



## Therapeutic Class Review<sup>SM</sup>

### GI: Antiemetics – 5-HT<sub>3</sub>-receptor Antagonists

February 2009

#### New Products for Review:

##### 5-HT<sub>3</sub>-antagonist antiemetics:

granisetron patch (Sancuso<sup>®</sup>) [ProStrakan]

palonosetron capsules (Aloxi<sup>®</sup>) [Eisai]

#### Dossier Provided by Manufacturer:

Medication	Dossier	Evaluation
Sancuso patch	Yes	2
Aloxi capsules	No	n/a

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; missing pharmacoeconomics model.
- 3 - Mfg. provided all relevant trials and information.

#### Executive Summary

##### Chemotherapy-induced nausea and vomiting (CINV):

- The 5-HT<sub>3</sub>-receptor antagonists, in combination with corticosteroids, are the standard of care in preventing chemotherapy-induced nausea and vomiting.
- The four medications that make up the 5-HT<sub>3</sub>-receptor antagonists class have similar overall safety and effectiveness.
- Of the four 5-HT<sub>3</sub>-receptor antagonists, palonosetron (Aloxi) may require less frequent dosing due to its long half-life.
- National Guidelines (NCCN and ASCO) consider the four medications in the 5-HT<sub>3</sub>-receptor antagonist antiemetic class to be interchangeable.
- New formulations of granisetron and palonosetron were recently approved for prevention of CINV:
  - granisetron transdermal patches (Sancuso).
  - palonosetron capsules (Aloxi).
- Although the new 5-HT<sub>3</sub>-receptor antagonist formulations may provide added convenience for some patient populations, they have not been shown to be better tolerated or more effective than currently available options.
- Topical administration of granisetron:
  - Does not eliminate the need for oral or injectable pre-chemotherapy medications.
  - Requires proper timing (apply at least 24 hours before chemotherapy) which may limit its utility.
  - Can lead to increased medication waste as a result of dose timing requirements.
- Generic ondansetron (Zofran) and granisetron (Kytril) provide the best value in the 5-HT<sub>3</sub>-receptor antagonist class.

### Post-operative nausea and vomiting (PONV):

Dolasetron, granisetron, and ondansetron all appear to be similarly effective when used for the treatment and prevention of PONV based on a systematic review of evidence by Cochrane.

## **Evidence**

### 5-HT<sub>3</sub>-receptor antagonists in CINV:

- Systematic reviews have not shown any significant differences between the different 5-HT<sub>3</sub>-receptor antagonists.
- Although differences have not been shown, current evidence cannot support a conclusion that dolasetron, granisetron, ondansetron, and palonosetron are all equally effective based on single comparisons (equivalency of all agents has not been established).
- A single, possibly useful study was identified that compared intravenous palonosetron (Aloxi) 0.25 mg with intravenous ondansetron (Zofran) 32 mg. The two regimens were found to be similarly effective in preventing nausea and vomiting in patients receiving highly emetogenic chemotherapy.
- Comparative safety information for the 5-HT<sub>3</sub>-receptor antagonists is confounded by large variations in study populations and dosing regimens that were studied in the trials.
- Headache and constipation are the two most prevalent adverse effects reported across the class.

### Granisetron transdermal patches (Sancuso):

There were two unpublished studies of granisetron transdermal patches (Sancuso).

- Both studies were designed to show that granisetron transdermal patches were similar to oral granisetron in preventing CINV.
- Evidence from both studies was appraised as uncertain because of several methodological flaws that threatened the validity of the results.

## **Decision**

### ***Injectable 5-HT<sub>3</sub> antiemetic products (Medical benefit):***

Generic ondansetron is preferred over other injectable 5-HT<sub>3</sub> antiemetics because it offers the best value in the class.

## Products

**Table A: Available 5-HT<sub>3</sub>-antiemetic medications**

Drug Products	FDA approval <sup>a</sup>	Patent Expiration(s) <sup>b</sup>	FDA approved indications	Usual Dose - Adults	Usual Dose - Pediatrics	Potential Off-label Uses <sup>c</sup>
<b>dolasetron</b>						
<b>Anzemet<sup>®</sup> tablet</b> <sup>[1]</sup>	9/1997	7/2011	<ul style="list-style-type: none"> <li>▪ Prevention of CINV</li> <li>▪ Prevention of PONV</li> </ul>	100 mg 60 min ā chemoRx 100 mg within 2 hr ā surgery	Ages 2-16 yr: 1.8 mg/kg <sup>d</sup> Ages 2-16 yr: 1.2 mg/kg <sup>d</sup>	Hyperemesis with pregnancy
<b>Anzemet<sup>®</sup> injection</b> <sup>[2]</sup>	9/1997	7/2011	<ul style="list-style-type: none"> <li>▪ Prevention of CINV</li> <li>▪ Prevention and treatment of PONV</li> </ul>	1.8 mg/kg 30 min ā chemoRx 12.5 mg 15 min ā cessation of anesthesia (or as n/v presents)	Ages 2-16 yr: 1.8 mg/kg <sup>d</sup> Ages 2-16 yr: 0.35 mg/kg <sup>d</sup>	RINV
<b>granisetron</b>						
<b>Kytril<sup>®</sup> tablet, solution</b> <sup>[3]</sup>	3/1995 6/2001	expired [generics]	<ul style="list-style-type: none"> <li>▪ Prevention of CINV</li> <li>▪ Prevention of RINV</li> </ul>	2 mg daily 60 min ā chemoRx 2 mg daily 60 min ā radioRx	Not recommended Not recommended	PONV; Hyperemesis with pregnancy
<b>Kytril<sup>®</sup> injection</b> <sup>[4]</sup>	12/1993	expired [generics]	<ul style="list-style-type: none"> <li>▪ Prevention of CINV</li> <li>▪ Prevention and treatment of PONV</li> </ul>	10 mcg/kg 30 min ā chemoRx 1 mg ā induction of anesthesia (or as n/v presents)	Ages 2-16 yr: 10 mcg/kg Not recommended	RINV
<b>Sancuso<sup>®</sup> patch</b> <sup>[5]</sup> (34.3 mg patch)	9/2008	9/2011	<ul style="list-style-type: none"> <li>▪ Prevention of CINV</li> </ul>	1 patch applied at least 24 hrs ā chemoRx (delivers granisetron for up to 7 days)	Not recommended	RINV; hyperemesis w/ pregnancy
<b>ondansetron</b>						
<b>Zofran<sup>®</sup> tablet, ODT, solution</b> <sup>[6]</sup>	12/1992 1/1997 1/1999	expired [generics]	<ul style="list-style-type: none"> <li>▪ Prevention of CINV</li> <li>▪ Prevention of RINV</li> <li>▪ Prevention of PONV</li> </ul>	8 mg BID; 24 mg ā chemoRx 8 mg TID 16 mg ā anesthesia induction	Ages 4-11 yr: 4 mg TID Not recommended Not recommended	Hyperemesis with pregnancy; nausea 2° to opioids
<b>Zofran<sup>®</sup> injection</b> <sup>[7]</sup>	1/1991	expired [generics]	<ul style="list-style-type: none"> <li>▪ Prevention of CINV</li> <li>▪ Prevention of PONV</li> </ul>	32 mg 30 min ā chemoRx or 0.15 mg/kg @ HR 0, 4, 8 4 mg ā anesthesia induction	Ages 6 mo to 18 yr: 0.15 mg/kg (HR 0, 4, 8) Ages 1 mo to 12 yr: 0.1 mg/kg up to 40 kg	
<b>palonosetron</b>						
<b>Aloxi<sup>®</sup> capsule</b> <sup>[8]</sup>	8/2008	4/2015	<ul style="list-style-type: none"> <li>• Prevention of CINV</li> </ul>	0.5 mg 60 min ā chemoRx	Not recommended	RINV
<b>Aloxi<sup>®</sup> injection</b> <sup>[9]</sup>	7/2003	3/2011	<ul style="list-style-type: none"> <li>• Prevention of CINV</li> <li>• Prevention of PONV</li> </ul>	0.25 mg 30 min ā chemoRx 0.075 mg ā anesthesia induction	Not recommended Not recommended	RINV

<sup>a</sup> Date applies to approval date for the original brand name medication where there are now generics available.

<sup>b</sup> Based on patents listed in Orange Book as of 12/10/2008.

<sup>c</sup> As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

<sup>d</sup> Maximum dose is usual adult dose.

## References

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