# Research Review

## PRODUCT REVIEW

**Granisetron tablets (Granirex)**

## About the Reviewer


### Dr John Childs

***MNZM; MB ChB; FRANZCR; FRACP***

*John Childs was the National Clinical Director, Cancer at the Ministry of Health for 7 years until 2012, and has been a specialist in radiation oncology with the Auckland District Health Board since 1991. He has also held appointments as Clinical Director of Radiation Oncology and Clinical Leader of Medical Services. He also consults at Auckland Radiation Oncology in Auckland and at a satellite clinic in Whangarei. John has held various national roles including a member of the Cancer Control Council, the chair of the National Cancer Treatment Working Party and a number of other national advisory committees. He is currently chair of the National Bowel Cancer Screening Advisory Group. He has also been a council member for the Royal Australia and New Zealand College of Radiologists (RANZCR), a board member of the Faculty of Radiation Oncology, and an examiner in radiation oncology for the RANZCR. He has a particular interest in urological, gastrointestinal, haematological, chest malignancies and palliative radiation oncology.*


**ABBREVIATIONS USED IN THIS REVIEW**

**(CI/RI/PO)NV** = (chemotherapy-induced/RT-induced/postoperative) nausea and vomiting
**IV** = intravenous
**OR** = odds ratio
**RCT** = randomised controlled trial
**RT** = radiotherapy
**TBI** = total body irradiation




Chemotherapy, RT and surgery can be associated with troublesome NV. This review presents a review of evidence in support of the newly-funded granisetron tablets (Granirex) for the prevention and treatment of CINV, RINV and PONV. Antiemetic agents available for the prevention and treatment of these conditions in NZ are summarised and described, after which the properties and details of granisetron are described. Details on the emetogenic potentials of different chemotherapeutic treatments are also provided, followed by evidence for the use of granisetron, including findings of important RCTs and meta-analyses. The international recommendations for managing CINV, RINV and PONV are presented and discussed in the context of the NZ setting.


## Incidence/prevalence of CINV, RINV and PONV

NV can be a distressing adverse effect with chemotherapy, RT and surgery, due to the toxic nature of the agents/procedures.[1–4] Although vomiting and nausea are related, they may occur via different mechanisms. Stimulation of neurotransmitter receptors in the chemoreceptor trigger zone, the vomiting centre in the medulla and gastrointestinal tract can trigger a multistep reflex pathway that culminates in vomiting to remove 'poisons' from the stomach. Nausea is a subjective sensation of an urge to vomit without the muscular movements required to expel the contents of the stomach. An unproductive attempt at vomiting is commonly termed 'retching'. An emetic episode is an episode of vomiting or retching.

Chemotherapeutic agents and their metabolites are usually toxic to normal human physiology, and as such elicit responses similar to other poisons, including NV via activation of neurotransmitter receptors, primarily serotonin ($5\text{-}HT_3$) and dopamine.[1,3] Emesis due chemotherapy and radiotherapy may be due to induction of serotonin release from small intestinal cells. CINV can be immediate (30–120 minutes after chemotherapy administration), acute (≤24 hours) or delayed (>24 hours), with the latter not uncommon. The incidence of CINV varies significantly from >90% to <10% depending on the types and combinations of agents used (see section 'Emetic risk groups' for more detail).

Anticipatory NV is a conditioned response that occurs prior to planned chemotherapy administration following a previous negative experience, and often affects younger patients due to having received more aggressive chemotherapy. Vomiting despite prophylactic treatment that requires rescue antiemetic agents is referred to as breakthrough emesis, while emesis during treatment cycles when antiemetic prophylaxis and/or rescue therapy have failed in earlier cycles is referred to as refractory emesis.

The cause of RINV is not fully understood, although it may be caused by damage to rapidly dividing cells in the small intestine with abdominal RT. However, the mechanisms of RINV after RT to other sites is largely unknown, but are thought to be similar to CINV.[2,5] RINV is characterised by a latent asymptomatic 1- to 2-hour period after RT, followed by a 6- to 8-hour period of NV, although one study has reported a median time of 3 days for a first episode of NV following radiotherapy.[6]

Large observational studies have reported that 50–80% of patients undergoing RT may experience NV, although the incidence is now less than one-third of patients because of improved radiation techniques with more accurate targeting of radiation to reduce radiation dose to sensitive structures and increased use of antiemetics.[2,5–8] RT to the whole body or upper abdomen is associated with higher rates of NV than RT to other areas, and the risk of RINV is increased when larger volumes are irradiated or larger doses per fraction are used.[3,8] Reports have suggested that the majority of patients who experience RINV are not prescribed antiemetics.

PONV is the most common complication during the immediate postoperative period. The overall incidence of PONV is estimated at ~25–30% (40–50% nausea, 25–30% vomiting) across all surgical patients,[9] but depends on the specific surgical population studied, with certain high-risk populations (e.g. tonsillectomy, strabismus, laparoscopy patients) having incidences as high as 70–80% in the absence of prophylactic antiemetic therapy. The use of volatile anaesthetics (e.g. sevoflurane, desflurane), nitrous oxide and opioids also increases the risk of early PONV (2–6 hours postsurgery), while opioid use and motion sickness due to transport have been implicated in late PONV (24–48 hours postsurgery).[10] Utilising regional or total IV anaesthesia can help to lower the risk of early PONV. Females, nonsmokers, younger patients and those with a prior history of PONV or motion sickness are also at increased risk of PONV.

## About Research Review

*Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas.*

*Product Reviews feature independent short summaries of major research affecting an individual medicine or technique. They include a background to the particular condition, a summary of the medicine and selected studies by a key New Zealand specialist with a comment on the relevance to New Zealand practice.*

*Research Review publications are intended for New Zealand medical professionals.*

## Burden of NV

NV can lead to dehydration, electrolyte imbalances, bodyweight loss, malnourishment, epigastric pain, oesophageal bleeding, hiccups and anticipatory NV. Depression can result, which may contribute to general apathy, fear and isolation.[1,3,9] NV also has significant impacts on quality of life, functioning and costs.[2–4,9] Control of CINV and RINV is important to enable anticancer treatment to continue; controlling NV can significantly improve the tolerability of chemotherapy and enable completion of planned treatment courses. Moreover established vomiting can become refractory to simple treatments, so prevention and, failing that, early intervention are important.

