Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Advisory Committee Briefing Document

Briefing Document for FDA Gastrointestinal Drugs Advisory Committee Meeting Regarding Serotonin (5-hydroxytryptamine) Receptor 4 Agonists [17 November 2011]

Experience Related to Cisapride

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TABLE OF CONTENTS

TABLE OF CONTENTS 2

LIST OF IN-TEXT TABLES 4

LIST OF IN-TEXT FIGURES 5

LIST OF ABBREVIATIONS 6

1. INTRODUCTION 8
1.1. Meeting Purpose 8
1.2. Cisapride Regulatory Background 8
1.3. Cisapride Development Experience 10

PART I: CISAPRIDE: AGGREGATE SUMMARY INFORMATION ON CARDIAC SAFETY AND POINTS TO CONSIDER BASED ON EXPERIENCE 11

1. BACKGROUND TO DRUG-INDUCED VENTRICULAR ARRHYTHMIAS 11

2. NON-CLINICAL STUDIES 13
2.1. Cardiovascular Non-Clinical Safety Data 13
2.2. Non-Clinical Studies Performed by the Sponsor When QT Prolongation Was Identified 14
2.2.1. Cardiac Repolarization and the hERG Channel 16
2.2.2. Single Cell Studies 17
2.2.2.1. The Cardiac Delayed-Rectifier Potassium Current 17
2.2.2.1.1. I_{Kr} Cultured Cells HEK 293 17
2.2.2.1.2. In Vitro Isolated Myocytes 17
2.2.3. Other Cardiac Channels 18
2.2.4. Drug Interaction Studies in Single Cells 18
2.2.5. Conclusions 18
2.3. Non-Clinical In Vivo Studies 18
2.3.1. Dogs 19
2.3.2. Guinea-Pigs 19
2.3.3. Rabbits 20
2.3.4. Pigs 20
2.3.5. Cisapride Enantiomers and Metabolites 20
2.3.6. Cisapride and In Vivo Models of Torsades de Pointes 20
2.4. Platelet Aggregation 23
2.5. Relevance of Non-Clinical Studies of Cisapride to Clinical Use 23
2.6. Overview of Non-Clinical Cardiac Ischemic Events 24

3. CLINICAL PHARMACOLOGY STUDIES 25
3.1. Overview 25
3.2. Clinical Pharmacology of Cisapride 26
3.2.1. Summary of Results of Studies Between First-In-Human dosing and First Marketing (April 1988) 26
3.2.2. Post-Marketing Clinical Pharmacology Investigations (1988 – early 2000s) 28
3.2.2.1. Post-Marketing Human Metabolism and Drug Interaction Update 28
3.2.2.2. Post-Marketing Human CV-Safety Update in Healthy Volunteer Studies 30
3.2.2.3. Summary of Effects on the Cardiovascular System 32

4. PRE-APPROVAL CLINICAL TRIALS 32

5. CUMMULATIVE REVIEW OF CASES RETRIEVED FROM THE COMPANY SAFETY DATABASE FOR CISAPRIDE 33

6. LIMITED ACCESS PROGRAM (LAP) – UNITED STATES 33

PART II SUMMARIES AND CONCLUSIONS OF LITERATURE REVIEWS ON VENTRICULAR ARRHYTHMIA AND ISCHEMIC EVENTS AS REQUESTED BY FDA **35**

1. INTRODUCTION AND METHODS **35**
1.1. Ventricular Arrhythmias Related to Cisapride 35
1.1.1. Non-Clinical Use 35
1.1.2. Effects on the Human Cardiovascular System 36
1.1.2.1. Adults 36
1.1.2.2. Neonates, Premature Neonates, Infants and Children 37
1.1.2.3. Elderly 42
1.1.2.4. Organ Impaired Population 42
1.1.2.5. Diabetic Patients 42
1.1.2.6. Pharmaco-Epidemiology Studies 44
1.2. Ischemic Cardiac Events Related to Cisapride 46

PART III **47**

1. POINTS TO CONSIDER BASED ON EXPERIENCE WITH CISAPRIDE **47**
1.1. Non-Clinical 47
1.2. Clinical 47
1.3. Post-Approval Safety Surveillance 48

