National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Pain

Date: 15 October 2015

Medication: Ondansetron lyophilisate formulation.

Indication: Prevention of vomiting, in patients unable to tolerate oral preparations.

Final Question: How does the efficacy of an orally-disintegrating ondansetron tablet compare with a conventional oral ondansetron tablet in the prevention of chemotherapy-induced vomiting as an outpatient treatment in patients undergoing emetogenic chemotherapy?

P: patients undergoing emetogenic chemotherapy
I: orally-disintegrating ondansetron tablet
C: conventional oral ondansetron tablet
O: chemotherapy-induced vomiting

Evidence-based Answer: An orally-disintegrating ondansetron tablet provides similar efficacy as compared to a conventional oral ondansetron tablet in the prevention of chemotherapy-induced vomiting. Therefore, either formulation can be considered for an effective anti-emetic treatment on an outpatient basis for patients undergoing emetogenic chemotherapy. (Strength of Recommendation= B, based on two limited-quality controlled trials with patient-oriented evidence, an anti-emesis guideline and a guideline update).

Evidence Summary:

A randomized, multicenter, double-blind controlled trial was performed among 427 cancer patients receiving cyclophosphamide chemotherapy.[1] The study compared the anti-emetic efficacy and safety of orally-disintegrating tablet (ODT) with the conventional oral ondansetron tablet (OT). Patients were randomly assigned to receive 8 mg of an orally-disintegrating ondansetron tablet twice daily (ODT, n=215) or 8 mg of the conventional oral ondansetron tablet (OT, n=212) twice daily, for 3 days. In total, 78% (167/215) of patients in the ODT group achieved complete or major control of emesis on days one through three of chemotherapy, defined as less than two emetic episodes and no rescue medications, compared to 80% (169/212) of patients in the OT group (90% CI -8.6% to 4.4%). The 90% CI was within the predetermined
-15% to 15% interval and therefore, no significant difference was found between the two groups and ODT was determined to be equivalent to OT in controlling emetic episodes. A limitation of this study may be the alternate cytotoxic agents patients were

receiving while enrolled in the trial, which may have altered the emetic risk category of the chemotherapy regimens.

A randomized, controlled, phase two trial was performed among 134 breast cancer patients receiving high-dose epirubicin.[2] The study compared the efficacy and safety of the novel orally-disintegrating tablet of ondansetron (ODT) and the conventional oral ondansetron tablet (OT) in chemotherapy-induced nausea and vomiting. Patients were randomly assigned to receive 8 mg ODT twice daily (n=66) or 8 mg OT twice daily (n=68), for 3 days. In total, 46 patients (70%) in the ODT group achieved complete or major control of emesis over the three day period, defined as zero to two emetic episodes and no rescue medications, compared to 52 patients (76%) in the OT group (p=0.28). A statistically significant difference was observed in the rate of complete emesis control (no emetic episodes and no rescue medications) for days one through three of chemotherapy, with 34 patients (52%) in the ODT group having no emetic episodes compared to 49 patients (72%) in the OT group (p=0.02). Limitations of this study may include lack of blinding, as well as subjective reporting of emetic episodes through the use of diary cards.

Recommendations from others:

The National Comprehensive Cancer Network (NCCN) published evidence driven guidelines for the management of emesis control in cancer patients.[3] Recommendations made in these guidelines are based on the NCCN Categories of Evidence and Consensus (Categories 1, 2A, 2B, 3; based on level of evidence and overall NCCN consensus on appropriateness of the intervention). The guidelines recommend the use of ondansetron in anti-emetic therapy because it has shown to be effective in reducing nausea and vomiting resulting from chemotherapy. However, the use of orally-disintegrating ondansetron tablet compared to the conventional oral ondansetron tablet is not discussed in these guidelines.

In 2011, the American Society of Clinical Oncology (ASCO) published an update to the 2006 ASCO antiemetics guidelines in oncology.[4] This update was evidence driven and based on a systematic review of the current oncology literature to evaluate newly added therapies. The guideline update states that the orally disintegrating ondansetron tablet is equivalent to the standard oral ondansetron tablet in controlling both emesis and nausea resulting from chemotherapy.

