



Therapeutic Class ReviewSM

lubiprostone (AmitizaTM)

July 2006

New Product for Review:

Lubiprostone (AmitizaTM) [Sucampo]

Dossier Provided by Manufacturer: No

Dossier Evaluation: not applicable

1- dossier w/missing components

2- all components present, except pharmacoeconomic model

3- all components present (comprehensive)

Available Therapeutic Alternatives:

Preferred/Formulary	Non-preferred/non-formulary
polyethylene glycol 3350 (Miralax TM) [generics]	lubiprostone (Amitiza TM) [Sucampo]
lactulose syrup (Chronulac [®]) [generics]	tegaserod (Zelnorm [®]) [Novartis]
Over-the-counter (OTC) products (not part of prescription benefit)	
bulk-forming laxatives	stool softeners
stimulants	lubricants
	saline laxatives
	osmotic agents

Reason for Review:

Determine the formulary status for lubiprostone (Amitiza), a new medication indicated for the treatment of chronic idiopathic constipation in adults.

Executive Summary

- Constipation:
 - Affects more than 30 million Americans.
 - Results in more than 2.5 million visits to physicians annually.
 - Is more likely to affect females than males.
 - Is more likely to occur in older patients; exponential increase after age 65.
 - Accounts for \$708 million in OTC laxative sales in 2004.
- Chronic constipation is believed to be a disorder of colonic motility.
- Idiopathic constipation refers to the fact that there is no known cause for the constipation (not due to other diseases or drugs).
- A standard definition for constipation is problematic because bowel habits vary greatly among individuals.

- There are many effective OTC medications available for treating constipation.
- In addition to its labeling for treatment of chronic idiopathic constipation, lubiprostone (Amitiza) is also being studied in constipation predominant irritable bowel syndrome (IBS).
- Although clinical trials with these medications have been for short durations (from 2 to 12 weeks), chronic use of these medications is likely.

Evidence

- Two trials provide possibly useful evidence for the efficacy of lubiprostone (Amitiza) in the treatment of chronic idiopathic constipation:
 - Spontaneous bowel movements (SBMs) at the end of week 1 was followed as the primary endpoint.
 - The number of responders was reported at the end of each week of the trial (≥ 4 SBMs/week).
 - The NNT for responders was 5 over 4 weeks.
- There are no long-term trials that establish the efficacy of lubiprostone (Amitiza) beyond 4 weeks.
- There are no head-to-head trials with that provide evidence for efficacy of lubiprostone (Amitiza) relative to any other product used to treat constipation.
- Available harms information is not reliable for purposes of long-term safety of lubiprostone (Amitiza).
- Nausea was the most common harm reported during controlled trials, occurring in 31.4% (placebo 5.5%) of patients.
- The NNH for all gastrointestinal adverse events was 3 over 4 weeks.
- The NNH for discontinuations due to adverse events was 10 over 4 weeks.
- Use of lubiprostone (Amitiza) in pregnant women may lead to pregnancy loss (chemical structure is similar to prostaglandin E₁).

Considerations in subpopulations:

- *Pediatrics*: There is no useful evidence to establish the safety and efficacy in pediatric patients.
- *Geriatrics*: There is no package labeling regarding this population. In a subpopulation analysis, no differences in efficacy of lubiprostone (based on signs and symptoms related to constipation) were noted between older (≥ 65 years of age) and younger patients. Out of 479 patients in Phase III trials, 52 (10.8%) were 65 years of age or older.
- *Race, ethnicity*: Current clinical experience has not identified differences in safety or efficacy based on race or ethnicity.
- *Gender*: In a subpopulation analysis, no difference in the efficacy of lubiprostone (based on signs and symptoms related to constipation) were noted between genders (approximately 12% of the subjects in the Phase III trials were men).

Conclusion

Lubiprostone (Amitiza) is non-preferred/non-formulary because:

- There are several effective, lower cost preferred options available to our members for treating chronic constipation.
- There is no evidence that lubiprostone (Amitiza) is more effective, safer, or better tolerated than preferred alternatives.

Products

Drug Products	FDA approval ^a	FDA approved indications	Usual Dose/Route	Cost ^b	Potential Off-label Uses ^c
lubiprostone (Amitiza™) ¹	01/2006	1. Chronic idiopathic constipation in adults	24 mcg p.o. BID (with food)	\$183	<ul style="list-style-type: none"> ▪ IBS with constipation ▪ Constipation 2° to other causes (eg. narcotics)
lactulose syrup ^c (Chronulac®) - - generics	06/1979	1. Constipation 2. Hepatic encephalopathy	20 to 30 Gm (30 to 45 ml) p.o. TID to QID	\$25 to \$48	<ul style="list-style-type: none"> ▪ Post-op pain after hemorrhoidectomy ▪ Lactose intolerance
polyethylene glycol 3350 (Miralax™) ² - - generics	02/1999	3. Occasional constipation (2 weeks or less or as directed by physician)	17 Gm p.o. QD (in 8 oz. of fluid)	\$26	<ul style="list-style-type: none"> ▪ Dysfunctional voiding ▪ Fecal impaction
tegaserod (Zelnorm®) ³	07/2002	1. Irritable bowel syndrome (IBS) with constipation 2. Chronic idiopathic constipation	6 mg p.o. BID (before meals)	\$222	<ul style="list-style-type: none"> ▪ Constipation 2° to other causes (eg. narcotics)

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Cost estimate based on AWP (average wholesale price) listed in First Data Bank or MAC (maximum allowable cost) as of May 2006 for 1 month of therapy.

^c As listed in © 1974 - 2006 Thomson MICROMEDEX database or as referenced.

References

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3. Zelnorm® (tegaserod) Prescribing Information. Novartis Pharmaceuticals Corporation: East Hanover, NJ, August 2004.
4. Center for Drug Evaluation and Research. Approval package for application number NDA 21-908; Medical Review. Available at: http://www.fda.gov/cder/foi/nda/2006/021908s000_Etreva_MEDR.pdf. Accessed on 6/1/2006.
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