



The Newest Treatment for Constipation Predominant Irritable Bowel Syndrome: 5-HT₄ Agonists

Learning Objectives

1. Recognize the most common symptoms associated with irritable bowel syndrome.
2. Identify patients for whom tegaserod is appropriate.
3. List the potential side effects of tegaserod.
4. Discuss drug therapy for constipation-predominant irritable bowel syndrome currently in clinical trials.

Introduction

Irritable bowel syndrome (IBS) is a disorder of disrupted gastric motility and increased visceral sensations with physiological and psychological influences.¹⁻³ The main symptoms of IBS are abdominal pain or discomfort, bloating, and bowel irregularity.^{2,4-6} The disorder is accompanied by high direct and indirect medical costs.⁷ Approximately \$1.6 billion is spent on physician visits and prescription therapy, while another \$19.2 million is lost in missed work and reduced productivity.⁷ People diagnosed with IBS are three times more likely to miss work than those without the disease.⁷

Because there is no pathognomonic blood test to diagnose the condition, it must be recognized by its symptomatology.^{1,4} When other etiologies have been ruled out, patients are diagnosed using the Rome II criteria.^{6,8} Individuals must have been suffering with abdominal pain associated with a change in bowel habits for 12 weeks during the previous year.⁸ The diagnosis is supported by additional symptoms of bloating and straining to defecate.⁸ A person with IBS will typically suffer from constipation or diarrhea, or alternate between the two.² In all, estimates suggest IBS afflicts 10-22% of Westerners, with two to three times more women diagnosed than men.^{1,2,4,9} Depression and/or anxiety are fairly common problems in patients who seek treatment for IBS.⁹ Consequently, symptomatic treatment should seek to improve these comorbidities rather than exacerbate them.

Irritable bowel syndrome therapy is directed at the patients' overall well-being and not just at symptoms.⁸ Patients need a trusting relationship with their care providers who provide patients with the tools to understand their disease.⁸ Emphasis is placed on following an appropriate diet and making certain lifestyle changes.⁸ If necessary, drug therapy can be used to address patients' complaints.⁸ Until recently, only antispasmodics and tricyclic antidepressants were available to address pain, and only fiber or laxatives were available to maintain regularity.⁸ Now, a new group of drugs that interact with serotonin receptors has been developed for IBS.⁸ Psychotherapy can also be beneficial in some patients and centrally acting

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Amber Goedken received her Doctor of Pharmacy degree from the University of Iowa in May. She developed an interest in drug information while completing a clerkship at the Iowa Drug Information Network and is currently serving as our Drug Information/Informatics Resident.

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medications like the tricyclics and selective serotonin reuptake inhibitors can address depression or anxiety.⁸ The focus of this article will be on the new serotonin agonist, tegaserod maleate.

Treatment of IBS

Symptoms

The central nervous system (CNS) modulates gastrointestinal (GI) motility, secretion, immune function, and blood flow.¹⁰ The abdominal pain and altered bowel habits in patients with irritable bowel syndrome can be brought on by dysfunction in the GI tract (like infections or dietary indiscretions), lifestyle changes (like vigorous physical activity or traveling), or stress. The CNS filters signals from the GI tract and returns signals to control GI activity. Serotonin is one of the most active chemical modulators in the GI tract containing both serotonin 3 (5-HT₃) receptors and serotonin 4 (5-HT₄) receptors. In irritable bowel syndrome these receptors may be hypersensitive.

Patients are classified as having either constipation-predominant (IBS-C), diarrhea-predominant (IBS-D); or alternating (IBS-A) irritable bowel syndrome.^{1,11} None of the currently available therapies address all the problems associated with IBS, but the new serotonin agents improve more symptoms than older therapies.

If constipation, bloating, and abdominal pain are the major complaints, treatment is directed at the 5-HT₄ receptors. Activation of 5-HT₄ receptors in the gut leads to the release of chemicals that initiate peristalsis, promoting passage of undigested material through the digestive tract.^{1,3,4,8,12} Stimulation of 5-HT₄ receptors on visceral afferent neurons also reduces sensations from the gut.^{1,3,4} Agonists of 5-HT₄ receptors increase and normalize GI motility and were designed to treat the abdominal pain and constipation associated with IBS-C.^{1,12}

Diarrhea-predominant irritable bowel syndrome's hallmark is increased GI motility, so the 5-HT₃ antagonists are employed rather than the 5-HT₄ agonists.^{5,6} Lotronex® (alosetron) is a 5-HT₃ antagonist that was approved for

use in IBS-D, but was temporarily withdrawn due to reports of ischemic colitis and severe constipation.^{5,6} The drug is now available, but its use is restricted.^{5,6} Cilansetron is another drug in this class that is under development. It too has been linked to ischemic colitis.⁶ Considerable work needs to be done to help control the symptoms of this form of IBS.

