (TdP) or SCD in adults (9). Cases were matched to up to 40 controls according to age, sex and practice. Use of domperidone at the index date was classified by determining the duration of each prescription (total number of units issued divided by the number of units prescribed daily) and exposure was classified as current (index date fell during or a maximum of 7 days after the end of the last prescription), past (use more than 7 days prior to the index date) or never use. Among current users, the effect of daily doses <30mg, 30mg or >30mg was assessed.

There were 1304 cases of SCD (13,480 matched controls), ten of which were current users of domperidone. After adjusting for potential confounders (including known risk factors for VA/SCD, among others), current use of domperidone was found to increase the risk of SCD (adjusted odds ratio (OR) 1.92; 95% CI 0.78-4.73). Analysis by dose suggested a higher risk for patients prescribed domperidone at higher doses (>30 mg/day), although there were only 4 exposed cases in each group and the 95% confidence intervals overlapped: OR 11.4 (1.99–64.9) for patients prescribed >30 mg/day, compared with 0.99 (0.23–4.23) for patients receiving 30mg/day. The risk of VA could not be assessed as there were no cases in patients currently exposed to domperidone.

Johannes and colleagues evaluated the combined risk of serious idiopathic VA (TdP; VT or VF) and SCD in current users of oral domperidone compared to current users of PPIs (chosen as a control, to reduce the chance of confounding by indication) or current users of neither medication in Canada (10). This is the largest and most robust study in terms of exposed cases (MHRA) – it included 1,608 cases (1559 SCD and 49 idiopathic VA) matched to 6,428 controls (by age, sex and diabetes status), of which 169 (482) had current exposure to domperidone (defined as last dispensing ≤ 37 days before the index date). There were no age restrictions, but the age range at the index date was 20-95 years (so only adults were included).

In the multivariate adjusted analysis, the OR for SCD/VA among current users of domperidone compared to current users of PPI was 1.44 (95% CI 1.12-1.86). In analyses stratified by age and sex, a slightly higher risk for patients older than 60 years (OR 1.47 [1.14–1.91]) compared with those younger than 60 years (OR 1.23 [0.32–4.76]) was suggested, although the 95% confidence intervals overlapped. The researchers could not accurately estimate the dose of domperidone due to a lack of information in the database on the number of days supplied and the dose, so they were unable to investigate the dose-response relationship.

Considerations:
The PRAC considered a number of other sources, in addition to these epidemiological studies, when reviewing domperidone (including for example unpublished data, non-clinical studies, and case reports from the safety databases). The studies above were all published prior to the initial recommendations made by the PhVWP following its 2011 review; it is therefore likely that the decision to further restrict the use of domperidone was based on other reviewed data that would not be available from the medical literature, including consideration of the continued case reports of cardiac events despite the previous measures taken.

The study by Van Noord et al suggested that the risk of SCD may be higher in patients receiving a dose of domperidone greater than 30mg daily, but the number of cases in each dose group was small, and the confidence intervals for the odds ratio for >30mg daily and 30mg daily groups overlapped. Considering the other limitations of such studies, including the reliance on outpatient prescription data to classify exposure, the evidence for an effect of dose in risk is relatively weak based on this study alone. It is however possible that the decision to limit the dose of domperidone to 30mg daily in adults was taken after consideration of this data in combination with observations from case reports, and other sources considered at the time of the review [no details on the exact data behind the dose restriction are currently available from the EMA or the MHRA; it could also be due to the available evidence of efficacy considered].

Both epidemiological studies discussed above considered QT-prolonging drugs and CYP3A4 inhibitors as potential confounders. Johannes et al note in their discussion that they did not find any evidence of an interaction between current domperidone exposure and current exposure to either QT-prolonging agents or CYP3A4 inhibitors (data not presented). It is likely that the decision to contraindicate the use of domperidone in combination with other medications known to prolong QT or potent CYP3A4 inhibitors was based on reported cases in combination with drug interaction studies, as outlined in information from the EMA.

