# Drug Class Review

# Newer Antiemetics

**Final Report Update 1**

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DRUG EFFECTIVENESS REVIEW PROJECT

Drug Effectiveness Review Project
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# Inclusion criteria

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- **Populations**
  - Adults and children at risk for or with nausea and/or vomiting related to surgery, chemotherapy, radiation therapy, or pregnancy
- **Interventions**
  - Aprepitant (Emend®, oral)
  - Dolasetron (Anzemet®, intravenous or oral)
  - Fosaprepitant (Emend®, intravenous)
  - Granisetron (Kytril®, intravenous or oral)
  - Ondansetron (Zofran®, intravenous or oral)
  - Palonosetron (Aloxi®, intravenous or oral)

# Inclusion criteria

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- **Efficacy outcomes**
  - Prevention/reduction of emetic events (nausea, vomiting and/or retching)
    - Proportion of patients who had no symptoms
    - Change in mean number of emetic episodes
    - Change in severity of symptoms
    - Number of days without emesis
    - Delay in onset of emetic events
    - Use of rescue medication
    - Incidence of serious complications secondary to emesis
  - Satisfaction/quality of life
  - Resource utilization

# Inclusion criteria

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- **Safety outcomes**
  - Adverse events overall
  - Withdrawals due to adverse events
  - Serious adverse events
  - Specific adverse events (headache, constipation, dizziness, sedation, etc.)
- **Study designs**
  - For effectiveness or efficacy: Controlled clinical trials and good-quality systematic reviews
  - For adverse effects: Controlled clinical trials and observational studies

# Search strategy

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- Bibliographic databases
  - End date: October 2008
  - Sources: Cochrane Library (CCRCT, CDSR, DARE), Medline
- Pharmaceutical company submissions
  - Original report: Aprepitant, dolasetron, ondansetron
  - Update #1: Aprepitant, dolasetron, palonosetron
- Reference lists
- FDA reviews (drugs@fda)

# Search results

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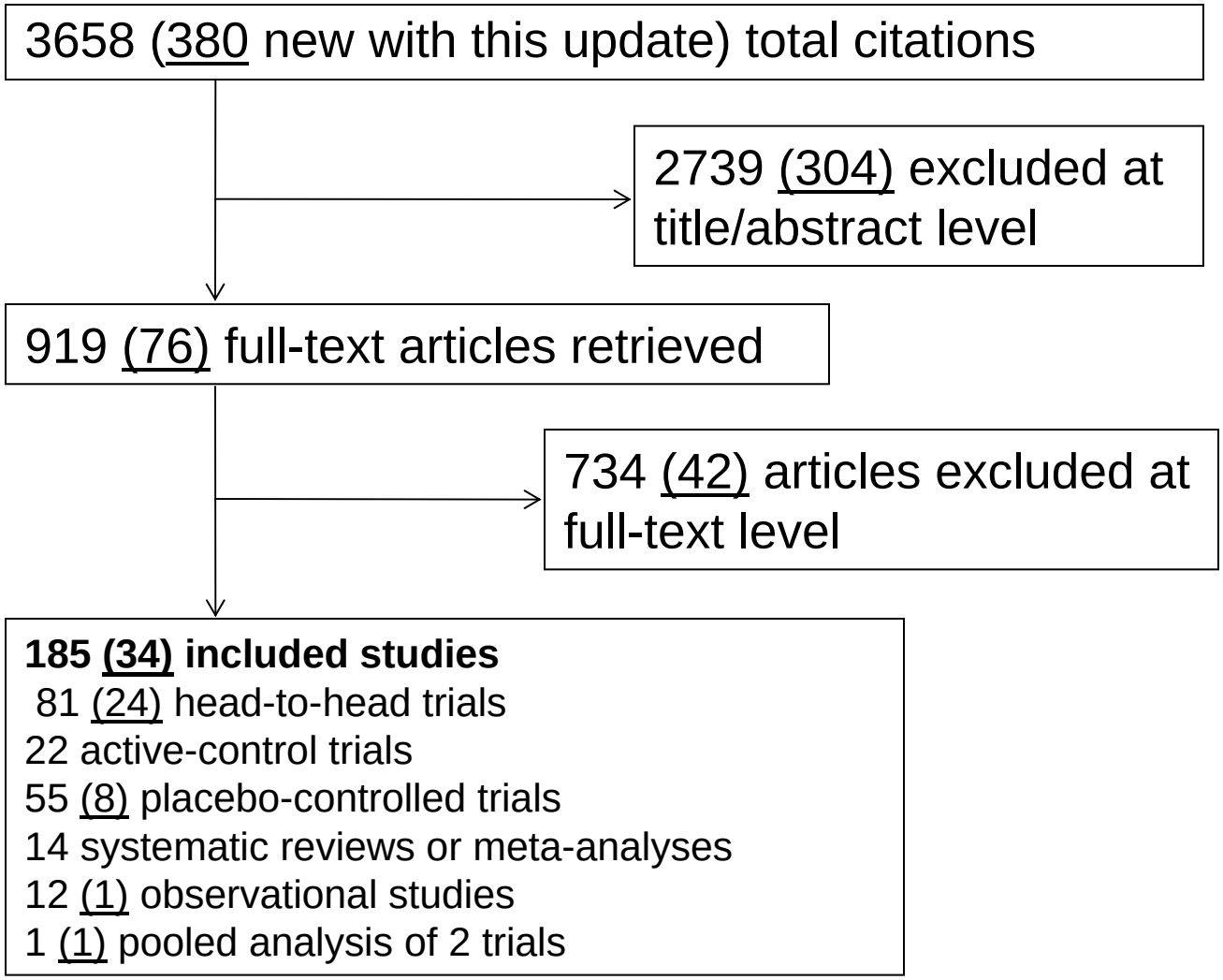