Tegaserod

Zelnorm® (tegaserod maleate) is a potent, selective partial agonist of 5-HT₄ receptors in the gut.^{2-4,12} It enhances GI motility, stimulates secretion of chloride ions and water into the gut, inhibits visceral sensations, and hastens passage of stool through the colon.^{3,4} Tegaserod use has not been shown to result in tachyphylaxis, but the clinical trials conducted have been too short to eliminate the possibility of tachyphylaxis.⁶ It is recognized that tegaserod does not cause the exaggerated response of a full agonist.¹²

Tegaserod was the first drug approved by the United States Food and Drug Administration (FDA) specifically for IBS-C. It is well absorbed and widely distributed.^{3,13} Peak plasma concentrations are approached one hour after ingestion. Administration with meals decreases its bioavailability by 50%.¹³ In clinical trials, subjects were instructed to administer the drug 30 minutes prior to morning and evening meals.² The manufacturer recommends tegaserod be taken twice a day before meals.¹⁴

Most clinical trials of tegaserod have enrolled patients with IBS-C.⁴ Irritable bowel syndrome is more common in women, so tegaserod studies have involved mostly women.¹ Of the three trials conducted and submitted for approval of tegaserod, only the study by Muller-Lissner and colleagues¹ has been published. This pivotal study enrolled 881 patients to receive either tegaserod 2 mg bid, tegaserod 6 mg bid, or placebo for 12 weeks.¹ Nearly all the

subjects were Caucasian (98%), and 83% of the study participants were women.¹ Efficacy was defined as either complete or considerable relief on $\geq 50\%$ of the final four weekly assessments or some relief on all of the final four weekly assessments.¹ Response in the tegaserod group was significantly improved compared to the placebo group (38.4% vs. 30.2%, respectively, $p < 0.05$).¹

The FDA required another study before it would approve tegaserod. A randomized, controlled trial (RCT) of 1519 participants with IBS-C compared tegaserod 6 mg bid to placebo.² To determine efficacy, patients were asked to report if they had complete relief, considerable relief, some relief, no relief, or less relief on a weekly basis.² Efficacy in this study was also defined as either complete or considerable relief on at least two of the final four weekly assessments or some relief on all four final assessments.² Response rates in the tegaserod group were significantly better than in the placebo group (43.5% vs. 38.8%, respectively, $p < 0.033$).²

Another RCT of 644 subjects (85.9% women, 14.1% men, 99% Caucasian) diagnosed with IBS (not IBS-D) compared tegaserod 6 mg bid to placebo.⁴ This study was not a pivotal study submitted to the FDA for approval of tegaserod. Here, response was defined as at least two weeks of satisfactory relief out of the first four weeks. Tegaserod was significantly better at providing relief than placebo (30.5% of the tegaserod group vs. 20.8% of the placebo group were responders, respectively, $p = 0.0060$).⁴

From these studies, tegaserod appears to be more effective at relieving IBS-C symptoms than placebo.^{1,2,4} However, two unpublished pivotal studies submitted for approval tell a different story.¹⁵ Study B307 found no statistically significant difference between response rates, and study B351 was discounted by the FDA after the definition of response was

changed when a significant difference could not be detected.¹⁵

If tegaserod is to be prescribed, it is important to look at the populations in which tegaserod was studied so it can be used most effectively. In the three previously mentioned studies, more than 80% of the participants were women.^{1,2,4} Because of the small numbers enrolled, the effects of the drug could not be analyzed in men. Thus, the FDA has approved tegaserod for females only. A majority (more than three-fourths) were Caucasian, and the average age was between 40 and 50 years, somewhat older than the peak ages of 20 to 40 years for IBS-C patients.^{1,2,4,5} The Muller-Lissner and colleagues¹ study enrolled subjects who had been dealing with symptoms for roughly 10 years, whereas the other two studies included patients with IBS-C for 16-17 years on average.^{2,4}

Side effects

Tegaserod is expected to cause certain GI side effects due to its mechanism of action. Increased movement of the GI tract can lead to diarrhea and abdominal pain. Table 1 lists the most common adverse events encountered in clinical trials of tegaserod.