While there has been a decrease in unexpected hospital admissions due to PONV, they still occur in ~0.5–2% of patients. Overall it has been reported that healthcare costs from PONV have increased due to unanticipated admissions, increased nursing care and delayed discharge from the postanaesthesia care unit or hospital.[9]

It is important that patients' NV is adequately managed with antiemetics to reduce distress, particularly when persistent delayed nausea is present.[1] While there are many antiemetic agents available (see Table 1), many patients are still affected. In the case of RINV, this may be due to radiation oncologists not considering RINV as a serious concern, and underprescribing of prophylactic antiemetics for RINV has been reported.[2,6,8] A web-based survey of oncologists prescribing RT, which included NZ oncologists, showed variation in risk estimates and management strategies, particularly for low- and moderate-risk RT cases, and the authors concluded that RINV is understudied.[11] One study has reported that one-third of patients who experienced RINV would have liked antiemetic treatment.[8] Similarly, inconsistency with antiemetic guidelines in CINV has also been reported.[12]

## Available antiemetics for preventing and managing NV in NZ

Over the last two decades, new effective antiemetic agents have been introduced, including 5-$HT_3$ (5-hydroxytryptamine; serotonin) receptor antagonists, NK1 (neurokinin-1) receptor antagonists and other agents, including corticosteroids.[4] In NZ, a number of antiemetics from several classes are available (Table 1).[1] Antihistamines, anticholinergics and 5-$HT_3$ antagonists act on the emetic centre, benzamines act on the chemoreceptor trigger zone, antihistamines and corticosteroids act on the cerebral cortex (corticosteroids also have other unknown sites of action), and metoclopramide and 5-$HT_3$ antagonists act peripherally. Ondansetron tablets and injections and tropisetron injections had been the only 5-$HT_3$ antagonists funded by Pharmac NZ.[13] However, as of Nov 1, 2014, funding for granisetron 1mg tablets (Granirex) became available. Other antiemetics funded in NZ include cyclizine (injections only), haloperidol, metoclopramide (tablets and injections) and prochlorperazine (tablets only).

## Granisetron

Granisetron is a selective, noncompetitive 5-$HT_3$ receptor antagonist with a binding constant of 0.26nM, but unlike other 5-$HT_3$ antagonists, granisetron has negligible affinity for dopaminergic, adrenergic, benzodiazepine, histaminic, opioid and other 5-HT receptors.[14–17] Emetogenic chemotherapies cause mucosal enterochromaffin cells to release serotonin, which stimulates 5-$HT_3$ receptors on vagal nerve terminals (peripherally) and the nucleus tractus solitarus (centrally). Granisetron appears to have an antagonist action on the serotonin-induced stimulation of vagal afferent activity. It is believed that serotonin has a central role in the mechanism of acute emesis but a lesser role in delayed emesis.[18]

### Pharmacokinetics

The pharmacokinetics of granisetron differ to other 5-$HT_3$ antagonists such as ondansetron (Table 2).[19] A unique property of granisetron among the 5-$HT_3$ receptor antagonists is that it is not metabolised via the cytochrome P450 2D6 pathway, meaning that patient responses are less variable due to factors such as pharmacogenomic differences.[17] Granisetron has a longer mode of action that ondansetron, with ondansetron having a half-life of ~3 hours. Granisetron is also associated with longer biological activity than ondansetron, as evidenced by 2.6-fold longer inhibition of cutaneous 5-HT-induced, axon-reflex flare, with activity still present 24 hours after a single granisetron dose of 40 µg/kg (compared with ondansetron 8mg and 16mg).[20,21] Also in contrast to ondansetron, granisetron insurmountably antagonises vagal afferent 5-$HT_3$ receptors, which is thought to be the underlying mechanism for its longer pharmacodynamic half-life with its plasma half-life.[22]

**Table 1. Antiemetic medications registered in NZ**[1,9,13,23]

| Class | Agent(s) | Usage |
|---|---|---|
| 5-$HT_3$ antagonists | Granisetron | CINV/RINV<br>Most effective combined with corticosteroid<br>Second-line for treatment failures with other classes<br>Oral (Granirex): indicated for prevention of acute/delayed NV associated with cytostatic therapy NZ<br>Injections: indicated in NZ for prevention and treatment of CINV in adults; prevention of RINV in adults; prevention of CINV in children<br>PONV<br>Injections indicated for prevention and treatment in NZ<br>Oral forms included in international guidelines (Table 5) |
| | Ondansetron | CINV/RINV<br>Indicated in NZ for management of CINV and RINV (oral and injections)<br>Most effective when combined with a corticosteroid<br>Second-line therapy for treatment failures with other classes<br>PONV<br>Indicated in NZ for prevention |
| | Tropisetron | CINV/RINV<br>Indicated in NZ for prevention (injection)<br>PONV<br>Indicated in NZ for treatment and prevention (injection) |
| | Palonosetron[a] | CINV<br>Indicated in NZ for prevention (injection) |
| Antihistamines | Cyclizine | CINV/RINV<br>Mild-to-moderate<br>Little effect for emesis due to in highly emetogenic chemotherapy[b]<br>PONV |
| Anticholinergics/ antimuscarinic | Hyoscine[c] | CINV<br>Useful as adjunctive therapy for delayed nausea or prolonged mild nausea<br>PONV |
| Benzodiazepine | Lorazepam[d] | CINV<br>Mild antiemetic activity<br>Effective for preventing anticipatory NV |
| Butyrophenones | Droperidol<br>Haloperidol[d] | CINV<br>Useful for moderate to highly emetogenic chemotherapy[e]<br>Optimal response as part of a multidrug regimen<br>PONV<br>Reduces NV |
| Corticosteroids | Dexamethasone[d] | CINV<br>Important component of drug regimens – mechanism unknown<br>Enhances efficacy of ondansetron<br>Monotherapy appears equal to or better than 5-$HT_3$ antagonists for delayed NV |
| Dopamine antagonists | Domperidone | CINV/RINV |
| NK1 inhibitors | Aprepitant[c]<br>Fosaprepitant[a] | CINV<br>Recently approved for highly and moderately emetogenic chemotherapy[e]<br>PONV<br>Aprepitant (oral) – prevention |
| Phenothiazines | Promethazine[c]<br>Levopromethazine[a] | CINV<br>Mild-to-moderate<br>Little effect for emesis due to highly emetogenic chemotherapy[b] |
| | Chlorpromazine[d]<br>Prochlorperazine[a] | PONV<br>Retractable NV |
| Substituted benzamides | Metoclopramide | CINV/RINV<br>Currently most commonly used<br>Mild-to-moderate nausea and/or breakthrough NV<br>PONV<br>Controls postoperative vomiting<br>Complicated by adverse reactions (e.g. restlessness, sedation, hypotension, diarrhoea) |

a. Not funded; b. See section 'Emetic risk groups'; c. Funding restrictions apply; d. Funded under other classes/indications