References:

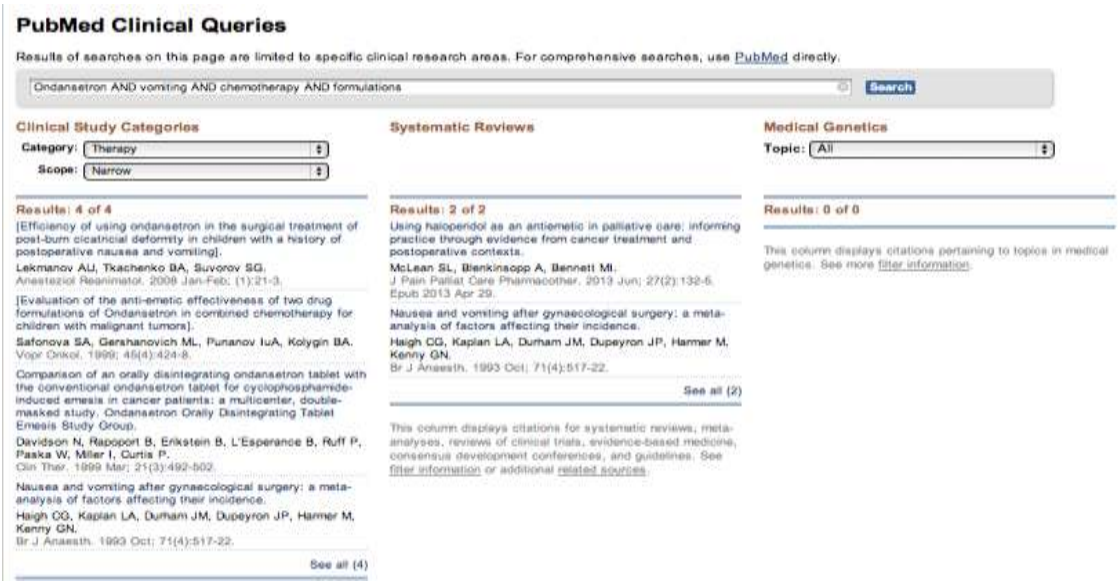
1. Davidson N, Rapoport B, Erikstein B, et al. Comparison of an orally disintegrating ondansetron tablet with the conventional ondansetron tablet for cyclophosphamide-induced emesis in cancer patients: a multicenter, double-masked study. *Clin Ther.* 1999;21(3):492-502.
2. Pectasides D, Dafni U, Aravantinos G, et al. A randomized trial to compare the efficacy and safety of antiemetic treatment with ondansetron and ondansetron zydis

in patients with breast cancer treated with high-dose epirubicin. *Anticancer Res.* 2007;27(6C):4411-4417.
3. Ettinger DS, Armstrong DK, Barbour S, et al. Antiemesis. *J Natl Compr Canc Netw.* 2012;10(4):456-485.
4. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2011;29(31):4189-4198.

Search Strategy:

Please note: The search strategy included additional clinical studies, but were not included as references in the Evidence Summary because they did not address the specific question for this clinical inquiry.

PubMed:



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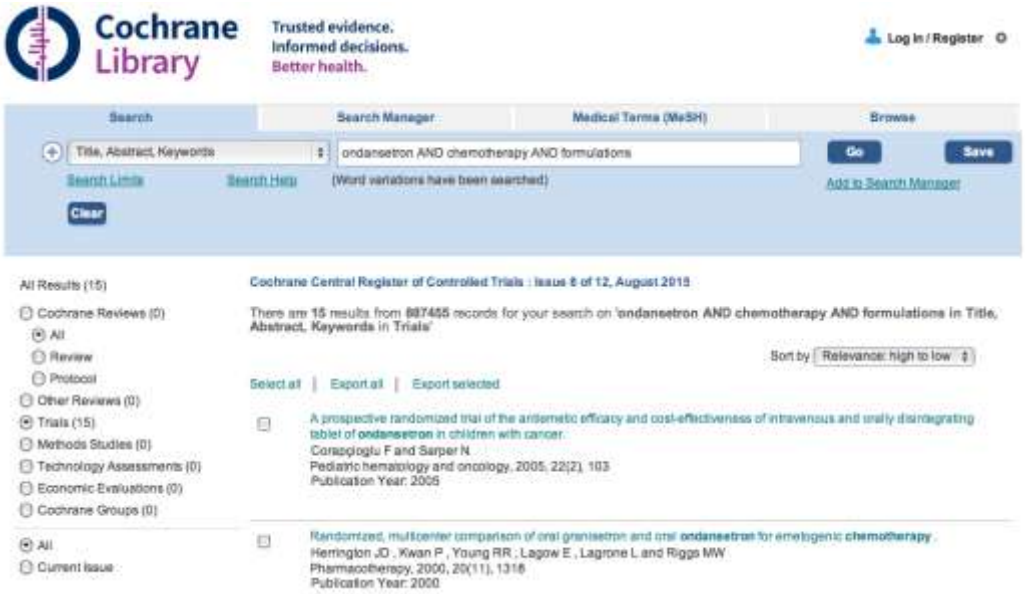
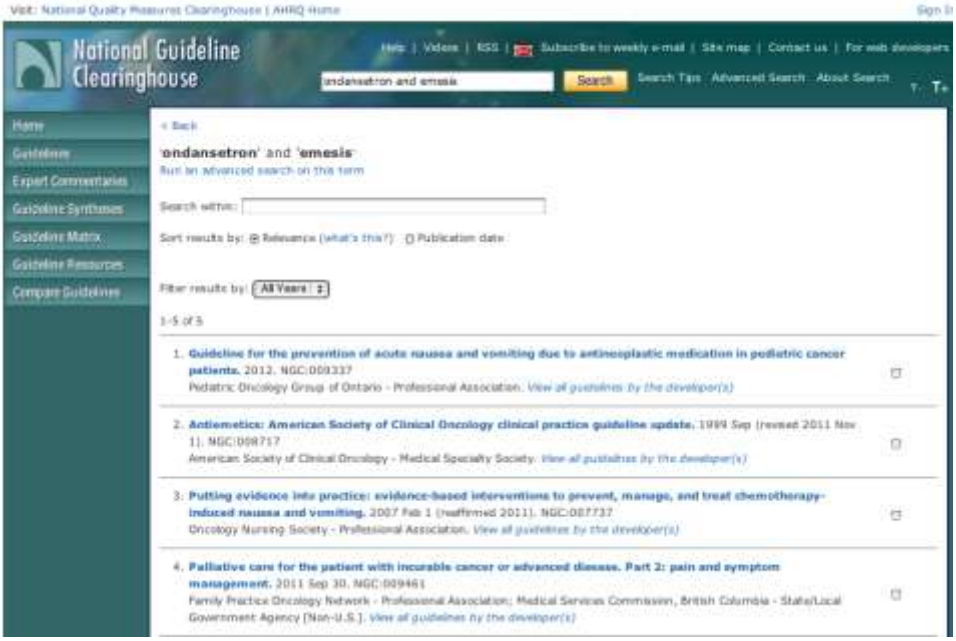
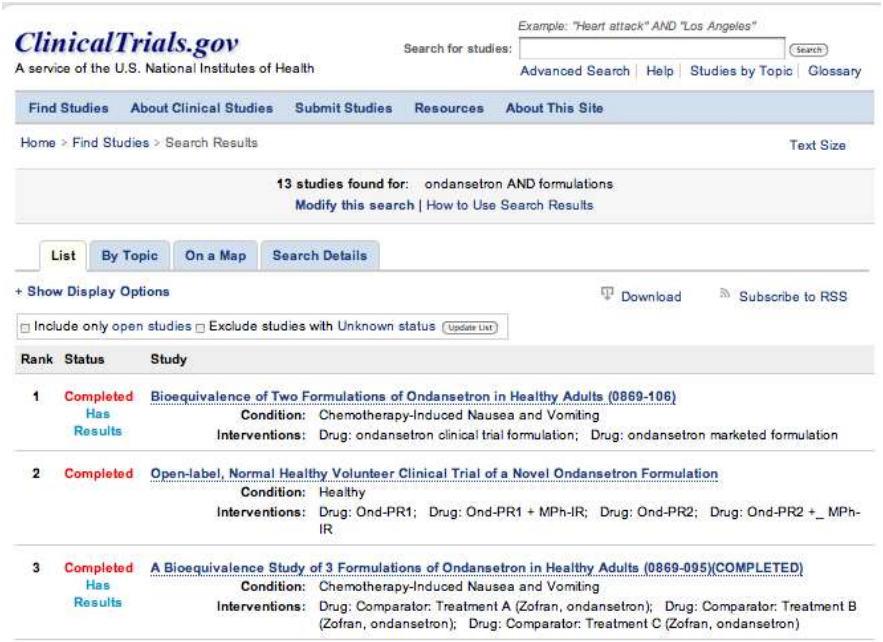


Guidelines:



Clinical Trials:



Abstracts:

1. Davidson N, Rapoport B, Erikstein B, et al. Comparison of an orally disintegrating ondansetron tablet with the conventional ondansetron tablet for cyclophosphamide-induced emesis in cancer patients: a multicenter, double-masked study. *Clin Ther.* 1999;21(3):492-502.