The only significant difference between tegaserod and placebo in terms of adverse events was the incidence of diarrhea.¹⁵ However, tegaserod does not act on the digestive system alone. The 5-HT₄ receptors are also found in the CNS, bladder, and atria.³ Activation of 5-HT₄ receptors in the atria of the heart can influence heart rhythm; these receptors are not present in the ventricles of the heart.^{3,12} Stimulation of receptors in the adrenal cortices releases aldosterone, potentially elevating blood pressure.^{12,15} Activation of 5-HT₄ receptors in the CNS leads to increased dopamine release, affecting memory and

Table 1.
Incidence of Adverse Events over 12 Weeks

	Novick and colleagues ² n = 1519		Nyhlin and colleagues ⁴ n = 644		M-Lissner and colleagues ¹ n = 881	
	Tegaserod	Placebo	Tegaserod	Placebo	Tegaserod	Placebo
Headache	9.0%	5.7%	8.0%	4.7%	27.3%	27.3%
Abdominal pain	6.4%	5.7%	4.9%	3.8%	16.7%	17.1%
Diarrhea	6.4%*	2.9%*	9.2%	1.3%	9.6%*	2.5%*
Nausea	6.8%	4.7%	5.5%	5.1%	7.2%	8.7%
Back pain					7.2%	7.3%
Dizziness					4.4%	3.9%
Upper RTI	3.5%	6.4%			4.4%	7.3%
Influenza-like symptoms					11.3%	9.8%

*p<0.05

cognition.¹² Receptor activation in the bladder increases detrusor tone and could result in urinary retention.¹²

Despite their potential, these adverse pharmacologic factors have had little impact on tegaserod's performance clinically. There is only one reported case of cardiac adverse effects. A 64 year-old male with coronary artery disease suffered a nonfatal myocardial infarction after only two doses of tegaserod.¹⁶ Cisapride, a drug similar to tegaserod, was removed from the market after it was linked to QT interval prolongation and heart arrhythmias.^{3,6} Cisapride is a 5-HT₄ agonist with weak antagonist activity at 5-HT₃ receptors, reducing its selectivity for the lower GI.³ In addition, one of the metabolites of cisapride is also a 5-HT₃ antagonist.³

Tegaserod was not studied in patients with preexisting cardiovascular diseases.¹⁶

Other 5-HT₄ Agonists

Prucalopride is a full serotonin (5-HT₄) agonist.³ It has not been studied in IBS-C, but has been studied in idiopathic constipation, a condition with similar symptoms.³ Prucalopride has also been evaluated by a placebo-controlled, randomized, double-blind phase II pilot study in spinal cord injury patients with chronic constipation.¹⁷ The first phase of the study randomized patients to either 1 mg/day or placebo for four weeks to assess safety.¹⁷ A new group of

subjects was then randomized to receive 2 mg/day or placebo, also for four weeks.¹⁷ Each phase included only 12 subjects.¹⁷ Approval of prucalopride was suspended due to concerns about cardiac arrhythmias and carcinogenesis.³

Several other compounds (norcisapride, mosapride, and renzapride) have been developed.⁶ Like cisapride, norcisapride has been associated with cardiac toxicity.⁶ Mosapride has not been tested in IBS and studies of renzapride in this disorder are under way.⁶

Conclusion

Tegaserod is currently the only drug approved in the U.S. specifically for constipation-predominant irritable bowel syndrome. Tegaserod has minimally significant effects in patients and needs to be directly compared to other therapies used for IBS. Other drugs under investigation look somewhat promising. None of the agents for IBS have been fully successful and they need to be looked at carefully due to their cost and lack of long-term safety data. Unfortunately, the arsenal of clinically effective drugs for irritable bowel syndrome remains limited.

References

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Accreditation Information

The University of Iowa College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. The ACPE program number is 020-000-04-022-H01. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

To earn continuing education credit, complete the assessment exercise, CE registration form and program evaluation on page 5, and return to Division of Drug Information Service with a \$5.00 check for the processing fee, made out to the College of Pharmacy. A certificate will be awarded upon achieving a passing grade of 70% or better. Please allow up to 4 weeks for processing. Pharmacists must complete this program by January 1, 2006 to receive credit.