**Table 2. Properties of granisetron**[15,16,24]

| | |
|---|---|
| **Molecular mass** | 312.41 g/mol |
| **Route of administration** | Oral (tablets) |
| **Bioavailability** | ~60% – not influenced by food |
| **Protein binding** | ~65% |
| **Metabolism** | Predominantly hepatic metabolism – biotransformation pathways involve *N*-demethylation and aromatic ring oxidation followed by conjugation |
| **Elimination** | 12% unchanged in the urine over 48h<br>Remainder as metabolites; 47% urinary and 34% faecal |
| **Terminal half-life** | 8.74h after 1mg oral dose |
| **Main toxicities** | Constipation and headache (causally linked)<br>Asthenia, somnolence, diarrhoea, abdominal pain, decreased appetite (main adverse events reported in clinical trials) |
| **Main drug interactions** | Potential for electrocardiographic irregularities with concomitant drugs known to prolong the QT-interval and/or are arrhythmogenic<br>Potential for serotonin syndrome with concomitant use of agents that may affect the serotonergic neurotransmitter system |
| **Dose adaptations** | **Elderly:** available clinical data suggest normal adult doses are safe and effective<br>**Paediatrics:** not been adequately studied<br>**Pregnancy/lactation:** safety not established – not recommended unless potential benefit to mother outweighs possible risk to foetus<br>**Hepatic impairment:** clearance is reduced by half (the dose response has not been determined) – dosage adjustments not required based on available data<br>**Renal impairment:** available clinical data suggest dosage reduction not required |

### Availability

Granisetron was approved in the UK in 1991, followed by the US in 1994. A transdermal patch was approved in the US in 2008, and an application for a long-acting SC injectable formulation was lodged in 2012. Granisetron tablets, marketed as Granirex in NZ, have recently been funded for use in NZ, and they are currently indicated by Medsafe for the prevention of acute and delayed NV associated with cytostatic therapy (including RT);[13,15] Granisetron has also been shown to be effective for PONV (refer to section 'Clinical trial data supporting the use of granisetron for NV: PONV'). Granirex film-coated tablets contain 1mg of granisetron each, and the usual dosage is 1mg twice daily for ≤7 days, with the first dose administered ≤1 hour before cytostatic therapy. Granisetron 1mg has been shown to be noninferior to 3mg, when combined with dexamethasone, for preventing acute CINV.[25,26]

## Emetic risk groups

Chemotherapeutic agents are divided into four Grunberg classes according to their emetogenic potential: high risk (≥90% of patients experience acute emesis), moderate risk (30–90%), low risk (10–30%) and minimal (<10%) (Table 3).[3] Highly emetogenic chemotherapy results in vomiting in >90% of patients, but pretreatment prophylactic antiemetic use can reduce this to around 30%. However, nausea is more difficult to control. Chemotherapeutic agents associated with delayed-onset NV (>24 hours) include cisplatin, carboplatin, cyclophosphamide and doxorubicin. The maximal intensity of NV with cisplatin occurs 48–72 hours postadministration, and can persist for 6–7 days. Anticipatory NV has been reported with varying incidences of 18–57%, and nausea is more common than vomiting.

For CINV, ondansetron (oral or IV) is a commonly used antiemetic for use with chemotherapy with an emetogenic potential >30%, but combined with dexamethasone if the emetogenic potential is >60%. The newly approved NK1 inhibitors are also effective in moderately to highly emetogenic chemotherapy, including the acute, delayed and overall phases.[27,28] Other available antiemetics are only recommended for chemotherapy with an emetogenic potential ≤30% and delayed NV.[1]

RT is also classified according to emetogenic risk: i) TBI or total nodal irradiation is considered high risk; ii) upper abdomen RT and half or upper body irradiation is moderate risk; iii) cranial, craniospinal, head and neck, lower thorax region and pelvic RT are low risk; and iv) RT of the breasts or extremities is minimal risk.[29] Another useful assessment tool for RT emetogenic risk includes scoring both by patient factors and the emetogenic risk of the RT site.[30,31]

**Table 3. Chemotherapeutic agents with moderate to high emetogenic potential**[3,29,69]

| Emetogenic risk level | Agents |
|---|---|
| High | Busulfan >10mg<br>Doxorubicin or epirubicin plus cyclophosphamide<br>Carmustine >250 mg/m$^2$<br>Cisplatin ≥50 mg/m$^2$<br>Cyclophosphamide >1500 mg/m$^2$<br>Dacarbazine<br>Doxorubicin >60 g/m$^2$<br>Epirubicin >90 g/m$^2$<br>Ifosfamide ≥10 g/m$^2$<br>Lomustine |
| Moderate | Aldesleukin >12–15 million IU/m$^2$<br>Azacitidine<br>Carboplatin<br>Carmustine ≤250 mg/m$^2$<br>Cisplatin <50 mg/m$^2$<br>Clofarabine<br>Cyclophosphamide ≤1500 mg/m$^2$<br>Cytarabine >200 mg/m$^2$<br>Dactinomycin<br>Daunorubicin<br>Doxorubicin ≤60 mg/m$^2$<br>Epirubicin ≤90 mg/m$^2$<br>Etoposide >120 mg/m$^2$<br>Idarubicin<br>Ifosfamide <10 g/m$^2$<br>Interferon alfa ≥10 million IU/m$^2$<br>Irinotecan<br>Melphalan<br>Methotrexate ≥250 mg/m$^2$<br>Oxaliplatin<br>Temozolomide (>75 mg/m$^2$/day) |

## Evidence for the use of granisetron for NV

### Acute and delayed-onset CINV

The use of antiemetic agents such as 5-HT$_3$ antagonists and NK1 antagonists have resulted in marked decreases in hospitalisation for chemotherapy and have nearly eliminated acute emesis.[32] A number of trials and meta-analyses have demonstrated efficacy of granisetron for acute and delayed CINV.

One retrospective assessment has suggested superiority of granisetron 10 µg/kg or 1mg over ondansetron 8mg, with and 8-fold reduction in the incidence of acute CINV among 224 women who had received cyclophosphamide for breast cancer.[33] However, other RCTs have shown no difference between granisetron and ondansetron for managing CINV in patients receiving higher emetogenic chemotherapy, including a first course, a first course of single-agent chemotherapy and cisplatin-based chemotherapy, or in patients receiving conditioning therapies frequently used prior to haematopoietic stem-cell transplantation.[34–38]

Two RCTs have shown granisetron to be superior to metoclopramide. One in patients receiving CHOP for NHL showed significantly better controls of both acute and delayed CINV and also reported a patient preference for granisetron; both agents were administered with dexamethasone on days 1–5.[39] The other, which also included dexamethasone therapy in each arm in patients receiving cisplatin-based therapy, reported significantly greater antiemetic control and a significantly greater delay to NV in the granisetron arm.[40] However, two trials have shown no difference between granisetron and metoclopramide, both with corticosteroids, in patients with controlled acute emesis.[41,42] A comparison of granisetron with prochlorperazine found that granisetron was superior at 24–48 hours, but not 72 hours, in patients receiving moderately emetogenic chemotherapy.[43,44]

A meta-analysis of seven trials comparing granisetron and tropisetron for acute CINV in patients receiving cisplatin-based therapy showed superiority of granisetron in six of the trials for complete absence of vomiting during the 24 hours after the start of chemotherapy (ORs >1), but the differences did not reach statistical significance.[45] In five trials of non-cisplatin-based regimens, an advantage of granisetron over tropisetron was seen in four of the trials, with statistical significance achieved in one. When data from all trials were pooled, granisetron was associated with a significant overall advantage over tropisetron (p=0.042), which was supported by the individual studies. The difference in response was more pronounced with non-cisplatin-based regimens than with cisplatin regimens in the ten trials in which an advantage with granisetron was seen (7.3% vs. 5.4%). A later meta-analysis of 44 randomised trials (n=12,343) by the same group showed that granisetron 2mg or 3mg was equivalent to ondansetron 24mg or 32mg, and was significantly better than tropisetron (p=0.018) for managing acute CINV.[25] Moreover, granisetron 3mg was found to be significantly superior to ondansetron 8mg for non-cisplatin-based therapy (p=0.015). No differences were seen between granisetron 1mg and 3mg doses.