REFERENCES **49**

SUPPORTING DATA **58**
Attachment 1: Cisapride United States Package Insert 58

LIST OF IN-TEXT TABLES

Table 1: 5-HT_4 Agonists – hERG Blockade is not a "Class Effect" 12
Table 2: Summary of Cardiovascular Effects 14
Table 3: The Sponsor's Non-Clinical Studies With Cisapride 16
Table 4: Cisapride Steady State Pharmacokinetics for Different Treatment Regimens 24
Table 5: Inhibition of Cisapride Metabolism in Human Liver Microsomes 29
Table 6: Effect of Metabolic Interactions on the Pharmacokinetics of Cisapride 30
Table 7: Summary of Effects of Cisapride and of the Combination of Cisapride With Metabolic Inhibitors on the QTc Interval 31

LIST OF IN-TEXT FIGURES

Figure 1: The Relationship Between hERG Blockade and Arrhythmogenic Risk..... 12
Figure 2: Comparison of Onset of Cisapride-Induced Torsades De Pointes (TdP) Between 0-2-Weeks and >4-Weeks Model After Atrioventricular Block. Cisapride at 1-10 Times of Clinically Relevant Maximum Daily Dose was Orally Administered in Conscious Animals in Each Model Studied. ECG was Monitored for 420 h Using Holter ECG Recording System..... 21
Figure 3: Summary of the Effects of a (I_{Kr}) Blocker on the ECG of the Chronic Atrioventricular Block Monkey Model. (12 Weeks After AV Block)..... 22
Figure 4: Electrocardiograms (leads aVL, aVF) Demonstrating Induction of Torsades De Pointes in an Anesthetized Rabbit Given Cisapride (0.3 pmol/kg/min IV). The Tachyarrhythmia was Induced After a Cumulative Dose of 1.1 pmoi/kg Cisapride. 22
Figure 5: Effects of Torsadogenic Compounds (Cisapride, Clofilium, Dofetilide, Quinidine) and Non-Torsadogenic Compounds (Amiodarone, Verapamil) on the Incidence of Torsades De Pointes (TdP) in Anesthetized Rabbits Without (black) and With (white) Failing Hearts..... 23

LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
AE	adverse event
APD	action potential duration
AUC	area under the curve
AV	atrioventricular
CI	confidence interval
CIC	chronic idiopathic constipation
C_{max}	maximum plasma concentration
CNS	central nervous system
CPMP	Committee on Proprietary Medicinal Products
CV	cardiovascular
CYP	cytochrome P
DB	double blind
DDI	drug-drug interactions
EAD	early after depolarization
EU	European Union
FDA	Food and Drug Administration
GA	gestational age
GERD	gastroesophageal reflux disease
GIDAC	gastrointestinal Drugs Advisory Committee
hERG	human ether a-go-go-related gene
HEK	human embryonic kidney
HR	heart rate
HSA	human serum albumin
IBS	irritable bowel syndrome
IC_{50}	concentration producing 50% inhibition
ICH	International Conference on Harmonisation
I_{Na}	sodium current carried by sodium channels
IND	Investigational New Drug
IK	potassium current
I_{K1}	potassiun current carried by the inward rectifier potassium channel
I_{Kr}	potassiun current carried by the rapid delayed rectifier channel
I_{Ks}	potassium current carried by the slowl delayed rectifier channel
IV	intravenous
LAP	Limited Access Program
LQT	Long QT Syndrome
MAP	mono-phasic action potential
NDA	New Drug Application
PCA	post conceptual age
PD	pharmacodynamics
PK	pharmacokinetics
PMN	polymorphonuclear leukocytes
PPI	proton pump inhibitor
q.i.d	four times daily
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcVdW	Qt interval corrected for heart rate using the Van de Water’s formula
SD	standard deviation
SIDS	sudden infant death syndrome
SGA	small for gestational age
SMQ	standard MEDRA Query

SQT	Short QT Syndrome
TdP	Torsades de pointes
tQT	thorough QT
UK	United Kingdom
US	United States
VA	ventricular arrhythmia

1. INTRODUCTION

1.1. Meeting Purpose

The purpose of this Food and Drug Administration (FDA) Gastrointestinal Drugs Advisory Committee Meeting is to discuss products in the class of serotonin (5-hydroxytryptamine) receptor 4 ($5HT_4$) agonists for the proposed indications chronic idiopathic constipation (CIC), irritable bowel syndrome (IBS), gastroparesis, and proton pump inhibitor (PPI)-refractory GERD [gastroesophageal reflux disease] and to make recommendations to the FDA on the design of premarket development programs for the evaluation of cardiovascular safety for drugs in the class.