A total of 427 cancer patients receiving cyclophosphamide chemotherapy participated in this multicenter, double-masked, double-dummy, parallel-group, randomized study comparing the antiemetic efficacy and safety of an 8-mg conventional ondansetron tablet (OT, n = 212) taken twice daily with an 8-mg orally disintegrating ondansetron tablet (ODT, n = 215) taken twice daily for 3 days. In the primary efficacy analysis, complete or major control of emesis (0 to 2 emetic episodes) between days 1 and 3 was seen in 80% of OT and 78% of ODT patients. The 90% confidence interval for the differences between treatments was -8.6% to 4.4% (defined interval of equivalence, +/-15%), showing that the formulations were equivalent. In the secondary efficacy analysis, no significant differences were observed in the rates of complete control of emesis (no episodes of emesis) over 3 days (63% and 64% of the respective groups) and on day 1 (84% and 81%, respectively) and in the complete control of nausea over 3 days (37% and 43%, respectively) and on day 1 (59% and 61% of patients, respectively). The taste of ODT was acceptable to the majority of patients (89%) who received it. OT and ODT were both well tolerated. Thus 8 mg ODT twice daily represents a palatable, well-tolerated, and effective antiemetic treatment for the control of cyclophosphamide-induced emesis and nausea and provides equivalent treatment to OT 8 mg twice daily.

2. Pectasides D, Dafni U, Aravantinos G, et al. A randomized trial to compare the efficacy

and safety of antiemetic treatment with ondansetron and ondansetron zydis in patients with breast cancer treated with high-dose epirubicin. *Anticancer Res.* 2007;27(6C):4411-4417.

Objective: The objective of this study was to compare the efficacy of a disintegrating tablet of ondansetron (ODT) and the conventional tablet formulation of ondansetron (OT) in controlling nausea and vomiting in breast cancer patients. Patients and Methods: A total of 134 breast cancer patients receiving high dose epirubicin participated in a randomized trial comparing the antiemetic efficacy and safety of an 8 mg OT given twice daily to an 8 mg orally ODT given twice daily, both for 3 days. Results: OT was significantly better in the complete control of emesis (72% versus 52%, p=0.020) and marginally better in the complete control of nausea (66% versus 48%, p=0.054) induced by high-dose epirubicin over days 1-3 compared to ODT. However, no differences were found in major control of emesis (0 to 2 emetic episodes, 76% versus 70%, p=0.28) over days 1-3. Conclusion: OT was significantly better in the complete control of emesis and marginally better in the complete control of nausea, but not in the major control of emesis and nausea induced by high-dose epirubicin compared to ODT. ODT may be an effective alternative to OT, particularly in patients who have difficulties in swallowing a conventional tablet.

3. Ettinger DS, Armstrong DK, Barbour S, et al. Antiemesis. *J Natl Compr Canc Netw.* 2012;10(4):456-485.

No abstract available.

4. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2011;29(31):4189-4198.

Purpose: To update the American Society of Clinical Oncology (ASCO) guideline for antiemetics in oncology. Methods: A systematic review of the medical literature was completed to inform this update. MEDLINE, the Cochrane Collaboration Library, and meeting materials from ASCO and the Multinational Association for Supportive Care in Cancer were all searched. Primary outcomes of interest were complete response and rates of any vomiting or nausea. Results: Thirty-seven trials met prespecified inclusion and exclusion criteria for this systematic review. Two systematic reviews from the Cochrane Collaboration were identified; one surveyed the pediatric literature. The other compared the relative efficacy of the 5-hydroxytryptamine-3 (5-HT3) receptor antagonists. Recommendations: Combined anthracycline and cyclophosphamide regimens were reclassified as highly emetic. Patients who receive this combination or any highly emetic agents should receive a 5-HT3 receptor antagonist, dexamethasone, and a neurokinin 1 (NK1) receptor antagonist. A large trial validated the equivalency of fosaprepitant, a single-day intravenous formulation, with aprepitant; either therapy is appropriate. Preferential use of palonosetron is recommended for moderate emetic risk regimens, combined with dexamethasone. For low-risk agents, patients can be offered

dexamethasone before the first dose of chemotherapy. Patients undergoing high emetic risk radiation therapy should receive a 5-HT3 receptor antagonist before each fraction and for 24 hours after treatment and may receive a 5-day course of dexamethasone during fractions 1 to 5. The Update Committee noted the importance of continued symptom monitoring throughout therapy. Clinicians underestimate the incidence of nausea, which is not as well controlled as emesis.