CE REGISTRATION

ACPE # 020-000-04-022-H01

VOLUME: 15 ISSUE: 3 SEPTEMBER 2004

TITLE OF EDUCATIONAL ACTIVITY (ARTICLE)

THE NEWEST TREATMENT FOR CONSTIPATION PREDOMINANT IRRITABLE BOWEL SYNDROME: 5-HT4 AGONISTS

NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

SOCIAL SECURITY NUMBER (OPTIONAL) _____

PHARMACY LICENSE NUMBER(S) _____

I HEREBY CERTIFY THAT I HAVE TAKEN THIS TEST:

Signature/Date _____

(circle the correct answer)

1. Which criteria are used to diagnose IBS?
 - a. IBS-A
 - b. Whitmore-Jewett
 - c. Gail Model
 - d. Rome II
2. To be diagnosed with IBS, a patient must have symptoms for at least _____ out of the preceding year.
 - a. 1 month
 - b. 3 months
 - c. 6 months
 - d. 9 months
3. In which patient would you most expect to see irritable bowel syndrome (IBS) diagnosed?
 - a. 20 year-old man
 - b. 30 year-old woman
 - c. 40 year-old man
 - d. 50 year-old woman
4. Tegaserod's effects on serotonin receptors can be described as which of the following?
 - a. 5-HT3 agonist
 - b. 5-HT3 antagonist
 - c. 5-HT4 agonist
 - d. 5-HT4 antagonist
5. Tegaserod can be prescribed to treat which of the following diseases?
 - a. IBS-C
 - b. IBS-D
 - c. IBS-A
 - d. Ulcerative colitis
6. What is Tegaserod's mechanism of action?
 - a. Softening fecal matter
 - b. Reducing sphincter tone
 - c. Slowing GI motility
 - d. Increasing GI motility
7. Compared to placebo, what is the only significant increase in adverse effects with tegaserod?
 - a. Constipation
 - b. Arrhythmia
 - c. Diarrhea
 - d. Abdominal pain
8. In the majority of clinical trials, tegaserod was administered at what dose?
 - a. 6 mg qd
 - b. 6 mg bid
 - c. 6 mg tid
 - d. 12 mg bid

9. Which prokinetic drug was removed from the market due to reports of QT prolongation?
 - a. Cisapride
 - b. Prucalopride
 - c. Metoclopramide
 - d. Tegaserod
10. Which 5-HT4 agonist's approval was stopped due to concerns of carcinogenesis?
 - a. Cisapride
 - b. Renzapride
 - c. Prucalopride
 - d. Mosapride

PROGRAM EVALUATION

	Excellent				Poor
Overall quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
Important to pharmacists	Agree			Disagree	
	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me _____ hours and _____ minutes to read this article and complete the assessment questions.

Administrative Change in the UI College of Pharmacy Announced



Hazel H. Seaba, R.Ph., M.S.
Director, DDIS/Professor (Clinical)

The University of Iowa College of Pharmacy has named Hazel H. Seaba, Professor (Clinical) and Director of the Division of Drug Information Service (DDIS), to a key position in its administrative leadership.

Professor Seaba will begin a new position within the college as Assistant Dean for Curriculum and Assessment, effective October 1. College of Pharmacy Dean Jordan Cohen said, "I am pleased to announce the addition of Hazel Seaba to our administration. She brings a distinguished level of knowledge and expertise to this new position and will help shape the future of the college."

As part of the college's Office of Academic Affairs, Seaba will coordinate curriculum and assessment activities, including a program to review and assess the pharmacy curriculum and monitor student outcomes. She will also continue to teach within the drug information component of the curriculum. She has had a long-standing interest in the professional curriculum and recently led the Collegiate self-study that resulted in full reaccreditation of the Pharm.D. program. Seaba related, "The College has been on the forefront of Pharm.D. education. As an early implementer of the all Pharm.D. program, the College created a new curriculum and built — in conjunction with Iowa pharmacy practitioners — a sophisticated network of early and advanced experiential training sites. In response to both our

aspiration to ensure the continued quality of the curriculum and our need to anticipate the complexities that will face future Pharm.D. students, the College has expanded its curriculum development activities and formalized assessment functions. I am delighted to be part of the College's team that focuses on the excellence of student programming and development."

Seaba has served as director of IDIS for 28 years. She will make the transition from DDIS to her new position while a search is under way for her successor, and she will work with the new DDIS director through July 2005.

2004 EXHIBIT SCHEDULE

American College of Clinical Pharmacy
(ACCP) 2004 Annual Meeting
Hyatt Regency by Reunion, Dallas TX
October 24-27, 2004
Booth #113

39th American Society of Health-System
Pharmacists (ASHP) Midyear Meeting
and Exhibit
Orange County Convention Center, Orlando FL
December 5-9, 2004
Booth #861

DIRECTOR, DIVISION OF DRUG INFORMATION SERVICE AND ASSOCIATE/PROFESSOR UNIVERSITY OF IOWA COLLEGE OF PHARMACY

The University of Iowa College of Pharmacy invites applications for Director of the Division of Drug Information Service (DDIS). As a service division of the College of Pharmacy, DDIS provides drug information systems and services throughout the world to improve human health care.