# Overview of evidence

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- Direct comparisons
  - Numerous head-to-head trials in adults for prevention of emesis following chemotherapy and surgery
- Placebo-controlled trials
  - Added evidence on patient satisfaction, quality of life and resource utilization
- No studies of antiemetic efficacy in
  - Pregnancy
  - Children undergoing radiation
  - Aprepitant/fosaprepitant in children

# Direct comparisons of dolasetron, granisetron, ondansetron: Included trials

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## Table 1. Numbers of trials (new in Update 1)

| Population | Comparisons to standard ondansetron | | | Dolasetron vs granisetron |
|---|---|---|---|---|
| | Granisetron | Dolasetron | Ondansetron ODT | |
| Adults | | | | |
| Chemotherapy | 32 (1) | 4 | 1 (1) | 2 |
| PONV—prevention | 10 (8) | 7 (2) | 2 (2) | 2 (2) |
| PONV—treatment | 1 (1) | 1 (1) | - | - |
| Radiation therapy | 1 | - | - | - |
| Children | | | | |
| Chemotherapy | 3 | - | - | - |
| PONV — prevention | - | 2 | - | - |

Abbreviations: ODT, orally disintegrating tablet; PONV, postoperative nausea and vomiting.

# Direct comparisons of dolasetron, granisetron, ondansetron: Similar efficacy

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## Table 1. Rates of complete response[a] (% patients)

| 5-HT3 antagonist | Populations | | | |
|---|---|---|---|---|
| | Chemotherapy: Adults | PONV Prevention: Adults | PONV Treatment: Adults | PONV Prevention: Children |
| Dolasetron | 40% to 76% | 39% to 76% | - | 68% to 86% |
| Granisetron | 48% to 53% | 46% to 75% | 60% to 68% | - |
| Ondansetron | 46% to 79% | 48% to 79% | 47% | 52% to 92% |

Abbreviations: PONV, postoperative nausea and vomiting.

[a] Complete response rates generally were defined as no emesis and no use of rescue medication.

# Direct comparisons of dolasetron, granisetron, ondansetron in subgroups: No consistent differences

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- No differences seen consistently among subgroups based on age, gender, race of patient, use of concomitant medications
- Potentially less effective in patients with history of motion sickness
  - Percent with emesis in subgroups of patients with and without motion sickness
    - Granisetron: 43% (25/58) vs 17% (72/425); *P*<0.0001
    - Ondansetron: 30% (12/40) vs 20% (88/443); NS

# Direct comparisons of dolasetron, granisetron, ondansetron: Gaps in evidence

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- Quality-of-life, patient satisfaction, hospital stay outcomes
  - Dolasetron (3 of 3 trials): better patient satisfaction than placebo in adults
  - Granisetron (3 trials), ondansetron (3 trials): shorter hospital stays than placebo in children
- Serious adverse events
  - Pregnancy outcome (1 observational study): similar for ondansetron and other older antiemetics
  - Lengthening of QTc (1 observational study): ondansetron, 20 ms; droperidol, 17 ms; *P*=NS

# Direct comparison of aprepitant/fosaprepitant with ondansetron: Included trials

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- Chemotherapy in adults
  - Aprepitant: 1 trial
  - Fosaprepitant: No trials of formulation/dose available in United States (115 mg); only 2 trials of 100 mg dose
- Prevention of PONV in adults
  - Aprepitant: 2 trials