The epidemiological studies look at domperidone use in a general population; they do not discuss the indications for use or present the findings in this way. Their results cannot be used to determine whether the increased risks of SCD/VA with domperidone vary according to indication.
Evidence for dosing of domperidone in the prevention of delayed nausea and vomiting following chemotherapy

There appears to be limited published data on the use of domperidone in the prevention of chemotherapy-induced nausea and vomiting; that available has often involved the IV formulation which was withdrawn in the 1980s. In addition the majority of the located studies (many in non-English language journals) were published around 20 years ago, so may not be relevant to the regimens used in current clinical practice. The license for domperidone in nausea and vomiting is very broad and does not specifically include its prevention of nausea and vomiting in patients receiving chemotherapy.

No controlled studies assessing the optimal oral dose of domperidone in this setting were located, so it is not possible to determine from the available published evidence whether higher doses currently used in clinical practice (e.g. 20mg QDS) are more effective than lower doses (e.g. 10mg TDS; maximum dose recommended by the MHRA).

No controlled studies comparing oral domperidone to oral metoclopramide in the prevention of chemotherapy-induced nausea and vomiting were located.

What do guidelines recommend?

Draft pan-London antiemetic guidelines, produced at UCH (revised November 2013), recommend the use of domperidone in the following settings (11):

- High-risk chemotherapy: 20mg QDS orally for 5 days after chemotherapy (start from day 2 if multiple-day treatment)
- Moderate-risk: 20mg TDS for 3-5 days after chemotherapy
- Low-risk: Consider prescribing 20mg TDS PRN for 5 days for the first course (no routine antiemetics are necessary)

Guidelines on antiemetics are available from ASCO, the European Society for Medical Oncology (ESMO)/the Multinational Association of Supportive Care in Cancer (MASCC), and the National Comprehensive Cancer Network (NCCN). The main recommendations of these guidelines are listed in the Appendix, so that they can be compared to current UK practice. These guidelines also go into some detail of different clinical scenarios including for example treatment of breakthrough nausea and vomiting, anticipatory nausea and vomiting, and the management of paediatric patients; for further details please refer to the full guidelines.

None of these guidelines include domperidone; in general dopamine antagonists are only recommended as one of the possible options for rescue therapy (ASCO) and/or for prevention of acute nausea and vomiting in patients receiving low-risk regimens (ESMO/MASCC; NCCN). Of note, domperidone is not licensed in the US.

The main differences between the draft pan-London guideline and the others include:

- The 5HT3 antagonist of choice for moderate-risk regimens – palonosetron (a long-acting agent) is recommended by ESMO/MASCC and ASCO (stat dose), whereas ondansetron or granisetron are recommended in the draft pan-London guidelines.

- Post-chemotherapy antiemetics for moderate-risk regimens: ESMO/MASCC and ASCO recommend continuation of dexamethasone (for 2-3 days) only, whereas the draft pan-London guidelines recommend combined use of dexamethasone and domperidone (for 3-5 days).

- Prevention of delayed nausea and vomiting for high-risk regimens – although the initial triple regimens of NK1 antagonist, 5HT3 antagonist and dexamethasone are similar, the ASCO, ESMO/MASCC, and NCCN guidelines recommend aprepitant and dexamethasone post-chemotherapy, whereas the draft pan-London guideline recommends that domperidone is used in addition to this.

Safety concerns with possible alternative agents

The medicines listed below have all been used for the prevention and/or treatment of nausea and vomiting either in palliative care or in patients receiving chemotherapy, and have been included for information. All have their own side-effects and safety concerns however, and therefore none would appear to offer a simple, widely acceptable alternative to domperidone.