Applicants must have an advanced professional or graduate degree and have demonstrated a minimum of 5 years in an administrative position that required excellent written and oral communication skills, successful teamwork and a knowledge of the health care system. Preference will be given to applicants with a pharmacy background, experience in drug information and/or informatics and knowledge of the operations of large database systems. Persons with a history of experience in related small business operations are encouraged to apply. Faculty appointment will be based upon the selected candidate's experience and qualifications.

DDIS is involved in the provision of drug information world-wide to academic, public and private organizations through the *Iowa Drug Information Service* database and the Iowa Drug Information Network. DDIS has 18 full time professional and support staff. Additional information about the Division of Drug Information Service is available at <http://www.uiowa.edu/~idis/> and for the College of Pharmacy at <http://pharmacy.uiowa.edu/>. Submit curriculum vitae, statement of interest and three references. Screening will begin in October and continue until the position is filled.

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The University of Iowa is an Equal Opportunity and Affirmative Action Employer.
Women and minorities are strongly encouraged to apply.



Attention *IDIS* Database Subscribers:

The 2005 subscription renewal materials for the *IDIS* Database will be mailed to you in early September. Please contact our office if you have not yet received the mailing or would like to make any changes to your current configuration; we would be happy to fax or e-mail the materials to you directly. To avoid any interruption in your service we should receive your subscription renewal order in our office by December 27th, 2004.

Thank you in advance for your prompt attention to your subscription renewal and your continued support of the *Iowa Drug Information Service*.

FDA DRUG/BIOLOGIC APPROVALS

Generic Name Trade Name (FDA Therapeutic Classification)*	Sponsor (Approval Date)	IDIS Drug Term Drug Number (IDIS Citations)	Indication/Use Dosage Form	IDIS Disease Term Modified ICD-9-CM Number
Apomorphine Hydrochloride <i>Apokyn</i> (1P)	Bertek (Apr. 20, 2004)	APOMORPHINE 56200001 (158 citations)	Parkinson's Disease Injection	Parkinson's Disease 332.
Azacitidine <i>Vidaza</i> (1PV)	Pharmion (May 19, 2004)	AZACITIDINE 10080405 (77 citations)	Myelodysplastic syndrome, (MDS) Injection	Neop, Nos- Hemapoiesis/Lymph 238.7
<p>Kornblith AB, Herndon JE, Silverman LR, Demakos EP, et al. Impact of azacitidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a cancer and leukemia group B study. <i>J Clin Oncol.</i> 2002; 20:2441-2452. (IDIS Article Number 486285).</p> <p>This randomized study of 191 patients with myelodysplastic syndrome assessed Quality of Life after a minimum of 4 months of azacitidine 75 mg/m² given subcutaneously, or supportive care, found that the azacitidine group experienced significant improvement in fatigue, dyspnea, physical functioning, positive affect, and psychological distress as well as a significantly greater treatment response and delayed time to acute myeloid leukemia or death, (p<0.001).</p>				
Human Secretin <i>Human Secretin</i> (1PV)	Chirhoclin (Apr. 9, 2004)	SECRETIN 36610001 (10 citations)	Diagnosis of pancreatic exocrine dysfunction and gastrinoma Injection	Disease, Pancreatic NEC 577. Diag Test-Digest/BMR 89.39 Neop, Nos-Digestive System 239.0
Insulin Glulisine <i>Apidra</i> (1S)	Aventis Pharms (Apr. 16, 2004)		Diabetes Mellitus Injection	Diabetes Mellitus 250.
Ovine Hyaluronidase <i>Vitrase</i> (1P)	Ista Pharms (May 5, 2004)		Adjuvant to increase absorption and dispersion of other injected drugs Injection	
Rifaximin <i>Xifaxan</i> (1S)	Salix Pharma (May 25, 2004)	RIFAXIMIN 8123006 (22 citations)	Travelers' diarrhea due to susceptible strains of <i>Escherichia coli</i> Tablet	Infection, Diarrhea 009.2 Infection, Intest, E Coli 008.0
<p>Steffen R, Sack DA, Riopel L, Jiang ZD, et al. Therapy of travelers' diarrhea with rifaximin on various continents. <i>Am J Gastroenterol.</i> 2003; 98:1073-1078. (IDIS Article Number 502876)</p> <p>The safety and efficacy of rifaximin in oral doses of 600 mg/day or 1200 mg/day for 5 days was compared with placebo in this double-blind, randomized, controlled trial that included 380 patients with acute travelers' diarrhea and that found rifaximin safe and efficacious at doses 600 mg/day or more, with the median time to the last unformed stool at 32.5-32.9 hours for both rifaximin groups and 60.0 hours for placebo (p=0.0001).</p> <p>DuPont HL, Jiang ZD, Ericsson CD, Adachi JA, et al. Rifaximin versus ciprofloxacin for the treatment of travelers' diarrhea: a randomized, double-blind clinical trial. <i>Clin Infect Dis.</i> 2001; 33:1807-1815. (IDIS Article Number 473209)</p> <p>In this double-blinded trial, adult tourists with travelers' diarrhea in Mexico and Jamaica were randomized to receive oral doses of rifaximin 400 mg twice a day or ciprofloxacin 500 mg twice a day for three days, and the investigators concluded that there was no significant difference between the outcomes of the two treatments, and that rifaximin was as safe and effective as ciprofloxacin for treating travelers' diarrhea.</p>				