The goal of the meeting is to provide a forum for discussion between the Agency, Sponsors, and academic community of the challenges as well as experience gained from $5\text{-}HT_4$ agonist studies.

The purpose of this document is to provide:

- Cisapride aggregate/summary information from non-clinical studies, clinical studies, post-marketing reports, and the US Limited Access Program (LAP) for known risks, eg, ventricular arrhythmias and for ischemic cardiac events
- Results of literature reviews on ventricular arrythmias and ischemic cardiac events related to cisapride
- Points to consider

The first part of this document (Part I) provides information to respond to the FDA's request for the Sponsor to provide its experience and research of ventricular arrhythmia (a known risk) and ischemic cardiac events in non-clinical and clinical studies, as well as post-marketing reports, and the US Limited Access Program (LAP) for cisapride. The sponsor has also summarized points to consider for future non-clinical and clinical development based upon experience with cisapride. Information in Part I will be presented at the Meeting.

Part II presents the methods and results of a literature review requested by the FDA. The results of the literature review will not be presented at the Advisory Committee Meeting.

Part III contains points to consider based on the Sponsor's experience gained with cisapride. Information in Part III will be presented at the Meeting.

1.2. Cisapride Regulatory Background

Cisapride is a $5\text{-}HT_4$ receptor agonist; it stimulates and coordinates propulsive motility throughout the gastrointestinal tract. Cisapride (Propulsid®, Prepulsid™) was launched in 1988. It had clear advantages over the original prokinetic benzamide drug, metoclopramide. With minimal central nervous system (CNS) penetration, and a different pharmacological profile, it was clinically effective, but had no overt CNS side effects. It was well tolerated, and the extensive non-clinical testing showed no notable cardiovascular risks.

Beginning in 1994, the emergence of spontaneous adverse-event reports began to raise suspicion of the very rare occurrence of serious and sometimes fatal ventricular arrhythmias (VA). In most reports of serious VA, cisapride had been inappropriately prescribed, ie, to a patient who either had underlying risk factors for VA or who, concurrently, was taking contraindicated medication(s).[161] The resulting increase in steady state plasma levels with such contraindicated co-medication(s) caused a prolongation of QT interval, and very rarely, Torsades de pointes (TdP) including a number of deaths. Since many of these cases occurred in patients taking drugs concomitantly with cisapride that inhibited CYP450-3A4 enzymes that metabolize cisapride, a "black boxed" warning was added to the cisapride label in 1995. This warning contraindicated the use of cisapride in patients taking medications that affected cisapride metabolism. As the use of cisapride continued to increase in the US between 1995 and 1998, the FDA expanded the black-box warning in June 1998 to contraindicate cisapride use in patients taking medications that could prolong QT intervals or in patients with baseline heart disease or other conditions that could predispose them to cardiac arrhythymias.[123] The current USPI for cisapride is located in Attachment 1.

Experience has been gained from cisapride (and other potentially QT-prolonging drugs, such as terfenadine, and hERG liability, clinical QT effects, metabolic profiling and drug/drug interactions are now carefully examined during drug development. To this day, Janssen (hereafter referred to as the Sponsor, which includes all Janssen operating companies) maintains a highly active research program investigating all aspects of QT-prolonging drugs and the development of arrhythmias. [49,142,143,144]

Based on patient exposure assumptions from three main regions, ie, United States (US), European Union (EU) countries and the rest of the world, the Sponsor estimated the rate of spontaneous postmarketing reports of QT prolongation, serious ventricular arrhythmia, and sudden death together to be between 0.5 and 7.6 cases per one million patient months of cisapride use. The wide range of estimates reflects dose and therapeutic use of cisapride, and variations in pharmacovigilance and reporting practices around the world.

In March 2000, the Sponsor made the decision to voluntarily discontinue Propulsid from the US market, while at the same time developing a patient access program (the Limited Access Program) designed to keep cisapride available to qualifying patients in need with no other viable therapeutic alternatives.

In June 2000, the German Health Authority presented a referral to the European Agency for the Evaluation of Medicinal Products, requesting that the Committee on Proprietary Medicinal Products (CPMP) review the overall benefit/risk profile of cisapride. As a result of that procedure, in May 2002, the European Commission issued a Decision, endorsing the opinion of the CPMP that the marketing authorizations for cisapride-containing products in the EU member states should be maintained, but restricting the use of the products.