[Please note that this is not a comprehensive summary of all adverse effects associated with these agents; for further information please see the relevant SPCs]

- 5-HT3 antagonists

These agents are currently part of standard antiemetic therapy for high and moderate emetogenic risk chemotherapy regimens. They therefore may not be considered as an alternative to domperidone; however if any of the recommendations in the guidelines discussed above are considered then this
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may include continued use of 5-HT3 post-chemotherapy (days 2-3) (recommended by NCCN as one of possibilities for moderate risk regimens) or the use of a long-acting 5-HT3 antagonist (palonosetron; recommended by ASCO and ESMO/MASCc for moderate-risk regimens). The cardiac safety of these agents may also need to be considered because of the possibility of using them in addition to domperidone, if the decision is made to continue its use in this setting.

ECG changes, including QT prolongation, have been reported rarely with the 5-HT3 antagonists. A review of the data for QT prolongation with ondansetron led to restrictions being placed on the IV dose (maximum single dose of 16mg), dosing frequency, and posology in older patients (15). The granisetron SPC therefore advises caution when using these agents in patients with cardiac comorbidities, on cardotoxic chemotherapy and/or with concomitant electrolyte abnormalities (16). The ondansetron SPC additionally notes that post-marketing reports of Torsades de Pointes (tdP) have been reported, and advises caution in patients who have or may develop prolongation of the QT interval, and in patients with cardiac rhythm or conduction disturbances, those treated with antiarrhythmic agents or beta-adrenergic blocking agents and those with significant electrolyte disturbances (17).

- **Metoclopramide**

The European CHMP reviewed the benefits and risks of metoclopramide in 2013, at the request of the French medicines regulatory agency. The review confirmed the well known risks of neurological effects (e.g. extrapyramidal disorders; tardive dyskinesia), and concluded that these risks outweigh the benefits in long-term or high-dose treatment (18). To help minimise the risk of potentially serious neurological adverse effects, the following restrictions have been made to the indications, dose, and duration of use (18):

- In adults, metoclopramide should only be used for prevention of postoperative nausea and vomiting, radiotherapy-induced nausea and vomiting, delayed (but not acute) chemotherapy-induced nausea and vomiting, and symptomatic treatment of nausea and vomiting, including that associated with acute migraine (where it may also be used to improve absorption of oral analgesics);

- In children, age 1–18 years, metoclopramide should only be used as a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting, and for treatment of established postoperative nausea and vomiting. It should not be used in children below 1 year of age.

- For adults, the maximum dose in 24 hours is 30mg (or 0.5mg/kg). The usual dose (all routes) is 10mg up to three times a day

- In children age 1 year or older, the recommended dose is 0.1–0.15 mg/kg, repeated up to three times a day. The maximum dose in 24 hours is 0.5mg/kg

- Metoclopramide should only be prescribed for short-term use (up to 5 days);

The BNF notes that this advice does not apply to unlicensed uses of metoclopramide (for example palliative care) (19).

Following a review of the available efficacy data, the CHMP concluded that data on the use of metoclopramide in acute chemotherapy-induced nausea and vomiting (CINV) were limited and suggested inferiority to 5-HT3 antagonists and a need for high doses, which are associated with an increased risk of adverse effects. There was more consistent evidence of comparability with 5-HT3 antagonists when used for delayed CINV, and also some evidence suggestive of a role in radiotherapy-induced nausea and vomiting (although again seemingly inferior to the 5-HT3 antagonists) (20).

The CHMP also noted in their review that there have been very rare reports of serious cardiovascular reactions associated with metoclopramide; these have been mainly associated with IV formulations given to patients with underlying risks for cardiac disease. The Committee advised therefore that special care should be taken in populations likely to be at an increased risk, including the elderly, patients with cardiac conduction disturbances, uncorrected electrolyte imbalance or bradycardia, and those taking other drugs known to prolong QT interval (20).

