

# FDA Gastrointestinal Drugs Advisory Committee Review of 5-HT<sub>4</sub> Agonists

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Johnson & Johnson Pharmaceutical  
Research & Development, LLC

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## Introduction

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- FDA invited J&J PRD to review cisapride experience with regard to nonclinical, clinical pharmacology, clinical, safety, and Limited Access Program to help the GIDAC advise FDA on future 5-HT<sub>4</sub> agonist drug development
- The two events of interest:
  - Ventricular Tachyarrhythmias
  - Cardiac Ischemia
- Points to consider

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# Agenda

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**Cisapride Overview**

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**Non-clinical  
Cardiovascular Safety**

**Rob Towart, PhD**

Director, Center of Excellence for Cardiovascular Safety

**Clinical Pharmacology**

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**Clinical and Post-  
marketing Safety**

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# Cisapride Overview

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## Cisapride Overview

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- Cisapride is a 5-HT<sub>4</sub> agonist, stimulates motility in the gastrointestinal tract
- Discovered and developed by Janssen Research Foundation. IND filed 1983
- Approved in Europe 1988
- Approved in US 1993
  - Indicated for the treatment of symptoms of nighttime heartburn due to gastro-esophageal reflux disease in adults

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## Cisapride Overview

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- 1988 – 1994 Sinus tachycardia emerged as a safety signal\*
- 1994 – 2000 Labeling updates
  - Very rare cases of QT prolongation and Torsade de Pointes (TdP)
  - CYP3A4 metabolic pathway elucidated
    - Azole antifungals
    - Macrolide antibiotics
    - Grapefruit juice
  - QT prolonging drugs
  - Risk factors including cardiac history, bradycardia, electrolyte disturbances (K, Ca, Mg)
- 2000
  - Voluntary discontinuation from US market
  - Initiation of US Limited Access Program

\*Olsson, S. and Edwards, IR. *BMJ*. 1992

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# Non-clinical Cardiovascular Safety

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Rob Towart, PhD

Director, Center of Excellence for  
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## Background

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- Most ventricular arrhythmias are caused by structural damage to the heart (e.g., after an ischemic insult)
- Some individuals have congenital mutations to cardiac ion channels (e.g., Long QT Syndrome)
- Drug effects on cardiac ion channels (e.g., hERG) can be another cause of rare arrhythmias, especially in those with risk factors (e.g., hypokalemia, CYP-inhibitors)
- Importance of cardiac hERG channel blockade (and potential QT-interval prolongation) recognized from 1995 to 1997

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## Drug-Induced Cardiac Arrhythmias Not Always Predictive from Non-clinical Studies

- Not all hERG blockers prolong the QT interval, and not all QT prolongation is arrhythmogenic
- Effects on other ion channels or membrane proteins can increase or decrease the propensity for arrhythmogenesis
- Effects on the action potential, dispersion or variations of cardiac signals between different regions in the heart may also play a role

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## Original Non-clinical CV Safety Data

- CV safety studies during development of cisapride concentrated on cardiac contractility and hemodynamics
  - QT intervals were not initially corrected for heart rate
  - ECGs were not routinely measured in chronic toxicological studies
- Cisapride had no statistically significant effects on the action potential duration in Purkinje fiber, trabecular muscle *in vitro*
- Dog studies *in vivo* concluded that cisapride had no effects on QT interval
- In 16 clinical pharmacology and 18 therapeutic studies (~970 subjects) cisapride had no clinically significant effects on ECG, HR or BP

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## Studies after QT Prolongation Identified Clinically

- Wide range of additional non-clinical and clinical studies were performed by Janssen from 1995 – 2002
- Few effects were noted initially, as the use of more sensitive models (e.g., rabbit Purkinje fiber) was in its infancy
- Bradycardia and/or hypokalemia were initially needed to see effects
- The first studies with hERG began in 1998 ( $IC_{50} = 53 \text{ nM}$ )

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## 5-HT<sub>4</sub> agonists - hERG Blockade is not a “Class Effect”

Drug*	IC <sub>50</sub> Value (Source)
Metoclopramide	5,400 nM (Claassen & Zunckler, 2005)
<b>Cisapride</b>	<b>53 nM</b> (Hermans <i>et al.</i> , 1998)
Mosapride	>>30,000 nM (Potet <i>et al.</i> , 2001)
Renzapride	1,800 nM (Potet <i>et al.</i> , 2001)
Prucalopride	5,700 nM (Potet <i>et al.</i> , 2001)
Tegaserod	13,000 nM (GIDAC Background Material)
TD-5108	>>3,000 nM (Smith <i>et al.</i> , 2008)
PF-01354082	>300,000 nM (Mikami <i>et al.</i> , 2009)