The company complied with the requirements of the Commission Decision and created a registry program and clinical trials, as approved by the CPMP. However, in October 2003, as a result of a

review of the use of cisapride worldwide the Sponsor decided to discontinue marketing all cisapride-containing products.

1.3. Cisapride Development Experience

At the time of the US New Drug Application (NDA) submission in 1988, the main clearance pathway of cisapride was known to be hepatic metabolism: however, its dependence primarily on a single cytochrome, CYP3A4 was not known. The latter was revealed in the first half of the 1990s, on the basis of both evolved scientific understanding of the CYP system and on improved in-vitro methods. In follow up of that, the post-approval completion of an in-vivo healthy volunteer drug-drug interaction (DDI) studies with cardiovascular (CV) safety assessments, revealed the potential for clinically relevant drug interactions on the basis of inhibition of CYP3A4.

At the same time, the conclusions of cardiovascular safety investigations at the time of submission were mainly valid for the therapeutic dose-range, although it is now known that these conclusions are not the same for multiples of the dose-range investigated in healthy volunteer and in patient treatment studies. Whereas electrocardiograms (ECGs) were included as part of the standard safety battery in pharmacokinetic (PK) and pharmacodynamic (PD) studies, given that the concept of "thorough QT" study did not exist in the 1980's, these pre-approval clinical studies were not designed, powered, executed and analysed the same way as could be expected from CV-safety studies in the 1990s and beyond. The original submission did not contain what we today know and refer to as a "thorough QT" (tQT) study (ICH E14 Guidance 2005[71]).

In today's clinical pharmacology research and regulatory environment, these considerations are incorporated in every new development program. In-depth knowledge on clearance pathways, both qualitative and quantitative, and confirmed with relevant in-vivo DDI studies, is currently an expectation and prerequisite for approval of NDAs. In addition, safety and tolerability investigations do include multiples of the therapeutic dose ranges, in order to account for possible increases in plasma exposure due to relevant intrinsic/extrinsic factors that influence the PK/PD of the compound.

Based on the experience of QT-interval prolongation and VA in 5-HT_4 agonist compounds (not all of these experiences are necessarily related to cisapride itself), the Sponsor conducted comprehensive non-clinical testing and identified aspects that should be carefully considered for any 5-HT_4 agonist, which are summarized in the section on points to consider based on experience with cisapride (Part III) of this document.

These tests include the "core tests" recommended by International Conference on Harmonisation (ICH) S7A and S7B[72,73], and because of our experience and the possibility of drug effects on other ion channels, the Sponsor recommends a more comprehensive series of additional and supplemental tests to generate a broad profile of the cardiovascular profile at therapeutic and supra-therapeutic dose levels.

PART I: CISAPRIDE: AGGREGATE SUMMARY INFORMATION ON CARDIAC SAFETY AND POINTS TO CONSIDER BASED ON EXPERIENCE

This section highlights the Sponsor's experience and research of ventricular arrhythmia (a known risk) and ischemic cardiac events in non-clinical studies, clinical studies, pre-approval clinical studies, as well as post-marketing reports, and information on the US Limited Access Program (LAP) in cisapride.