- **Cyclizine**

Cyclizine is a sedating antihistamine with antimuscarinic activity (martindale) licensed for the prevention and treatment of nausea and vomiting including motion sickness, nausea and vomiting caused by narcotic analgesics and by general anaesthetics in the post-operative period, and vomiting associated with radiotherapy (especially for breast cancer since cyclizine does not elevate prolactin levels). It may also be of value in relieving vomiting and attacks of vertigo associated with Meniere's disease and other forms of vestibular disturbance. It is given orally or via intramuscular or subcutaneous injection at a dose of 50mg up to three times a day in adults; the tablets are additionally licensed for use in children aged 6-12 years (21, 22).
Although sedation is common with the older antihistamines, the sedative effects of cyclizine are not marked. Other adverse effects of sedating antihistamines include headache, psychomotor impairment, and antimuscarinic effects such as urinary retention, constipation, dry mouth, thickened respiratory-tract secretions, blurred vision, and gastro-intestinal disturbances (19, 21).

Other rare side-effects of antihistamines include hypotension, palpitation, arrhythmias, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, hypersensitivity reactions, blood disorders, liver dysfunction, and angle-closure glaucoma. Children and the elderly are more susceptible to side-effects (19).

Due to its antimuscarinic effects it should be used with caution in prostatic hypertrophy, urinary retention, susceptibility to angle-closure glaucoma, hepatic disease (latter SPC only) and pyloroduodenal obstruction. Occasional reports of convulsions in patients taking antihistamines suggest a need for caution in patients with epilepsy (19, 21-22). It should also be used with caution in patients with severe heart failure as it may cause a fall in cardiac output associated with increases in heart rate, mean arterial pressure and pulmonary wedge pressure. Cyclizine should be avoided in porphyria (22).

- **Antipsychotics**
  The D2 antagonism of all antipsychotics is likely to provide antiemetic activity in the CTZ. Most have moderate or high affinity at several receptors, some of which are involved in the transduction of emetic signals. Thus most are, to a variable extent, broad-spectrum antiemetics. Haloperidol is however a selective dopaminergic agent (23).

General precautions for antipsychotics (as highlighted in the BNF) include (19):

- Cardiovascular disease (some SPCs recommend ECG and other monitoring)
- Parkinson’s disease (may exacerbate the disease)
- Epilepsy (may lower the epileptic threshold)
- Depression
- Myasthenia gravis
- Prostatic hypertrophy
- Susceptibility to angle-closure glaucoma
- Severe respiratory disease
- History of jaundice
- Blood dyscrasias

General side-effects of antipsychotics (as highlighted in the BNF) include (19):

- Extrapyramidal symptoms – Parkinsonian symptoms (more common in the elderly; may appear gradually); dystonia and dyskinesia (occur more commonly in children or young adults and appear after only a few doses); akathisia (usually occurs after large initial doses); tardive dyskinesia (usually after high-dose or long-term therapy)
- Hyperprolactinaemia (more common with typicals [PF])
- Sexual dysfunction
- **Cardiovascular side-effects** such as tachycardia, arrhythmias and hypotension (risk of QT interval prolongation is higher with IV administration). The elderly may be particularly susceptible to postural hypotension.
- An increased risk of stroke/TIA and a small increased risk of mortality have been associated with antipsychotics in elderly patients with dementia (the relative risk for individual drugs has not yet been determined [20]).
- Hyperglycaemia/ glucose intolerance (patients with diabetes should have appropriate glycaemic monitoring during treatment)
- Neuroleptic malignant syndrome (rare but potentially fatal)

All antipsychotic drugs can precipitate coma if used in hepatic impairment; phenothiazines are hepatotoxic. As photosensitisation may occur with higher dosages, patients should avoid direct sunlight (19).

Further information on individual agents:

**Levomepromazine**

This phenothiazine antipsychotic is licensed for use as an adjunct in the relief of pain and accompanying distress in patients with terminal illness; it is also used for the relief of nausea and vomiting in this setting (unlicensed).