\* Drugs presented in order of discovery

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## Overview of Cisapride and Ischemic Events

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- In perfused rabbit hearts cisapride does not cause coronary constriction
- In dog coronary arteries, cisapride was neither an agonist nor antagonist of 5-HT-induced relaxation. In pig coronary arteries cisapride blocked 5-HT-induced contractions (5-HT<sub>2</sub> antagonist effect)
- *In vitro* cisapride does not significantly affect human platelet aggregation
- In volunteers, cisapride does not significantly influence hemostatic parameters (bleeding time, hematocrit, platelet numbers, TxB<sub>2</sub> levels) when compared with placebo
- Cisapride was only a weak inotropic partial agonist on human atrial 5-HT<sub>4</sub> receptors

Non-clinical studies with cisapride detected no effects related to ischemic events

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## Non-clinical Points to Consider

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- hERG blockade is not a class effect of 5-HT<sub>4</sub> agonists
- Drug-induced QT-interval prolongation is now known to be multifactorial; therefore, a non-clinical evaluation of CV safety should be multifactorial
- There were no non-clinical signals for cardiac ischemia with cisapride

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# Clinical Pharmacology

Erik Mannaert, PhD

Clinical Pharmacology Therapeutic  
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# Pharmacokinetics

- Facts known at registration and approval
  - Almost complete absorption after oral dosing
  - Significant first pass, oral bioavailability only 40-50%
    - Extensive cytochrome P450 mediated metabolism
    - Excretion as metabolites, divided between urine/feces
- Post-approval investigations
  - Metabolism depends primarily on one P450 enzyme: CYP3A4
  - Clinically relevant interaction with potent CYP3A4 inhibitors:

<b>CYP3A4 inhibitor</b>		<b>Cisapride</b>	<b>N</b>	<b>Ratio C<sub>max</sub></b>	<b>Ratio AUC</b>
Ketoconazole	(200 mg b.i.d.)	10 mg SD	14	2.59	7.90
Erythromycin	(500 mg q.i.d.)	10 mg q.i.d.	12	1.97	2.05
Grapefruit juice	(200 mL q.i.d.)	10 mg q.i.d.	14	1.46	1.50

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## Pharmacodynamics

- Healthy subjects: Tolerability, PK and PD at approval
  - Dose-range investigated
    - Single dose 2.5 – 40 mg
    - Repeated dose 5 mg t.i.d. – 10 mg q.i.d.
  - No relevant effects on BP, HR, ECG, respiration rate, temperature
    - 16 studies including 173 healthy subjects
    - Standard battery of ECG and safety assessments (no thorough QT approach)

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## Pharmacodynamics

- Post-approval CV-safety studies in healthy subjects

Year	Study/ Objective	CIS Dose	N	Mean C <sub>max</sub> ng/mL	Mean ΔQT <sub>c,max</sub> msec	Mean ΔQT <sub>c,avg</sub> msec
1996	CIS-USA-98 Repeated Dose	10 mg q.i.d.	22	79.0	0.4 (NS)	3.7
		20 mg b.i.d.	21	101	8.2	4.5
		20 mg q.i.d.	21	135	0.9 (NS)	3.9
2000	CIS-NED-32 Escalating Single Dose	PLAC	20	0	9.8	0.8 (NS)
		10 mg	20	44.9	12.2	1.3 (NS)
		20 mg	19	72.7	8.3 (NS)	2.8 (NS)
		40 mg	18	122	<b>37.2</b>	<b>17.0</b>
		80 mg	17	178	<b>30.1</b>	<b>17.5</b>
		130 mg	15	242	<b>44.9</b>	<b>28.8</b>

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## Clinical Pharmacology Points to Consider

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- In-depth knowledge on clearance pathways qualitatively and quantitatively
  - Identification of intrinsic/extrinsic factors determining absorption, metabolism and excretion of the drug
  - Confirmed with relevant *in vivo* DDI studies
- Safety and tolerability investigations
  - To include **relevant multiples** of the therapeutic dose-range
  - Properly designed **thorough QT study in humans** to detect treatment effects (assay sensitivity, placebo, size)

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## Cisapride: Clinical and Post-marketing Safety

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## NDA Clinical Development

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- 1257 subjects (979 exposed to cisapride)
- Most common AEs reported (NDA)
  - Headache: 17%
  - Diarrhea: 15%
- At the time of approval, FDA concluded that frequencies of heart rate and cardiac rhythm disorders similar in cisapride-versus placebo-treated subjects

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## Cisapride Safety Review: Ventricular Tachyarrhythmia and Cardiac Ischemia Related Events