1. Background to Drug-Induced Ventricular Arrhythmias

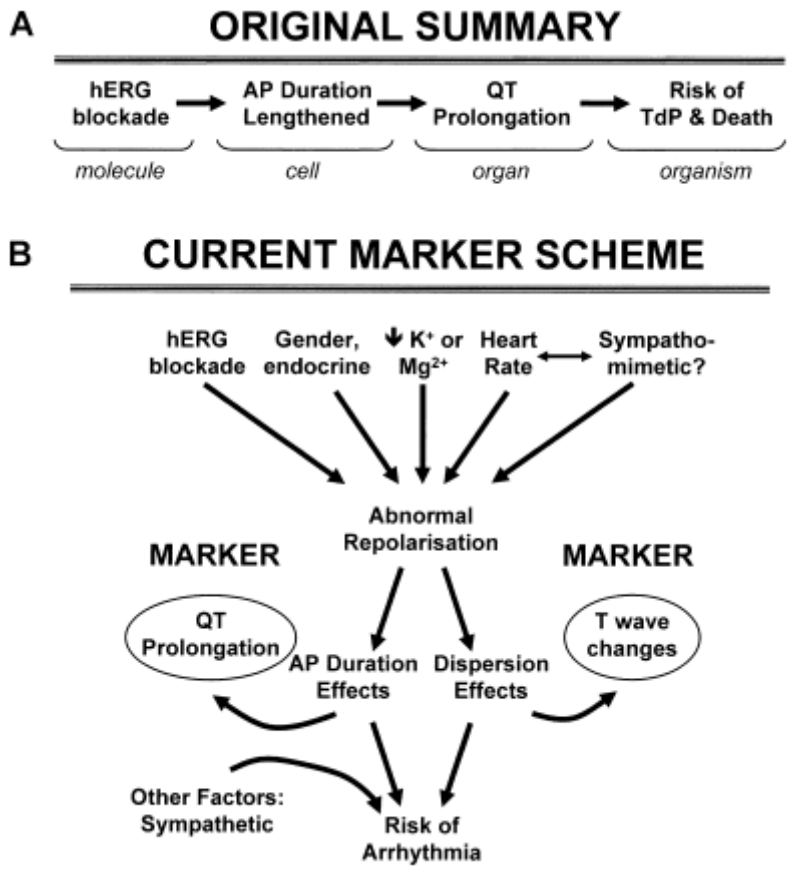
Most ventricular arrhythmias are caused by structural damage to the heart, eg, after an ischemic insult. However a small number of individuals have congenital mutations to proteins involved in the ion channels involved in the heart's electrical activity. Most of these manifest themselves as Long QT Syndromes (LQTs), although there are other mutations that cause Short QT (SQT) syndrome.

Drug effects on cardiac ion channels are another cause of arrhythmias, especially if the individuals have one or several of the (now) well-known risk factors (eg, hypokalemia, polypharmacy, pre-existing cardiovascular disease, diabetes). Drug-induced arrhythmias have been known since the introduction of quinidine in 1918, but the plethora of new drugs in the second half of the 20th century produced many more examples. Thioridazine was one of the earliest ones to be recognised (eg, Stratmann and Kennedy, 1987[127]). Some such drugs were withdrawn because of their association with ventricular arrhythmias (eg, terodiline, in 1991). In the mid 1990s it was recognised that most of these pro-arrhythmic drugs blocked the cardiac human ether a-go-go (hERG) channel, and in the last decade most new drugs have been screened for hERG block and/or QT prolongation. Many drugs have been withdrawn because of their arrhythmogenic potential (eg, terfenadine, grepafloxacin). In addition many in silico algorithms have been developed to identify chemical structures associated with pro-arrhythmia even at the pre-synthesis stage.

The situation is more complex than originally believed in the late 1990s (See Figure A in Figure 1). Not all hERG blockers prolong the QT interval, and not all QT prolongation is arrhythmogenic. In addition, some drugs inhibit the synthesis of the hERG protein, or prevent its post-expression modification and/or trafficking to the cell membrane. Also, effects on other ion channels or membrane proteins can increase or decrease the propensity for arrhythmogenesis. Other effects, such as triangulation of the action potential (AP), or variations in dispersion (the mistiming of cardiac signals between different regions within the heart), seem to play a role. In addition, many drugs are metabolised by cytochrome P450 enzymes (mainly in the liver): thus hepatic insufficiency or inhibitors of cytochrome (CY) P enzymes can markedly increase the circulating levels of an otherwise innocuous-seeming drug. The steady state plasma levels of the recommended dose (10 mg q.i.d.) of cisapride, for example, increase by a factor of around 8-fold when co-administered with the CYP3A4 inhibitor ketoconazole. [23,98]

For these reasons a comprehensive non-clinical testing strategy is now required to examine the safety of a new drug.

Figure 1: The Relationship Between hERG Blockade and Arrhythmogenic Risk



(A) Original summary and (B) Current marker scheme. AP, cardiac action potential; TdP = Torsades de pointes.[159]

Since cisapride has now been shown to be a potent blocker of the cardiac hERG channel, it may be useful to point out that hERG blockade is sometimes found to be a "class effect" of certain types of drugs (eg, antipsychotics, fluoroquinolone antibacterials). However, a literature review suggests that hERG blockade is not a class effect of 5-HT_4 agonists; cisapride is the only 5-HT_4 agonist with potent hERG blockade (Table 1).