It is given by mouth or by subcutaneous injection. When used as an antiemetic in palliative care, the BNF suggests an initial dose of 6mg or 6.25mg at bedtime (use a quarter of a 25mg tablet or a 6mg tablet; the latter is available from specials manufacturers), titrated if necessary to 12.5-25mg twice daily (19). Doses above 25mg/24hr tend to cause drowsiness and also postural hypotension; this limits dose titration (23). Levomepromazine may cause severe orthostatic hypotension, and patients taking large initial doses, patients over 50 years of age, or those given injections, should be lying down. Children are very susceptible to the hypotensive and sedative effects of levomepromazine (21).
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Levomepromazine and its non-hydroxylated metabolites are potent inhibitors of cytochrome P450 2D6 (24).

Prochlorperazine
This phenothiazine is a dopamine antagonist that acts centrally by blocking the CTZ (19). It is licensed for the treatment of vertigo due to Meniere’s Syndrome, labyrinthis and other causes, and for nausea and vomiting from whatever cause including that associated with migraine. It may also be used for schizophrenia (particularly in the chronic stage), acute mania and as an adjunct to the short-term management of anxiety. For the prevention of nausea and vomiting in adults, the licensed dose is 5-10mg 2-3 times daily (25). For the treatment of nausea and vomiting, a buccal tablet formulation and injection are also available.

As well as the general precautions summarised above, prochlorperazine should be avoided in patients with liver or renal dysfunction, hypothyroidism, phaeochromocytoma and agranulocytosis (FBC monitoring is recommended) (25). Prochlorperazine has been associated with dystonic reactions particularly after a cumulative dosage of 0.5 mg/kg. These are commoner in children and young adults and usually occur within the first four days of treatment or after dose increases, and it should be used with extreme care in children (25). Antimuscarinic effects are very common (20).

Haloperidol
Haloperidol is a typical antipsychotic D2 antagonist. The BNF states that it is used by mouth in an initial dose of 1.5 mg once or twice daily (can be increased if necessary to 5–10 mg daily in divided doses) for most metabolic causes of vomiting (e.g. hypercalcaemia, renal failure) in palliative care (19).

Haloperidol can cause potentially fatal prolongation of the QT interval and TdP, particularly if given IV, and the risks-benefits should be fully assessed before treatment is commenced and patients with risk factors for ventricular arrhythmias should be monitored carefully. As Haloperidol is metabolised by the liver, caution is advised in patients with liver disease. Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported (26). The metabolism of haloperidol is mediated by several routes including the cytochrome P450 system, particularly the isoenzymes CYP3A4 and CYP2D6 (21).

Olanzapine
Olanzapine is a thienobenzodiazepine atypical antipsychotic, with affinity for several receptor types (21). It is therefore a broad-spectrum and potent antiemetic; this has been confirmed in Phase I and II trials in cancer patients receiving either moderately or highly emetogenic chemotherapy (23). More recently it was shown in a Phase III study to possibly be superior to aprepitant (both used in combination with palonosetron and dexamethasone) for the prevention of delayed nausea in patients receiving cisplatin or doxorubicin with cyclophosphamide. These findings do however need to be replicated in a larger study (27).

Olanzapine is not licensed for the treatment or prevention of nausea and vomiting in any setting, and the BNF does not discuss its use for this indication. The Palliative Care Formulary recommends a dose of 1.25-2.5mg PO/SC stat every 2 hours PRN and at bedtime, increasing up to 5mg BD if necessary (23). The Phase III study referred to above utilised a dose of 10mg once daily for four days (27). In chemotherapy antiemetic guidelines, it is generally referred to in the setting of breakthrough treatment – for example the NCCN guidelines recommend a dose of 10mg daily for 3 days (14).

Common side-effects include drowsiness and weight gain; others include dry mouth, constipation, orthostatic hypotension, agitation, dizziness and peripheral oedema. The incidence and severity of drug-induced movement disorders are significantly less than with haloperidol (23).

Elevated plasma glucose, triglyceride, and liver enzyme values, oedema, orthostatic hypotension, and blood dyscrasias have also been reported. Weight gain, sedation, and liver enzyme values, lipid, and prolactin alterations may be greater in adolescents than in adults (21). The antimuscarinic effects of olanzapine contra-indicate its use in patients with angle-closure glaucoma; caution is also advised in those with conditions such as benign prostatic hyperplasia or paralytic ileus (21).