In a trial looking specifically at delayed CINV, patients receiving new chemotherapy with doxorubicin, epirubicin, cisplatin, carboplatin or oxaliplatin were randomised to receive: i) palonosetron plus dexamethasone on day 1 with prochlorperazine on days 2–3 (n=234); ii) granisetron plus dexamethasone on day 1 with prochlorperazine on days 2–3 (n=234); iii) aprepitant plus palonosetron plus dexamethasone on day 1 with aprepitant plus dexamethasone on days 2 and 3 (n=241); or iv) palonosetron plus dexamethasone on day 1 with prochlorperazine plus dexamethasone on days 2–3 (n=235).[46] No difference was seen between granisetron and palonosetron for controlling delayed CINV, and adding dexamethasone on days 2–3 improved the effectiveness.

### *Antiemetic refractory patients*

The antiemetic efficacy and tolerability of granisetron for CINV has also been evaluated during chemotherapy cycles in 456 patients who had failed metoclopramide, dexamethasone and ondansetron antiemetic therapy.[47] A complete response was seen in 53–60% of the patients, with antiemetic efficacy sustained throughout six successive chemotherapy cycles. Granisetron was found to be less effective with high-dose cisplatin regimens than other cytostatic regimens. An RCT in patients refractory to ondansetron plus dexamethasone following highly emetogenic chemotherapy showed there is no complete cross-resistance between 5-$HT_3$ antagonists.[48] The participants were randomised to receive granisetron 3mg plus dexamethasone 10mg (n=19) or continuation of ondansetron 8mg plus dexamethasone 10mg (n=21). Complete protection against CINV was seen in nine participants who switched to granisetron versus one who continued with the ondansetron regimen (p=0.005). The effectiveness of granisetron for preventing CINV in patients who have not responded to ondansetron has been possibly attributed to the lack of the cytochrome P450 2D6 involvement in granisetron's metabolism, meaning it is not subjected to genetic polymorphisms that could affect efficacy.[49]

### *Paediatrics*

An early trial in 88 children receiving ifosfamide showed significantly less NV with IV granisetron 20 µg/kg compared with IV chlorpromazine 0.3–0.5 mg/kg plus dexamethasone.[50] One trial comparing a single dose of granisetron with IV ondansetron infusions in 33 children with acute lymphoblastic leukaemia receiving moderately emetogenic chemotherapy showed no difference in clinical outcomes;[51] however, another study in 60 children receiving high-dose methotrexate for acute lymphoblastic leukaemia showed that oral granisetron 1mg was more effective than oral ondansetron 4mg 30 min before surgery for preventing delayed emesis.[52] There is also some limited evidence that granisetron is effective in children who are refractory to standard antiemetic therapy.[24]

## RINV, in highly and moderately emetic radiation sites

The efficacy of 5-$HT_3$ antagonists over placebo for preventing both emesis and nausea associated with RT (respective relative risks 0.70 [95% CI 0.57, 0.86] and 0.84 [0.73, 0.96]) has been established in a meta-analysis of nine trials, although only one trial investigated granisetron.[53] The efficacy of granisetron for RINV prophylaxis has been studied in patients scheduled to receive 10–30 fractions of upper abdominal RT. The trial participants were randomised to receive oral granisetron 2mg (n=134) or placebo (n=126) once daily starting 1 hour before RT.[54] Compared with placebo, granisetron was associated with a significantly longer median time to first emesis and first nausea (35 vs. 9 days and 11 vs. 1 day, respectively), and significantly greater emesis-free and nausea-free rates (57.5% vs. 42.1% and 30.6% vs. 16.7%).

A study in 30 patients receiving highly emetogenic fast-dose-rate, single-fraction TBI before bone-marrow transplantation compared granisetron with the combination of metoclopramide, dexamethasone and lorazepam for controlling RINV.[55] Compared with the combination regimen, granisetron was associated with a greater response rate at 24 hours (53% vs. 13%), significantly better control of vomiting over 24 hours and 7 days and significantly fewer doses of rescue therapy.

Oral granisetron 2mg and ondansetron 8mg administered 1 and 1.5 hours, respectively, before the same TBI regimen were compared in 90 patients scheduled for bone-marrow transplantation; a historical control group without 5-$HT_3$ antagonist therapy were also included in the analyses.[56] Compared with the respective ondansetron and control groups, granisetron was associated with a significantly greater proportion of participants with no episodes of emesis over 4 days (primary endpoint; 33.3% vs. 26.7% and 0%) and 24 hours (61.1% vs. 46.7% and 6.7%). Granisetron was similar to ondansetron and superior to the control group for complete emetic control over 4 days, and granisetron was also associated with fewer participants experiencing >5 episodes of emesis over 4 days than the control group, but not ondansetron recipients.

An Italian study enrolled 15 patients receiving RT 1.8–4.9Gy (for cancers) who were refractory to dopamine antagonists for RINV.[57] Treatment with oral granisetron 1–2 mg/day for 7–8 days, starting 1–2 hours before RT, resulted in immediate NV remission in 33% of the patients, and remission in 1–3 days in all patients.

## PONV

The available evidence favours the effectiveness of granisetron in PONV, with most studies reporting similar or better efficacy compared with other 5-$HT_3$ antagonists. One RCT randomised patients undergoing laparoscopic surgery to receive oral granisetron 1mg 1 hour before surgery (n=104) or IV ondansetron 4mg after surgery (n=105), with appropriate placebos to achieve blinding.[58] These researchers found no significant difference between the groups for the incidences of postdischarge NV, rescue antiemetic requirements and quality of recovery. Similarly, no differences were seen in PONV outcomes between patients undergoing abdominal hysterectomy randomised to receive granisetron 0.1mg plus dexamethasone 8mg (n=87) compared with those randomised to receive ondansetron 4mg plus dexamethasone 8mg (n=89).[59] However, another study in 75 adults undergoing laparoscopic cholecystectomy showed granisetron was more effective than ondansetron and metoclopramide for managing PONV.[60] In this RCT, the participants received IV granisetron 3mg, ondansetron 4mg or metoclopramide 10mg administered 5–10 minutes before induction of anaesthesia. While no difference was seen for PONV scores at 0–2 hours, granisetron was found to be more effective than both the comparators at 2–6 hours, and patient satisfaction scores favoured granisetron over the other agents at 12–24 hours, but not >24 hours.