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- During post-marketing surveillance:
  - Ventricular tachyarrhythmia was identified as a signal and has been well characterized
  - Cardiac ischemia was not identified as a signal either through surveillance or literature review
- A cumulative aggregate review\* of cases reporting ventricular tachyarrhythmia and cardiac ischemia related events was conducted
- This cumulative review confirmed findings from post-marketing experience

\* Cumulative to 25 July 2011

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## Limited Access Program (LAP) Overview

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- Initiated in 2000 after discontinuation
- Intended for patients without other therapeutic options who meet inclusion criteria
- Adult and pediatric protocols
  - GERD, gastroparesis, pseudo-obstruction, severe chronic constipation
- Safety monitored and reported to FDA

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## LAP Details

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- Diagnostic evaluation and safety monitoring
  - Baseline diagnostic evaluation, including radiology/endoscopy
  - Baseline screening tests, including laboratory tests and ECG to rule out contraindicated risk factors
  - Clinical re-evaluation at regular intervals with laboratory tests, ECG, and physician attestation of continued patient benefit

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## LAP Baseline Diagnoses

	Adults (%) n=1286	Pediatrics (%) n=283	Combined (%) n=1569
<b>GERD</b>	32.8	54.4	36.7
<b>Gastroparesis</b>	56.9	22.3	50.7
<b>Pseudo-obstruction</b>	6.7	19.1	8.9
<b>Severe chronic constipation</b>	2.7	3.2	2.8

Gender distribution (%):  
 Adults: 26/74, M/F  
 Pediatrics:50/50, M/F

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## Safety Data from LAP

- Reasons for discontinuation:
  - Cured/asymptomatic
  - No longer benefits
  - Appearance of risk factors
  - SAE (including QTc greater than study-defined limits)
- No TdP
- No signal for cardiac ischemic events

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## Summary

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- hERG channel blockade is not a 5-HT<sub>4</sub> agonist class effect
- Understanding evolved
  - Drug metabolism
  - Drug-drug interaction
  - Evaluation of QT prolongation
- No safety signal was identified for cardiac ischemic events with cisapride use
- Cisapride LAP enrollment suggests a continued unmet medical need

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## Back-up Slides

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## Cisapride History

Date	Event	Labeling changes
April 1988	European Approval	
July 1993	FDA Approval	
Feb 1995	Labeling changes, letter to HCP	Drug interaction: ketoconazole, itraconazole, troleandomycin, miconazole
Sep 1995	Labeling changes, letter to HCP	Drug interaction: erythromycin, clarithromycin, fluconazole
June 1998	Labeling changes, letter to HCP, and FDA talk paper	Contraindication: disorders that may predispose patients to arrhythmias with cisapride Drug interaction: drugs known to prolong the QT interval and increase the risk of arrhythmia
June 1999	Labeling changes, letter to HCP	Contraindication: clinically significant bradycardia Drug interaction: grapefruit increases the bioavailability of cisapride
Jan 2000	Labeling changes, letter to HCP, and FDA talk paper	Monitoring: electrocardiogram required before starting cisapride, and starting therapy not recommended if QTc value > 450 msec Contraindication: electrolyte disorders hypokalemia, hypocalcemia, hypomagnesemia); patients taking diuretics should have electrolytes checked before start of therapy and periodically thereafter
Jul 2000	United States marketing voluntarily discontinued; available through the Limited Access Program	
Oct 2003	Marketing discontinued worldwide	

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## LAP Subject Disposition (Back-up)

### Cumulative\* Exposure to and Discontinuation of Treatment With Cisapride

Study #	Received Drug	Discontinued Treatment	Completed Treatment/ Cured	Ongoing Drug Treatment
CIS-USA-154	1309	1055	71	254
CIS-USA-156	286	234	37	52

\*Cumulative through 31 May 2011

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## CIOMS Threshold Criteria

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- According to the source
  - 1a. Evidence from individual cases
    - Eg, Positive rechallenge, positive dechallenge, lack of confounding factors, lack of alternative explanation
  - 1b. Evidence from clinical trials/studies
    - Eg, Statistically significant difference, consistent trend in studies, positive dose response
- Supportive evidence from both of the above sources
  - Eg, Consistency of pattern of presenting symptoms, identifiable subgroup at risk
- Previous knowledge of the AE or the Drug/Class
  - Eg, biological plausibility
- Other factors
  - Eg, outside turbulence (publicity) surrounding the drug, status/credibility of reporter

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## Pediatric Trial for SBS

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- Cisapride Improves Enteral Tolerance in Pediatric Short-bowel Syndrome With Dysmotility, Bram P. Raphael BP, et. al. Children's Hospital Boston, Harvard Medical School, Boston, MA.
- JPGN 2011;52: 590–594

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