Financial impact
As well as the possible alternatives listed above, options may include increasing the use of aprepitant and/or 5HT3 antagonists, or introducing palonosetron (long-acting 5HT3 antagonist) as recommended in the ESMO/MASCC and ASCO guidelines. It is difficult to provide a meaningful estimate of the financial impact of these options, considering the variation in current practice; the individual costs have therefore been presented below for consideration.

*Please note: The costs presented here are basic prices, exclusive of VAT, and they do not take into account any local procurement discounts. This should be considered when reviewing the local cost implications.
Wider use of aprepitant
Aprepitant is given orally at a dose of 125mg one hour before chemotherapy, then 80mg daily as a single dose for the next two days (there are some data for its use for a longer period of time for patients receiving multiple-day chemotherapy but it is not currently licensed for use beyond three days).

Assuming use for the licensed three days, the additional cost of adding aprepitant to a corticosteroid and 5HT3 antagonist antiemetic regimen would be £47.42 per patient* (19).

Wider use of generic 5HT3 antagonists
The NCCN guidelines recommend that unless palonosetron was used on day 1 for moderate-risk regimens, 5HT3 antagonists should be continued on days 2-3. The SPC for ondansetron tablets notes that in order to protect against delayed or prolonged emesis after the first 24 hours, oral treatment should be continued for up to five days after a course of treatment. Granisetron is licensed for use at a dose of 2mg daily (2mg OD or 1mg BD) for up to seven days following chemotherapy or radiotherapy.

As an example, the use of ondansetron at a dose of 8mg BD for a total of five days would cost £3.58 per patient* (based on use of the 4mg tablets). The use of granisetron 2mg daily for five days would cost £50.38 per patient* (19). [As these are currently given only as stat doses, these costs would be very similar to the additional costs per patient.]

Introduction of palonosetron
Palonosetron is a long-acting 5HT3 antagonist that is given as a single dose (0.25mg IV or 0.5mg PO) approximately one hour before the start of chemotherapy. Each dose, regardless of route, costs £55.89. Assuming an approximate cost of £0.36 for a single dose of ondansetron and £10 for a single dose of granisetron, the use of palonosetron as an alternative would be associated with an additional cost of approximately £45-55 per patient* (19)

References:
6. Personal communication; received 7th May 2014


16. Kytril 2mg tablets SPC (last revised 21/10/13)

17. Zofran injection SPC (last revised 14 June 2013)


22. Cyclizine 50mg tablets SPC (Amdipharm Mercury Company Limited; last revised


24. Nozinan tablets SPC (last revised 24/12/13)

25. Stemetil tablets SPC (last revised 25/7/13)

26. Haldol 2mg/mL oral liquid SPC (last revised 3/12/13)


The document reflects the views of LCNDG and may not reflect those of the reviewers.