Table 1: 5-HT_4 Agonists – hERG Blockade is not a "Class Effect"

Drug	IC_{50} Value (Source)
Metoclopramide	5,4000 nM[18]
Cisapride	53 nM [61]
Mosapride	30,000 nM[112]
Renzapride	1,8000 nM[112]
Prucalopride	5,700 nM[112]
Tegaserod	"no cause for concern" [44]
TD-5108	3,000 nM [124]

2. NON-CLINICAL STUDIES

This section summarizes the Sponsor's experience and research on ventricular arrhythmia and ischemic cardiac events in non-clinical studies.

Non-clinical cardiovascular safety studies in the 1980s concentrated on cardiac contractility and hemodynamics, not the ECG. Once the potential for QT-prolongation was observed in the 1990s, the Sponsor developed a comprehensive non-clinical research program to determine the effects of cisapride on QT intervals.

2.1. Cardiovascular Non-Clinical Safety Data

QT intervals were not initially corrected for heart rate (which increased in some studies, possibly masking any prolongation of QTc interval). Similary, ECGs were not always routinely measured in chronic toxicological studies in the 1980s. In vitro studies concluded that cisapride had no effect on cardiac action potential In vivo dog studies concluded that cisapride had no effect on the ECG or QT interval (Table 2).

Table 2: Summary of Cardiovascular Effects

Technique	No. of Animals	Cisapride Treatment	Results
In vitro: - dog Purkinje fibers - dog trabecular muscle - guinea pig auricular muscle Intracellular micro-electrode techniques	8* 10* 12*	0.5 mg/l in tyrode sln. for 30 min.	No effect on action potential duration, rate of rise, membrane potential, recovery time, conduction velocity, spontaneous activity or diastolic depolarization. Minor increase in the effective refractory period of dog trabecular muscle.
In vivo: Mongrel dogs Acutely instrumented anesthetized	7	0.5, 0.12, 0.25, 0.50 and 1.0 mg/kg	No effect ECG - 0.5 to 1.0 mg/kg: decrease in AoPs and AoPd; increase in LV dp/dt max, Aov max, Aodv/dt max and [LV dp/dt max]/P - 0.12 to 1.0 mg/kg: decrease in SVR - 0.25 to 1.0 mg/kg: increase in HR - 0.50 to 1.0 mg/kg: increase in CO; decrease in LVEDP and PVR No effect on PAPs, PAPd, PRP, SV, LVSW or RVSW
Labrador dogs Chronically instrumented unanesthetized	6	0.63 mg/kg IV	Slight excitement post-injection. No effect on SBP, DBP, HR, QRS complex, QT or PQ intervals, pressure-rate product, LV dp/dt max, [LV dp/dt max]/P or behavior.
	3	2.5 mg/kg IV	Aggression, defecation, tachycardia and hypertension
Labrador dogs Chronically instrumented unanesthetized	7	1.25 mg/kg IV	During first hour slight increase in HR, SBP, DBP, [LV dp/dt max]/P and pressure-rate product; slight decrease in PQ interval. Decrease in arterial PCO2 for more than 4 hours. No change in QT interval, QRS complex, LV dp/dt max, arterial pH, PO2 or base excess.
Labrador dogs Chronically instrumented unanesthetized	7	1.25 mg/kg PO	Decrease in arterial PCO2, starting within 1 hour, lasting over 4 hours, tendency to decrease in arterial base excess and increase in arterial pH. No effect on behavior, SBP, DBP, HR, QT and PQ intervals, QRS complex, pressure-rate product, arterial PO2, LV dp/dt max or [LV dp/dt max]/P
Labrador dogs Chronically instrumented unanesthetized	7	2.5 mg/kg PO	Decrease in arterial pH. 90 min. after dosing: increase in LV dp/dt max and [LV dp/dt max]/P; decrease in PQ interval. Tendency to decrease in aortic BP. 3 hours after dosing: decrease in pressure-rate product. No effect on HR, QT interval, QRS complex, arterial PCO2, PO2 or base excess.

*In vitro studies
References[146,134,145,25,26,27]

2.2. Non-Clinical Studies Performed by the Sponsor When QT Prolongation Was Identified

The potential electrophysiological effects of cisapride under normal and abnormal (eg, hypokalemia, bradycardia) experimental conditions were investigated initially using isolated cardiac tissue, and later, involving either hERG-transfected cells or isolated cardiomyocytes.