A 2013 meta-analysis of five RCTs comparing granisetron with ondansetron for PONV prevention in patients undergoing laparoscopic cholecystectomy found that although statistical significance was not reached, there was a trend for granisetron to be more effective than ondansetron in terms of early (≤12 hours) and total incidences of PONV (34.3% vs. 42.9% and 34.2% vs. 38.7%, respectively).[61] Superiority of granisetron over ondansetron was also seen in another recent study in which 60 adults undergoing laparoscopic surgery were randomised to receive postsurgical IV granisetron 2mg or ondansetron 4mg.[62] Compared with ondansetron, granisetron was associated with a significantly greater proportion of participants with no PONV and no need for rescue antiemetic therapy (86% vs. 75%), and no significant difference in the postanaesthesia recovery times.

In contrast to patients undergoing laparoscopic procedures, oral granisetron 2mg was found to be less effective than ondansetron 4mg at controlling PONV in 90 women undergoing modified radical mastectomy, but granisetron was still superior to placebo.[63] In another RCT, 203 women undergoing thyroidectomy were randomised to receive IV granisetron 3mg, ondansetron 4mg, tropisetron 5mg or placebo at induction of anaesthesia.[64] Compared with placebo, granisetron was the most effective of the 5-$HT_3$ antagonists, with reductions in the incidences of nausea at 6–18 hours and vomiting at 6–12 hours. In contrast, ondansetron reduced NV incidence at 6 hours but not at later timepoints, and the NV incidences with tropisetron did not differ significantly from those with placebo.

A comparison of four 5-$HT_3$ antagonists has been undertaken in a meta-analysis of 85 studies (n=15,269).[65] For PONV prevention, granisetron was found to be significantly superior to ondansetron and dolasetron (respective ORs 1.53 [95% CI 1.15, 2.00] and 1.67 [1.12, 2.38]) in preventing PONV, but when only postoperative vomiting prevention was considered, the efficacy of granisetron was not significantly better than ondansetron, tropisetron and dolasetron; the ORs were ≥1.32, but all lower limits of the confidence intervals were <1.00. This meta-analysis also confirmed that these four 5-$HT_3$ antagonists were all superior to placebo for preventing PONV and postoperative vomiting.

### *Paediatrics*

There are limited data on the efficacy of granisetron for PONV in children. One study showed oral granisetron at doses 20 µg/kg and 40 µg/kg administered 20 minutes before anaesthesia induction was significantly superior to placebo in 73 children undergoing strabismus surgery.[66] The granisetron recipients had less postoperative vomiting, fewer severe vomiting episodes and were discharged earlier than placebo recipients. Postoperative vomiting outcomes did not differ significantly between the two granisetron doses.

## Safety

Granisetron has generally been well tolerated in clinical trials (refer to Table 2). Compared with ondansetron, granisetron in RCTs has been associated with lower rates of: i) dizziness and vision abnormalities;[37] ii) headache, constipation and dizziness;[62] and iii) headache, constipation, abdominal pain and loose bowel motions.[52] Srivastava et al. reported lower rates of mild constipation with granisetron than with ondansetron or metoclopramide, while headache, the only other adverse event reported with granisetron, occurred at similar incidences.[60]

# Treatment of NV and key international guidelines

There are a number of principles that need to be considered in managing NV (see below), which is improved by adherence to clinical practice guidelines.[1,4] As new antiemetic options continue to be developed, it is important for clinicians to stay up to date with changes in guidelines.[4] 5-$HT_3$ antagonists have an important role in the management of NV, particularly in treatments with moderate-to-high emetogenic potential. They are most effective in scheduled prophylactic regimens rather than as-needed, but they are not very effective for stopping pre-existing NV and have a 'ceiling dose' above which little or no antiemetic effect is seen.[1]

**General Principles for managing NV (adapted from Culverwell 2008)**[1,67]

- Prophylaxis is better than treatment of vomiting
- Antiemetic regimens should be individualised for each patient
- Consider switch to as-needed therapy if no nausea for 24 hours
- Titrate dose to patient tolerance
- Combination regimens provide optimum control
- Avoid agents from same pharmacological category
- For CINV, effective prophylaxis during first chemotherapy cycle can minimise anticipatory NV
- If it's not broken, don't fix it!
- Oral administration, with adequate time for absorption before chemotherapy, is preferred for prevention of emesis

There is general consensus from international guidelines on the role of granisetron in CINV. The MASCC/ESMO (Multinational Association of Supportive Care in Cancer and European Society of Clinical Oncology; see Table 4), NCCN (National Comprehensive Cancer Network) and ASCO (American Society of Clinical Oncology) guidelines are consistent with each other and other international guidelines (e.g. UK NHS, which uses slightly different emetogenic potential classifications) with respect to 5-$HT_3$ antagonist use, and are the basis for the guidelines of many other organisations (e.g. Boston Medical Center).[3,29,68–70] As many anticancer regimens include multiple chemotherapeutic agents with or without RT, the appropriate antiemetic treatment option should be that which applies to treatment with the greatest emetic risk.

**Table 4. MASCC/ESMO guidelines for CINV and RINV according to emetogenic potential**[5,29]

| **High emetogenic potential** | |
|---|---|
| **CINV** | **RINV** |
| **Acute NV**<br>A 3-drug regimen of single doses of a 5-$HT_3$ antagonist, dexamethasone and an NK1 antagonist<br>Paediatric: 5-$HT_3$ antagonist plus dexamethasone<br>**Delayed NV**<br>Patients receiving cisplatin treated with a combination of an NK1 antagonist, a 5-$HT_3$ antagonist and dexamethasone to prevent acute NV: dexamethasone plus aprepitant or dexamethasone alone on days 2–3 if fosaprepitant is used on day 1<br>Paediatric* | 5-$HT_3$ antagonist (e.g. granisetron 2mg oral or 0.01 mg/kg IV) plus dexamethasone |
| **Moderate emetogenic potential** | |
| **Acute NV**<br>Palonosetron plus dexamethasone<br>Patients (particularly women with breast cancer) receiving an anthracycline plus cyclophosphamide: a 3-drug regimen of single doses of a 5-$HT_3$ antagonist, dexamethasone and an NK1 inhibitor administered before chemotherapy<br>Paediatric: 5-$HT_3$ antagonist plus dexamethasone<br>**Delayed NV**<br>Multiple day oral dexamethasone<br>Patients receiving anthracycline + cyclophosphamide: aprepitant or none if fosaprepitant is used on day 1<br>Paediatric* | 5-$HT_3$ antagonist with optional dexamethasone |
| **Low emetogenic potential** | |
| **Acute NV**<br>Single antiemetic agent such as dexamethasone or a 5-$HT_3$ or dopamine receptor antagonist<br>Paediatric*<br>**Delayed NV**<br>None | Prophylactic or rescue with 5-$HT_3$ antagonist |
| **Minimal emetogenic potential** | |
| **Acute NV**<br>None in patients with no NV history<br>Paediatric*<br>**Delayed NV**<br>None | Rescue with 5-$HT_3$ or dopamine antagonist |
| **Multiple-day cisplatin** | |
| 5-$HT_3$ antagonist plus dexamethasone for acute CINV and dexamethasone for delayed CINV | N/A |
| **Cisplatin given on days 1–5** | |
| Consider adding an NK1 receptor antagonist starting no later that day 3 | N/A |
| **Anticipatory NV** | |
| Treat as for acute and delayed NV and consider behavioural therapies<br>Benzodiazepines can decrease occurrence, but efficacy decreases as chemotherapy treatment continues | N/A |
| ***no data – treat as for adults with appropriate dose adjustments** | |