About the Author:

Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the IDIS database, overseeing the Drug and Descriptor vocabulary and contributing articles for the *World of Drug Information* newsletter.

Generic Name Trade Name (FDA Therapeutic Classification)*	Sponsor (Approval Date)	IDIS Drug Term Drug Number (IDIS Citations)	Indication/Use Dosage Form	IDIS Disease Term Modified ICD-9-CM Number
Telithromycin <i>Ketek</i> (1S)	Aventis Pharms (Apr. 1, 2004)	TELITHROMYCIN 8121223 (48 citations)	Bronchitis, sinusitis, pneumonia, and pharyngitis/tonsillitis Tablet	Bronchitis, Acute 466.0 Sinusitis, Acute 461. Pharyngitis, Acute 462.
<p>Dunbar LM, Hassman J, Tellier G. Efficacy and tolerability of once-daily oral telithromycin compared with clarithromycin for the treatment of community-acquired pneumonia in adults. <i>Clin Ther.</i> 2004; 26:48-62. (IDIS Article Number 511842)</p> <p>This was a double-blind clinical trial of 448 patients with community acquired pneumonia who were randomized to receive either a 10-day treatment of telithromycin 800 mg once a day plus placebo once daily or clarithromycin 500 mg twice daily. The authors concluded that telithromycin 800 mg daily was equivalent to high dose clarithromycin therapy in efficacy and tolerability.</p> <p>Quinn J, Ruoff GE, Ziter PS. Efficacy and tolerability of 5-day, once-daily telithromycin compared with 10-day, twice-daily clarithromycin for the treatment of group A beta-hemolytic streptococcal tonsillitis/pharyngitis: a multicenter, randomized, double-blind, parallel-group study. <i>Clin Ther.</i> 2003; 25:422-443. (IDIS Article Number 494443)</p> <p>A total of 463 patients were randomized to treatment with oral doses of telithromycin 800 mg once a day for 5 days plus placebo, or oral clarithromycin 250 mg twice daily for 10 days, in this study that found bacterial eradication was achieved in 91.3% of the patients treated with telithromycin and in 88.1% of those treated with clarithromycin, with adverse events occurring slightly more often in the telithromycin group.</p>				
Tinidazole <i>Tindamax</i> (1SV)	Presutti Labs (May 17, 2004)	TINIDAZOLE 8122823 (235 citations)	Treatment of trichomoniasis, giardiasis, amebiasis and amebic liver abscess Tablet	Trichomoniasis NEC 131. Giardiasis 007.1 Amebiasis NEC 006.
Trospium Chloride <i>Trospium</i> (1S)	Indevus (May 28, 2004)	TROSPIUM 12080040 (14 citations)	Treatment of overactive bladder Tablet	Disorder, Bladder NEC 596.
<p>Lopez Pereira P, Miguelez C, Caffarati J, Estornell F, Anguera A. Trospium chloride for the treatment of detrusor instability in children. <i>J Urol.</i> 2003; 170:1978-1984. (IDIS Article Number 508893)</p> <p>This multi-center, single-blind, randomized trial assessed the dosing and efficacy of trospium chloride (TCl) in 58 children who were randomized to 21-day treatment with 10, 15, 20 or 25 mg daily of oral TCl or placebo, and found that 10-25 mg TCl daily, given in two doses, was effective for treating detrusor instability in children.</p> <p>Frohlich G, Bulitta M, Strosser W. Trospium chloride in patients with detrusor overactivity: meta-analysis of placebo-controlled, randomized, double-blind, multi-center clinical trials on the efficacy and safety of 20 mg trospium chloride twice daily. <i>Int J Clin Pharmacol Ther.</i> 2002; 40:295-303. (IDIS Article Number 483923)</p> <p>Data from 2 independent randomized trials with a total of 517 patients, treated with trospium chloride 20 mg twice daily or placebo, was included in this meta-analysis that found trospium chloride was well tolerated and effective in treating detrusor overactivity.</p>				

***Chemical Type:**

1 - New molecular entity

Therapeutic Potentials:

P - Priority Review - Significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease.