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May 2014
## APPENDIX

### 1: DRAFT PAN-LONDON GUIDELINES (revised November 2013)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Pre Chemotherapy Schedule (for each day of chemotherapy)</th>
<th>Post Chemotherapy (day after chemotherapy finished)</th>
</tr>
</thead>
</table>
| **High (risk of emesis >90%)** | **Single day treatment:**  
  **Aprepitant** (125mg PO 1hr pre-chemotherapy)  
  +  
  dexamethasone 8-12mg PO/IV  
  +  
  5HT3 antagonist (granisetron 2mg PO or 1mg IV; ondansetron 8mg PO/IV; or other locally approved)  
  **Multiple day treatment**  
  **Day 1:** As above  
  **Subsequent days:**  
  **Aprepitant** (80mg PO 1 hr pre-chemotherapy)  
  +  
  Dexamethasone 8mg IV  
  +  
  5HT3 antagonist (as above)  
  +  
  Domperidone 20mg PO QDS | **Aprepitant** (80mg PO OD for 2 days)  
  +  
  Dexamethasone (8mg PO daily in either one or two divided doses for 2-3 days)  
  +  
  Domperidone (20mg PO QDS for 5 days)  
  **Consider:** Levomepromazine 6mg (unlicensed) nocte PRN |
| **High–moderate (risk of emesis 60-90%)** | **For breast cancer patients having anthracyclines+cyclophosphamide containing regimens give:**  
  **Aprepitant** 125mg PO on day 1 ONLY  
  **With the below**  
  **Dexamethasone** 8mg-20mg PO/IV  
  +  
  5HT3 antagonist (locally approved) | **Dexamethasone** (8mg PO daily in either one or two divided doses for 2-3 days)  
  +  
  Domperidone (20mg PO TDS for 5 days) |
| **Low-moderate (risk of emesis 30-60%)** | **Dexamethasone** 8mg-20mg PO/IV  
  +  
  5HT3 antagonist (locally approved) | **Dexamethasone** (8mg PO daily in either one or two divided doses for 2-3 days)  
  +  
  Domperidone (20mg PO TDS for 3-5 days) |
| **Low (risk of emesis < 30%)** | No routine anti-emetics are necessary | No routine anti-emetics are necessary. For first course consider prescribing  
  **Domperidone** 20mg PO TDS PRN for 5 days |
## 2: ESMO/ MASCC guideline

This guideline only recommends the use of dopamine receptor antagonists as one possible option for acute nausea and vomiting in patients receiving low-risk regimens (12).

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Prevention of acute nausea and vomiting</th>
<th>Prevention of delayed nausea and vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk regimens (&gt;90%)</strong></td>
<td><strong>Aprepitant (125mg PO) or fosaprepitant</strong>&lt;br&gt;(150mg IV)&lt;br&gt;<strong>5HT3 antagonist</strong>&lt;br&gt;<strong>Dexamethasone (12mg)</strong>&lt;br&gt;Single doses of each given prior to chemotherapy</td>
<td><strong>Aprepitant (80mg PO OD for 2 days after chemotherapy)</strong>&lt;br&gt;<strong>Dexamethasone (8mg BD for 3-4 days; or 8mg OD if used with aprepitant or fosaprepitant)</strong>&lt;br&gt;<strong>(Dexamethasone only on days 2-4 if fosaprepitant used on day 1)</strong></td>
</tr>
<tr>
<td><strong>Moderate risk regimens</strong>&lt;br&gt;(other than AC) 30-90%</td>
<td><strong>Palonosetron</strong> (a long-acting 5HT3 antagonist; 0.25mg IV or 0.5mg PO stat) + <strong>dexamethasone</strong> 8mg IV stat</td>
<td><strong>Dexamethasone</strong> (8mg daily for 2-3 days)</td>
</tr>
<tr>
<td>Anthracycline and cyclophosphamide</td>
<td><strong>Aprepitant (125mg PO) or fosaprepitant</strong>&lt;br&gt;(150mg IV)&lt;br&gt;<strong>5HT3 antagonist</strong>&lt;br&gt;<strong>Dexamethasone (12mg)</strong>&lt;br&gt;Single doses of each given prior to chemotherapy</td>
<td><strong>Aprepitant (80mg PO OD for 2 days after chemotherapy)</strong>&lt;br&gt;[None if fosaprepitant was used on day 1]</td>
</tr>
<tr>
<td>Low-risk (10-30%)</td>
<td><strong>Dexamethasone</strong> (4-8mg stat)&lt;br&gt;<strong>Or 5HT3 antagonist</strong>&lt;br&gt;<strong>Or Dopamine receptor antagonist</strong> (e.g. metoclopramide; no dosing stated)</td>
<td>No routine prophylaxis</td>
</tr>
<tr>
<td>Minimal risk (&lt;10%)</td>
<td>No routine prophylaxis</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>
3: **ASCO guideline**

Dopamine antagonists are only recommended as a possible option in the setting of rescue therapy in patients with emesis or nausea despite optimal prophylaxis (13).