The recommendations for antiemetics in CINV and RINV in the Perugia Consensus Conference on Antiemetic Therapy, published in June 2009, are largely consistent with these guidelines.[71] They state that 5-$HT_3$ antagonists combined with corticosteroids should be considered the standard of care in CINV, and that the levels of consensus and confidence are both 'high' for their use in RINV. The route of administration of these agents was also discussed in detail, with the conclusion that provided that the patient has an intact GI tract and is compliant with treatment, oral administration of granisetron is equally as efficacious as IV injections.

While guidelines sometimes recommend a specific 5-$HT_3$ antagonist, often the recommendation is for 'a 5-$HT_3$ antagonist'. In such cases, the choice of agent should consider factors such as patient age group (and evidence strength for that age group), duration of action, previous therapy, patient preference, cost and funding criteria.

The cost of Granirex under the current Pharmac schedule is $5.98 per 50 tablets, while the cost of ondansetron for a comparable dose for use in NV (8mg) is $6.19 per 50 tablets.[13]

### *Multiple day chemotherapy regimens*

Managing CINV in patients receiving multiple day chemotherapy is complicated by the potential for acute and delayed NV to overlap. International guidelines recommend antiemetic therapy according to the emetic potential of the chemotherapeutic agent each day it is administered and 2 days afterward if appropriate; the option of transdermal granisetron patches (where available) is also offered to these patients rather than daily 5-$HT_3$ antagonist therapy.[68]

### *PONV*

The consensus guidelines for the management of PONV by the Society for Ambulatory Anesthesiology give IV granisetron 0.35–3mg administered at the end of surgery an A1 evidence rating for the prevention of PONV in adults at moderate risk.[72] The guidelines also note that granisetron in combination with dexamethasone or cyclizine is better than monotherapy in this setting. For adults at high risk of PONV, a 5-$HT_3$ antagonist combined with dexamethasone or droperidol is recommended with an A1 evidence rating. Ondansetron is the preferred 5-$HT_3$ antagonist for preventing PONV and postoperative vomiting in children. Low-dose 5-$HT_3$ antagonist therapy is recommended to treat patients who develop PONV, unless it has been given prophylactically preoperatively, in which case an antiemetic from another class should be chosen.

## Treatment in NZ

Although in NZ Granirex is indicated for the prevention of acute and delayed NV associated with cytostatic therapy in adults, injectable granisetron (granisetron-AFT) is indicated in adults for the treatment (as well as prevention) of CINV and the prevention of RINV and PONV, and for the treatment and prevention of CINV in children.[15,73] Antiemetic guidelines in NZ are generally in line with international guidelines, but are often limited in their choice of agents, with ondansetron usually the 5-$HT_3$ antagonist of choice, likely due to it being the only oral agent from this class funded by Pharmac prior to Nov 1, 2014.[13,67,74,75] However, the guidelines do consider alternative agents; e.g. the Canterbury DHB Oncology Department guidelines recommend considering an alternative 5-$HT_3$ antagonist if significant acute CINV does not respond to first-line treatment.[67] The recommended doses and costs for 5-$HT_3$ antagonists available in NZ are presented in table 5.

**With the funding of granisetron in NZ, clinicians now have another option in their armamentarium for the management of CINV and RINV.** Granisetron's role in PONV is not yet established in NZ.

**Table 5. Antiemetic doses and costs for 5-$HT_3$ antagonists in NZ**[13,29]

| Drug | Dose | Funded cost (NZ$) |
|---|---|---|
| Granisetron | Oral: 1–2mg<br>IV: 1mg or 0.01mg/kg | 5.98 per 50×1mg tablet |
| Ondansetron | Oral: 16mg<br>IV: 8mg or 0.15mg/kg | 6.19 per 50×8mg tablet<br>5.51 per 50×4mg tablet |
| Tropisetron | Oral: 5mg<br>IV: 5mg | 8.95 per 2mL ampoule (1 mg/mL)<br>13.95 per 5mL ampoule (1 mg/mL) |
| Palonosetron | IV: 0.25mg | (not funded) |

## Concluding remarks and key points

Granisetron is one of several 5-$HT_3$ antagonists that have been proven in RCTs to be remarkably effective for the prophylactic and rescue use of NV associated with chemotherapy, radiotherapy and surgery. The 5-$HT_3$ receptor antagonists are the most effective drugs for managing CINV, and RCTs have shown that all 5-$HT_3$ antagonists are of equal efficacy. Guidelines support their routine prophylactic use for high and medium emetogenic chemotherapy regimens. RINV is usually less frequent and severe compared with chemotherapy; nevertheless, it can be a significant and distressing side effect. The prophylactic use of 5-$HT_3$ antagonists is recommended for patients having RT to sites where there is a moderate-to-high risk of NV and can be used effectively for rescue of NV from RT to lower risk treatment sites. Studies show that all 5-$HT_3$ antagonists are effective when used prophylactically or for the rescue of PONV. Granisetron is well tolerated; the most frequently reported adverse event is headache, with constipation, dizziness, asthenia and somnolence being less commonly reported. Several studies suggest that some of these side effects are less common compared with the other 5-$HT_3$ antagonists. The funding of Granirex means that clinicians now have access to another option for the management of CINV and RINV.