S - Standard Review - The drug appears to have therapeutic qualities similar to those of one or more already marketed drugs.

V - Orphan Drug

Additional information on these newly approved drugs will be available in the FDA Approval Package [an official United States Food and Drug Administration (FDA) document] that is compiled for new drugs following approval. This document includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the IDIS database as they become available. Use descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the database.



Initial Pharmacotherapy in Early Parkinson's Disease

Hoehn and Yahr¹ described the natural history of untreated Parkinson's Disease (PD) in 856 patients seen by Neurology Service at Columbia-Presbyterian Medical Center from 1949 to 1964. They described the progression of parkinsonism in non-levodopa treated patients with systematic clinical evaluations. Their staging system was a tool for assessment of disease severity in individual patients that included the presence of signs and symptoms and an assessment of functional abilities.

The levodopa era began after major advances in the understanding of the neurochemical abnormalities associated with PD². Hornykiewicz and Ehringer in 1960 reported striatal dopamine depletion as a critical finding in the brains of PD patients. Following early reports of the antiparkinsonian efficacy of intravenous levodopa by Hornykiewicz and others, Cotzias et al³., demonstrated dramatic and sustained improvement in the symptoms of severely disabled patients with idiopathic PD using high dose oral levodopa therapy. Less than a decade later, in 1975 the combination of carbidopa-levodopa became commercially available.²

By 1974 Markham et al.⁴ at UCLA described the efficacy of levodopa in 100 patients who began therapy in 1968 or 1969, plus an additional 50 patients who were involved in special studies or presented special problems. Their description of the loss of improvement seen at five years relative to one year of levodopa therapy is classic. It appeared that PD was progressing in some patients on levodopa therapy. Even though levodopa therapy did not stop the progression of PD, they were able to report that only 35% of patients had become seriously disabled or died 16 years after diagnosis while on levodopa,

compared to 90% of patients who had become seriously disabled or died 16 years after diagnosis prior to the availability of levodopa.

Several of the major adverse effects of high dose levodopa therapy, including nausea, vomiting, and postural hypotension were greatly improved by the peripheral inhibition of dopa decarboxylase by carbidopa. Levodopa is now used in combination with one of several peripheral dopa decarboxylase inhibitors.

During the 1980's a long acting product Sinemet CRTM was claimed to provide more stable levodopa levels and hopefully more consistent efficacy. If the controlled release product is used doses 20-30% higher than regular SinemetTM must be used due to its reduced absorption. Some neurologists recommended dopamine agonists be used in early PD to avoid the motor complications associated with chronic levodopa use.

By the 1990's new information suggested that the neurochemical pathology of PD might involve an imbalance between at least two parallel dopamine output pathways from the striatum. Interested readers will find a detailed discussion and the rationale for

preferring dopamine agonists with D₂ rather than D₁ receptor subtype selectivity in the review by Gottwald and colleagues.⁵

American expert opinion on the medical management of PD has been restated by a group of movement disorder experts three times in the past decade, most recently in 2001 in the form of an algorithm for the management of PD.⁶ The editors were compelled to publish an update after only three years because of recent developments. The current algorithm includes the following statements:

"... pulsatile stimulation of striatal dopamine receptors now appears to be the key to the induction of levodopa related motor complications."

"...levodopa and short acting dopamine agonists are more likely to induce dyskinesia in MPTP treated monkeys than are long acting dopamine agonists."

"It is likely that the decreased incidence of motor complications observed with dopamine agonists is related to their relatively long half-lives rather than their specific molecular structure."

"... in the MPTP treated monkey, long acting dopamine agonists such as ropinirole

... prevent the appearance of dyskinesia that occurs with levodopa treatment or intermittent administration of a short-acting dopamine agonist.”

Taken together these statements indicate that American expert opinion has concluded the cause of the motor complications of chronic levodopa therapy relate to its short half life and the need for frequent daily doses.