# Direct comparison of aprepitant with ondansetron: Aprepitant noninferior to superior

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- PONV-prevention in adults (2 trials)
  - 24-hour complete response: aprepitant noninferior
    - Aprepitant, 43% to 64% of patients; ondansetron, 42% to 55%
  - 24-hour no vomiting: aprepitant superior
    - Aprepitant, 84% to 97% of patients; ondansetron, 71% to 75%
- Chemotherapy in adults (1 trial)
  - 5-day complete response: aprepitant superior
    - 72% of patients compared with 61%; NNT=9
  - Improved quality of life: aprepitant superior

# Direct comparison of fosaprepitant 100 mg[a] with ondansetron: Differences in efficacy

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- Chemotherapy: Adults (2 trials)
  - Ondansetron was superior to fosaprepitant for complete response in 0-24 hours (2 trials)
    - Ondansetron, 83%; fosaprepitant, 36% to 44%; *P*<0.001
    - Ondansetron, 48%; fosaprepitant, 37%; *P*=NS
  - Fosaprepitant +/- oral aprepitant was superior to single-dose ondansetron for complete response on days 2-5 (2 trials)

[a]The fosaprepitant formulation and dose used in this study is not available in the United States.

# Aprepitant in gender and race subgroups: Inconclusive

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- Aprepitant may improve complete response to a greater extent in women
  - Women: aprepitant, 66%; placebo, 41%; *P*<0.001
  - Men: aprepitant, 69%; placebo, 53%; *P*<0.05
  - Limitations: only pooled 2 of 6 studies; post hoc
- No apparent difference in complete response based on age or race for aprepitant compared with dolasetron or ondansetron
  - Limitations: Unpublished subgroup analyses submitted by the manufacturer; statistical analysis not undertaken due to small subgroups

# Direct comparison of palonosetron with other 5-HT3 antagonists: Included trials

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- Chemotherapy
  - Adults
    - Comparison with ondansetron
      - Moderately emetogenic: 1 trial
      - Highly emetogenic: 1 trial
    - Comparison with dolasetron: 1 trial
  - Children
    - Comparison with ondansetron: 1 trial

# Direct comparison of palonosetron 0.25 mg with other 5-HT3 antagonists in adults: Noninferior to superior efficacy


- Complete response in adults undergoing *moderately* emetogenic chemotherapy
  - Noninferior to dolasetron and ondansetron in individual trials
  - Superior in pooled analysis
    - 0 to 24 hours: risk ratio 1.18 (95% CI 1.1 to 1.3); NNT=9
    - Days 2 and 3: risk ratio 1.36 (95% CI 1.20 to 1.54); NNT=6
- *Highly* emetogenic chemotherapy: noninferior to ondansetron
- 0.75-mg dose: smaller differences than 0.25 mg when compared to 5-HT3 antagonists

# Direct comparison of palonosetron 0.25 mg with ondansetron in children: Palonosetron superior

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- Complete response in children undergoing *highly* emetogenic chemotherapy
  - Day 1: palonosetron, 92%; ondansetron, 72% (*P*=0.010)
  - Day 2: 72% and 46% (*P*=0.023)
  - Day 3: 78% and 54% (*P*=0.028)
- Limitation: More undernourished children in palonosetron group at baseline

# Direct comparisons for adverse effects overall: No consistent, significant differences

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- Adverse event data primarily from trials of chemotherapy-treated populations
  - Complicated by effects of underlying illness and chemotherapy?
- Substantial variability in adverse event rates
  - Overall adverse events: 4% to 87%
  - Headache: 2% to 53%
  - Diarrhea: 0% to 60%
  - Constipation: 0% to 40%

# Summary

DRUG EFFECTIVENESS REVIEW PROJECT

- **Dolasetron, granisetron, ondansetron**
  - No consistent, statistically significant differences
- **Aprepitant (oral)** compared with ondansetron
  - Noninferior to superior on complete response
  - Superior on 24-hour no vomiting
- **Fosaprepitant (intravenous)**
  - No studies of formulation and dose (115 mg) available in U.S.
  - Mixed findings in 2 trials of 100-mg dose
- **Palonosetron**: Complete response
  - Compared with dolasetron or ondansetron in moderately emetogenic chemotherapy: Noninferior to superior
  - Compared with ondansetron in highly emetogenic chemotherapy: Noninferior in adults; possibly superior in children




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