## References


1. Culverwell E. Nausea and vomiting during chemotherapy – a literature review. Intravenous Nursing New Zealand Newsletter, June 2008. Available from http://www.ivnnz.co.nz/newsletter/Articles/Other-issues/Nausea-and-Vomitting-during-Chemotherapy
2. Dennis K et al. Radiotherapy-induced nausea and vomiting. Expert Rev Pharmacoeconomics Outcomes Res 2011;11(6):685–92
3. Ettinger DS et al. Antiemesis. J Natl Compr Canc Netw 2012;10(4):456–85
4. Morrow GR et al. Clinical roundtable monograph: New data in emerging treatment options for chemotherapy-induced nausea and vomiting. Clin Adv Hematol Oncol 2014;12(3 Suppl 9):1–14
5. Feyer P et al. Radiation induced nausea and vomiting. Eur J Pharmacol 2014;722:165–71
6. Maranzano E et al., on behalf of The Italian Group for Antiemetic Research in Radiotherapy – IGARR. A prospective observational trial on emesis in radiotherapy: Analysis of 1020 patients recruited in 45 Italian radiation oncology centres. Radiother Oncol 2010;94(1):36–41
7. Feyer PC et al. Radiotherapy-induced nausea and vomiting (RINV): MASCC/ESMO guideline for antiemetics in radiotherapy: update 2009. Support Care Cancer 2011;19(Suppl 1):S5–14
8. Enblom A et al. One third of patients with radiotherapy-induced nausea consider their antiemetic treatment insufficient. Support Care Cancer 2009;17(1):23–32
9. Kovac AL. Update on the management of postoperative nausea and vomiting. Drugs 2013;73(14):1525–47
10. Gan TJ. Risk factors for postoperative nausea and vomiting. Anesth Analg 2006;102(6):1884–98
11. Dennis K et al. International patterns of practice in the management of radiation therapy-induced nausea and vomiting. Int J Radiat Oncol Biol Phys 2012;84(1):e49–60
12. Molassiotis A et al. Evaluation of risk factors predicting chemotherapy-related nausea and vomiting: results from a European prospective observational study. Pain Symptom Manage 2014;47(5):839–48
13. Pharmac NZ. Pharmaceutical schedule, Nov 2014;2(2). Available from http://www.pharmac.govt.nz/2014/11/01/HML.pdf
14. Aapro M. Granisetron: an update on its clinical use in the management of nausea and vomiting. The Oncologist 2004;9(6):673–86
15. Medsafe NZ. Granirex New Zealand data sheet. May 2014. Available from http://www.medsafe.govt.nz/profs/Datasheet/g/granirextab.pdf
16. Hoffmann-La Roche Limited. Kytril® (granisetron hydrochloride tablets) product monograph. June 2014
17. Tan M. Granisetron: new insights into its use for the treatment of chemotherapy-induced nausea and vomiting. Expert Opin Pharmacother 2003;4(9):1563–71
18. Rojas C & Slusher BS. Pharmacological mechanisms of 5-HT3 and tachykinin NK1 receptor antagonism to prevent chemotherapy-induced nausea and vomiting. Eur J Pharmacol 2012;684:1–7
19. Aapro MS. Review of experience with ondansetron and granisetron. Ann Oncol 1993;4(suppl 3):S9–14
20. Blower P & Aapro M. Granisetron vs. ondansetron: is it a question of duration of 5-HT3 receptor blockade? Br J Cancer 2002;86(10):1661–4
21. Upward JW et al. The clinical pharmacology of granisetron (BRL 43694), a novel specific 5-HT3 antagonist. Eur J Cancer 1990;26(Suppl 1):S12–5
22. Newberry NR et al. BRL 46470 potently antagonizes neural responses activated by 5-HT3 receptors. Neuropharmacology 1993;32(8):729–35
23. Medsafe. Medicine: data sheets. Available from http://www.medsafe.govt.nz/profs/Datasheet/DSForm.asp
24. Palmer R. Efficacy and safety of granisetron (Kytril) in two special patient populations: children and adults with impaired hepatic function. Semin Oncol 1994;21(suppl 5):22–5
25. Jordan K et al. A meta-analysis comparing the efficacy of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis. Support Care Cancer 2007;15(9):1023–33
26. Tsuji D et al. Comparative trial of two intravenous doses of granisetron (1 versus 3 mg) in the prevention of chemotherapy-induced acute emesis: a double-blind, randomized, non-inferiority trial. Support Care Cancer 2012;20(5):1057–64
27. Celio L et al. Safety, efficacy, and patient acceptability of single-dose fosaprepitant regimen for the prevention of chemotherapy-induced nausea and vomiting. Patient Prefer Adherence 2013:7(7):391–400
28. dos Santos LV et al. Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review. J Natl Cancer Inst 2012;104(17):1280–92
29. Multinational Association of Supportive Care in Cancer. MASCC/ESMO antiemetic guideline 2013. Available from http://www.mascc.org/assets/Guidelines-Tools/mascc_guidlines_english_2014.pdf
30. Feyer P. The importance of simple, easy-to-follow antiemetic guidelines. Acta Oncol 2004;43(Suppl 15):5–8
31. Feyer P et al. Radiotherapy-induced nausea and vomiting (RINV): antiemetic guidelines. Support Care Cancer 2005;13(2):122–8
32. Grunberg SM et al. Emerging treatments in chemotherapy-induced nausea and vomiting. Clin Adv Hematol Oncol 2013;11(2 Suppl 1):1–18
33. Dempsey CL et al. Antiemetic effectiveness of ondansetron and granisetron in patients with breast cancer treated with cyclophosphamide. Am J Health Syst Pharm 2004;61(8):781–6
34. Fox-Geiman MP et al. Double-blind comparative trial of oral ondansetron versus oral granisetron versus IV ondansetron in the prevention of nausea and vomiting associated with highly emetogenic preparative regimens prior to stem cell transplantation. Biol Blood Marrow Transplant 2001;7(11):596–603
35. Gralla RJ et al. Single-dose oral granisetron has equivalent antiemetic efficacy to intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. J Clin Oncol 1998;16(4):1568–73
36. Herrington JD et al. Randomized, multicentre comparison of oral granisetron and oral ondansetron for emetogenic chemotherapy. Pharmacotherapy 2000;20(11):1318–23
37. Perez EA et al. Comparison of single-dose oral granisetron versus intravenous ondansetron in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy: a multicentre, double-blind, randomized parallel study. J Clin Oncol 1998;16(2):754–60
38. Walsh T et al. Granisetron vs. ondansetron for prevention of nausea and vomiting in hematopoietic stem cell transplant patients: results of a prospective, double-blind, randomized trial. Bone Marrow Transplant 2004;34(11):963–8
39. Numbenjapon T et al. Comparative study of low-dose oral granisetron plus dexamethasone and high-dose metoclopramide plus dexamethasone in prevention of nausea and vomiting induced by CHOP-therapy in young patients with non-Hodgkin's lymphoma. J Med Assoc Thai 2002;85(11):1156-63
40. Heron JF et al. Oral granisetron alone and in combination with dexamethasone: a double-blind randomized comparison against high-dose metoclopramide plus dexamethasone in prevention of cisplatin-induced emesis. The Granisetron Study Group. Ann Oncol 1994;5(7):579–4
41. Aapro MS et al., Swiss Group for Clinical Cancer Research. A randomized double-blind trial to compare the clinical efficacy of granisetron with metoclopramide, both combined with dexamethasone in the prophylaxis of chemotherapy-induced delayed emesis. Ann Oncol 2003;14(2):291–7