Prospective double blind studies comparing initial treatment of PD with either ropinirole⁷ or pramipexole⁸ and levodopa have been completed. Both trials found significant reductions in motor complications associated with the long acting dopamine agonist when compared with levodopa therapy.

The first study to be reported was a five-year double blind comparison of ropinirole to levodopa in 286 untreated PD patients.⁷ Patients were randomized to begin treatment with ropinirole at a dose of 0.25mg three times daily or levodopa at a dose of 50 mg three times daily. Blinded study drug could be increased to maximal daily doses of 24 mg for ropinirole or 1200 mg for levodopa. Supplementary open-label levodopa could be added at any time if the investigator considered PD features to be inadequately controlled by the blinded study medication. The primary outcome measure was the presence of dyskinesia as indicated in the Unified Parkinson's Disease Rating Scale (UPDRS) assessments. Dyskinesia developed in 36/177 (20%) of the ropinirole group and in 40/88 (45%) in the levodopa group. Patients randomized to ropinirole had a significantly reduced risk for developing dyskinesia whether or not they required open-label levodopa. When the patients who were able to remain on ropinirole monotherapy were compared with those on levodopa monotherapy, only 5% the ropinirole group developed dyskinesia compared to 36% of the levodopa group. Although there were differences in the UPDRS motor and the activities of daily living scores in favor of levodopa, only the change in the motor score from baseline was significant for levodopa. The clinical relevance of the difference is

unclear since it was not reflected in any measurement of activities of daily living. Neuropsychiatric adverse events are a concern whenever levodopa or dopamine agonists are used in the treatment of PD. In this study there were more reports of hallucinations with ropinirole, 31 (17.3%), than with levodopa, 5 (5.6%). The hallucinations were described as mild and easily managed in most patients. Ropinirole significantly lowered the risk of dyskinesia when compared with levodopa but was associated with more neuropsychiatric adverse effects than levodopa.

Another study comparing pramipexole to levodopa in early PD was designed to evaluate the risk of developing motor complications.⁸ A total of 301 untreated PD patients who required dopaminergic therapy were randomized and followed for 24 months. Supplementation with open-label levodopa was allowed as in the ropinirole trial. The primary end point was the time to first occurrence of any of three motor complications: dyskinesia, wearing off or “on-off” effects. Fifty-one percent of levodopa patients reached the end point compared to only 28% of subjects randomized to pramipexole. When compared to levodopa, pramipexole treated subjects had less dyskinesia (10% versus 31%), wearing off effects (24% versus 38%), and “on-off” effects (1% versus 5%). As in the ropinirole study the UPDRS mean motor score was greater for levodopa. The clinical significance of the UPDRS motor scores differences is unclear, as the majority of patients in both groups did not require open label levodopa. Significantly more patients in the pramipexole group experienced somnolence, hallucinations than the levodopa group. Three subjects reported falling asleep while driving, 2 randomized to pramipexole and 1 to levodopa. Two of the events resulted in vehicle crashes one in each group. The trial supports a favorable motor complication profile for the dopamine agonist but with an increased incidence of neuropsychiatric side effects.

Recent experimental and clinical trial data both support the occurrence of fewer motor complications in early PD when patients are treated with dopamine agonists compared to levodopa. In any event, if needed the antiparkinsonian effect of the dopamine agonist could be supplemented at a later time with levodopa.

If patients are informed of the possibility of visual hallucinations as an adverse effect of levodopa or dopamine agonist therapy, they can easily distinguish them from reality. Patients can be assured the hallucinations are usually not a symptom of a psychiatric syndrome. The literature suggest the recent reports of “sleep attacks” with the dopamine agonists will reintroduce us to a syndrome common to all dopaminergic therapy and well described in the past with levodopa therapy and in PD. Obviously in patients who are driving, they may wish to refrain from driving especially during the upward dose titration of their dopamine agonist therapy until they have determined whether or not excessive sedation will be a problem.

Dopamine agonists have several actual or theoretical advantages over levodopa. First, they act directly on dopamine receptors and therefore act independently of the degenerating dopaminergic neurons. Second, plasma amino acids do not compete with dopamine agonists for absorption and transport into the brain. Third, the new dopamine agonists have a longer half life than either the immediate or controlled release levodopa products. Finally, they do not undergo oxidative metabolism and do not generate free radicals. Both ropinirole and pramipexole are non-ergot derivatives and are reasonably selective in stimulating D₂ or D₃ receptors.

Current expert opinion favors the early use of dopamine agonists in PD.

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