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Recommendation</th>
<th>Further information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk regimens</strong></td>
<td><strong>NK1 receptor antagonist</strong> (days 1-3 for aprepitant; day 1 only for fosaprepitant) + a 5-HT3 receptor antagonist (day 1 only) + Dexamethasone (12mg PO or IV day 1; 8mg days 2-3 or 2-4)</td>
<td>A study comparing olanzapine with aprepitant is noted; the guidelines say additional studies are required to define the role of olanzapine in this setting [this olanzapine-containing regimen is however recommended in NCCN guidelines; as below]</td>
</tr>
<tr>
<td>(including AC – reclassified in 2011)</td>
<td>If patients do not receive aprepitant, the dexamethasone dose should be adjusted to 20mg on day 1 and 16 mg on days 2-4</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate risk regimens</strong></td>
<td><strong>Palonosetron</strong>* (a long-acting 5HT3 antagonist; day 1 only) + dexamethasone (8mg PO or IV day 1-3)</td>
<td>If palonosetron is not available, clinicians may substitute a first generation 5HT3 antagonist, preferably granisetron or ondansetron. If the clinician opts to add aprepitant (limited evidence), any one of the 5HT3 antagonists is appropriate.</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td><strong>Low-risk</strong></td>
<td>Single dose of dexamethasone (8mg) prior to chemotherapy [no routine prophylaxis for delayed nausea and vomiting]</td>
<td></td>
</tr>
<tr>
<td><strong>Minimal risk</strong></td>
<td>No routine prophylaxis</td>
<td></td>
</tr>
</tbody>
</table>

*the preference for palonosetron is an extrapolation of data from a study in the setting of AC and cisplatin chemotherapy, when aprepitant is not used. In this setting, palonosetron plus dexamethasone was superior to granisetron plus dexamethasone.
4: NCCN guideline

The only role for dopamine antagonists discussed in this guideline is as a possible option for low-risk IV regimens and low to minimal risk oral regimens (14).

<table>
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<tr>
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</thead>
</table>
| **High-risk (IV) regimens** | **NK1 antagonist** (aprepitant [125mg PO day 1, 80mg PO days 2-3] or fosaprepitant [150mg IV day 1 only] + 5HT3 antagonist (day 1) + Dexamethasone (days 1-4; dose depends on whether aprepitant or fosaprepitant used)
OR
Olanzapine 10mg PO days 1-4 + palonosetron 0.25mg IV day 1+dexamethasone 20mg IV day 1 | Some members use a 5-HT3 antagonist on days 2-3                                      |
| **Moderate risk (IV) regimens** | **5HT3 antagonist** (day 1) + Dexamethasone (12mg PO or IV) +/- NK1 antagonist  
OR
Olanzapine-containing regimen (as above) | Days 2-3 5HT3 monotherapy (unless palonosetron used day 1) OR Dexamethasone (8mg PO or IV) OR NK1 antagonist ± dexamethasone (if NK1 antagonist used on day 1)  
If olanzapine-containing regimen is given on day 1 then olanzapine is continued on days 2-4 (as above) |
| **Low-risk (IV)**          | **Dexamethasone** (12mg PO or IV) or metoclopramide (10-40mg PO or IV then every 4-6hr PRN), or prochlorperazine (10mg PO or IV and then every 6hr PRN), or 5HT3 antagonist | Repeat daily for multiday doses of chemotherapy                                       |
| **Minimal risk (IV)**      | No routine prophylaxis                                                          |                                                                                      |
| **Oral chemotherapy – high to moderate risk** | **5HT3 antagonist**                                                          |                                                                                      |
| **Oral chemotherapy – low to minimal risk** | **Metoclopramide** 10-40mg PO then every 4-6h, or prochlorperazine 10mg PO/IV then every 6h, or haloperidol 1-2mg PO every 4-6h PRN or 5HT3 antagonist | PRN dosing recommended                                                                  |