42. Gebbia V et al. Oral granisetron with or without methylprednisolone versus metoclopramide plus methylprednisolone in the management of delayed nausea and vomiting induced by cisplatin-based chemotherapy. A prospective randomized trial. Cancer 1995;15;76(10):1821–8
43. Burris H et al. Efficacy and safety of oral granisetron versus oral prochlorperazine in preventing nausea and emesis in patients receiving moderately emetogenic chemotherapy. Cancer J Sci Am 1996;2(2):85–90
44. Friedman CJ et al. Oral granisetron for the prevention of acute late onset nausea and vomiting in patients treated with moderately emetogenic chemotherapy. Oncologist 2000;5(2):136–43
45. Jordan K et al. Granisetron versus tropisetron for prophylaxis of acute chemotherapy-induced emesis: a pooled analysis. Support Care Cancer 2005;13(1):26–31
46. Roscoe JA et al. Prevention of delayed nausea: a University of Rochester Cancer Center Community Clinical Oncology Program study of patients receiving chemotherapy. J Clin Oncol 2012;30(27):3389–95
47. Carmichael J et al. Use of granisetron in patients refractory to previous treatment with antiemetics. Anticancer Drugs 1998;9(5):381–5
48. de Wit R et al. Effective cross-over to granisetron after failure to ondansetron, a randomized double blind study in patients failing ondansetron plus dexamethasone during the first 24 hours following highly emetogenic chemotherapy. Br J Cancer 2001;85(8):1099–101
49. de Wit R. Current position of 5HT3 antagonists and the additional value of NK1 antagonists; a new class of antiemetics. Br J Cancer 2003;88(12):1823–7
50. Hahlen K et al. A randomized comparison of intravenously administered granisetron versus chlorpromazine plus dexamethasone in the prevention of ifosfamide-induced emesis in children. J Pediatr 1995;126(2):309–13
51. Jaing TH et al. Single-dose oral granisetron versus multidose intravenous ondansetron for moderately emetogenic cyclophosphamide-based chemotherapy in pediatric outpatients with acute lymphoblastic leukemia. Pediatr Hematol Oncol 2004;21(3):227–35
52. Siddique R et al. Ondansetron versus granisetron in the prevention of chemotherapy induced nausea and vomiting in children with acute lymphoblastic leukemia. Mymensingh Med J 2011;20(4):680–8
53. Salvo N et al. Prophylaxis of radiation-induced nausea and vomiting using 5-hydroxytryptamine-3 serotonin receptor antagonists: a systematic review of randomized trials. Int J Radiat Oncol Biol Phys 2012;82(1):408–17
54. Lanciano R et al. The efficacy and safety of once-daily Kytril (granisetron hydrochloride) tablets in the prophylaxis of nausea and emesis following fractionated upper abdominal radiotherapy. Cancer Invest 2001;19(8):763–772.
55. Prentice HG et al. 1995.Granisetron in the prevention of irradiation-induced emesis. Bone Marrow Transplant 1995;15(3):445–8
56. Spitzer TR et al. Double-blind, randomized, parallel-group study on the efficacy and safety of oral granisetron and oral ondansetron in the prophylaxis of nausea and vomiting in patients receiving hyperfractionated total body irradiation. Bone Marrow Transplant 2000;26(2):203–10
57. Krengli M et al. [The use of granisetron per os in radiotherapy-induced emesis.] Minerva Med 1996;87(12):605–8 *[Italian; abstract in English]*
58. White PF et al. The use of oral granisetron versus intravenous ondansetron for antiemetic prophylaxis in patients undergoing laparoscopic surgery: the effect on emetic symptoms and quality of recovery. Anesth Analg 2006;102(5):1387–93
59. Gan TJ et al. A randomized, double-blind study of granisetron plus dexamethasone versus ondansetron plus dexamethasone to prevent postoperative nausea and vomiting in patients undergoing abdominal hysterectomy. Anesth Analg 2005;101(5):1323–9
60. Srivastava B et al. Antiemetic prophylaxis with granisetron, ondansetron and metoclopramide in laparoscopic cholecystectomy: a comparison. J Adv Res Biol Sci 2012;4(4):279–87
61. Wu S-J et al. Comparison of the efficacy of ondansetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy: a systematic review and meta-analysis. Surg Laparosc Endosc Percutan Tech 2013;23(1):79–87
62. Chidambaram A et al. A comparative study of ondansetron and granisetron for prevention of nausea and vomiting following laparoscopic surgeries. Internet J Anesthesiol 2010;29:1
63. Bhatnagar S et al. Preemptive antiemesis in patients undergoing modified radical mastectomy: oral granisetron versus oral ondansetron in a double-blind, randomized, controlled study. J Clin Anesth 2007;19(7):512–6
64. Metaxari M et al. Antiemetic prophylaxis in thyroid surgery: a randomized, double-blind comparison of three 5-HT3 agents. J Anesth 2011;25(3):356–62
65. Tang DH & Malone DC. A network meta-analysis on the efficacy of serotonin type 3 receptor antagonists used in adults during the first 24 hours for postoperative nausea and vomiting prophylaxis. Clin Ther 2012;34(2):282–94
66. Munro HM et al. Oral granisetron for strabismus surgery in children. Can J Anaesth 1999;46(1):45–8
67. Canterbury District Health Board – Oncology Department. Antiemetic guidelines for chemotherapy and radiation therapy. June 2012. Available from https://www.cdhb.health.nz/Hospitals-Services/Cancer-Blood-Services/Cytotoxic-Biotherapy/Documents/Oncology%20Antiemetic%20Policy.pdf
68. Basch E et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2011;29(31):4189–98
69. Avon, Somerset and Wiltshire NHS Cancer Services. ASWCS antiemetic guidelines for adult patients receiving chemotherapy and radiotherapy. Feb 2012. Available from http://www.avon.nhs.uk/aswcs-chemo/NetworkPolicies/ASWCSAntiemeticPolicyFinal_amended120517.pdf
70. Boston Medical Center. Clinical coverage guidelines – antiemetics: policy number 9.104. Jul 2013. Available from http://www.bmchp.org/app_assets/antiemetics_20130626t120717_en_web_7d1a22f5a5a0434fbcb19a330a2770d4.pdf
71. Gralla RJ et al. Perugia consensus conference on antiemetic therapy – June 2009. Springer Books
72. Gan TJ et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014;118(1):85–113
73. Medsafe NZ. Granisetron-AFT New Zealand data sheet. May 2014. Available from http://www.medsafe.govt.nz/profs/Datasheet/g/granisetron-AFTinj.pdf
74. West Coast District Health Board. Anti-emetic guidelines for chemotherapy patients (controlled document). Available from http://www.westcoastdhb.org.nz/publications/policies_n_procedures/policies_n_procedures_docs/nursing/cytotoxic/Anti-Emetic%20Guidelines%20For%20Chemotherapy%20Patients.pdf
75. Starship & National Child Cancer Network. National guidelines - paediatric oncology and haematology – nausea and vomiting. Available from https://www.starship.org.nz/for-health-professionals/national-guidelines-paediatric-oncology-and-haematology/n/nausea-and-vomiting/


This publication has been created with an educational grant from REX Medical Ltd.

The content is entirely independent and based on published studies and the authors' opinions. It may not reflect the views of REX Medical Ltd. Please consult the full Data Sheet at www.medsafe.govt.nz before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician.