

TABLE OF CONTENTS

	Page #
Tab 1 Overview and Risk Management Issues for Lotronex™ (alosetron HCl) Tablets	1
Tab 2 Summary of Gastrointestinal Serious Adverse Events	8
Tab 3 Risk Management Options.....	13
Tab 4 Risk Interventions and Their Evaluation	18

APPENDICES

Appendix 1

Background information on irritable bowel syndrome, complications of constipation, ischemic colitis, and liver toxicity

- Mayer EA, Thompson WG, Dent J. "Introduction" in Proceedings of a Symposium: Irritable Bowel Syndrome: Diagnosis, Subgrouping, Management and Clinical Trial Design. *AJM*. 1999; 107:1S-S..... 30
- Mayer EA. "Emerging disease Model for Functional Gastrointestinal Disorders" in Proceedings of a Symposium: Irritable Bowel Syndrome: Diagnosis, Subgrouping Management and Clinical Trial Design. *AJM*. 1999; 107:12S-19S..... 34
- Camilleri M. "Therapeutic Approach to the Patient with Irritable Bowel Syndrome" in Proceedings of a Symposium: Irritable Bowel Syndrome: Diagnosis, Subgrouping, Management and Clinical Trial Design. *AJM*. 1999; 107:27S-32S..... 42
- Talley, NJ. "Treatment of the Irritable Bowel Syndrome" in *Therapy of Digestive Disorders*. Wolfe, MM, W.B. Saunders Company, Philadelphia, 2000..... 48
- Lennard-Jones JE. "Constipation" in *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management*. W.B. Saunders Company, Philadelphia 1998..... 59
- Haubrich WS, Schaffner F, Berk JE [ed.]. "Constipation: Complications" in *Gastroenterology*. W.B. Saunders Company, Philadelphia 1995; 109-111..... 83
- American Gastroenterological Association Medical Position Statement: Guidelines on Intestinal Ischemia. 1999..... 86
- Kaplowitz N; Avoiding Hepatic Injury From Drugs. *Gastroenterology*. 1999; 117:759..... 104
- Bass NM, Ockner RK. "Drug-Induced Liver Disease" in *Hepatology: A Textbook of Liver Disease*. W.B. Saunders company, Philadelphia 1996..... 105

Appendix 2

Lotronex™ (alosetron HCl) Tablets: reviews of efficacy and safety

- FDA review #1: overview of efficacy and safety (November 17, 1999)..... 161
- FDA review #2: review of safety (January 27, 2000)..... 218

Appendix 3

Lotronex™ (alosetron HCl) Tablets labeling

- Professional labeling (package insert) 253
- Patient labeling (patient package insert)..... 269

Appendix 4

Regulations, guidances, and examples applicable to risk management

a. Labeling

- Boxed warnings (examples)..... 274
- Patient package inserts/Medication Guides (examples) 277
- Medication guides (preamble to final rule and regulations) 278

b. Communications to healthcare providers and consumers

- Mailings of important information
 - Dear “healthcare provider” letters (examples)..... 289
 - Regulations 297
- Talk papers (examples) 299
- Public health advisories (examples)..... 307
- Questions & answers (example) 312
- List of MedWatch partners 318

c. Advertising

- Guidance for Industry: Consumer-Directed Broadcast Advertisements 323
- Guidance for Industry: Accelerated Approval Products
 - —Submission of Promotional Materials..... 330
 - Regulations pertaining to drug advertising 339

d. Restricted distribution

- Accelerated approval (preamble to final rule and regulations)..... 354

e. Cessation of marketing

- Withdrawal of approval (regulations)..... 360

Appendix 5

Published Literature

- Bogardus, ST, Holmboe E, Jekel JF. Perils, Pitfalls, and Possibilities in Talking About Medical Risk. *JAMA*. 1999; 281:1037-1041..... 368
- Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PC, Rubin HR. Why Don't Physicians Follow Clinical Practice Guidelines? *JAMA*. 1999; 282:1458-1465. and commentary by Montgomery AA, Peters TJ, Fahey T..... 373
- Dans AL, Dans LF, Guyatt GH, Richardson S. Users' Guides to the Medical Literature: XIV. How to Decide on the Applicability of Clinical Trial Results to Your Patient *JAMA*. 1998; 279:545-549. 382

- Ellrodt AG, Conner L, Riedinger M, Weingarten S. Measuring and Improving Physician Compliance with Clinical Practice Guidelines. *Ann. Intern. Med.* 1995; 122:277-282. 387
- Guyatt GH, Sinclair J, Cook DJ, Glasziou P. Users' Guides to the Medical Literature: XVI. How to Use a Treatment Recommendation. *JAMA.* 1999; 281:1836-1843. 393
- Levine M, Walter S, Lee H, Haines T, Holbrook A, Moyer V. Users' Guides to the Medical Literature: IV. How to Use an Article About Harm *JAMA.* 1994; 271:1615-1619. 401
- Wilson MC, Hayward RS, Tunis SR, Bass EB, Guyatt G. Users' Guides to the Medical Literature: VIII. How to Use Clinical Practice Guidelines. *JAMA.* 1995; 274:1630-1632. 406