In January 1995 the Sponsor submitted an "Action Plan" to the FDA, including non-clinical investigations of the effects of cisapride and its metabolite norcisapride on isolated canine and guinea-pig ventricular tissue.

The observations with cisapride in the clinic were shown to be mainly due to higher than normal plasma levels, especially with co-medication with drugs that can inhibit the metabolism of cisapride, and which themselves, could prolong the QT interval (eg, ketoconazole, erythromycin). However, the non-clinical study of QT prolongation was in its infancy in 1995, and there turned out to be marked differences in the susceptibility of cardiac tissues, and tissues from different species to what are now known to be hERG blockers. One of the most sensitive species for examining hERG blockade is the rabbit (which has a low "repolarisation reserve" because it expresses little I_{Ks}[42], but this was not known in 1995. Another problem in examining QT prolongation is the effect of drugs with mixed ion channel blocking activity. Verapamil is a potent hERG blocker, but this effect is offset by its calcium channel blocking activity. Terfenadine also has a mixed ion channel blocking activity, with hERG and calcium channel block, and it has proved difficult to show its effects on action potential duration (eg, Gintant et al., 2001[50]). Cisapride blocks hERG and calcium channels, and both internal and external studies[50] have shown biphasic effects on action potential duration in isolated cardiac tissue.

The initial non-clinical studies showed little effect of cisapride on the cardiovascular system.

Additional non-clinical safety pharmacology studies were reported in early 1995 using the canine Purkinje fibre model (because the action potential duration (APD) of Purkinje fibres had previously been shown to be prolonged by certain drugs[1], thus proving it to be a potentially useful assay. Cisapride showed little effect on the various parameters measured (including APD) up to a concentration of 10^{-6}M, even under conditions of hypokalemia[93]. Indeed, a concentration of 10^{-5}M shortened the action potential duration. The only effect was a lengthening of APD at low frequency of stimulation (0.5 Hz) when treated with 10^{-6}M cisapride[93].

A similar study in guinea-pig papillary muscles followed, but this preparation was more sensitive to cisapride[157].

To properly investigate the effects of cisapride, the mechanism of action, and to understand the relevance of risk factors in the clinic, the Sponsor's non-clinical studies continued, using a variety of in vitro and in vivo models, and carefully examining published reports of external studies[34].

As research with QT-prolonging drugs continued, both by the Sponsor and externally, it became apparent that different tissues, from different species, behaved differently, and that different parameters (eg, action potential duration, triangulation of AP, and early afterdepolarization (EADs) were all potentially important markers of a drug's pro-arrhythmic potential [94,96] that the rabbit purkinje fibre, not the canine, was one of the most sensitive species for examining QT-prolonging drugs[94].

Table 3: The Sponsor's Non-Clinical Studies With Cisapride

Species	Tissues	Study Dates
Canine	Purkinje fibers (with bradycardia, hypokalemia)	March-April 1995
Guinea-pig	Papillary muscle	1995
Guinea-pig	Ventricular strips	1995
Canine (anesthetized)	hERG channels	1998, 1999
Rabbit	Purkinje fibers	1999
Guinea-pig (isolated)	Ventricular myocytes	1999
Guinea-pig (anesthetized)	In vivo: hemodynamics and ECG intervals	2000
Canine (instrumented, awake)	In vivo: hemodynamics and ECG intervals	2000
Rabbits (anesthetized, challenged with methotrexate)	In vivo: ECG intervals and occurrence of TdP	2000
Langendorff	Heart	2001

In 1995 academic researchers found that mutations in a particular cardiac potassium channel (hERG) in cardiac muscle were responsible for congenital QT interval prolongation (Section 2.2.1), and it was suggested that a block of this channel was probably responsible for the arrhythmias occasionally observed with certain drugs[118,115]. A detailed non-clinical examination of cisapride was continued by the Sponsor, using both existing models, and the new scientific methods (eg, hERG transfected cells) which were being developed at that time by academic laboratories. This non-clinical investigation continued until the year 2002.

2.2.1. Cardiac Repolarization and the hERG Channel

The focus of drug effects on cardiac electrophysiology was originally to increase the refractory period of cardiac tissues, and thus to produce an antiarrhythmic effect. It has long been known that some drugs could increase both action potential duration and refractory period. However, this was regarded as an antiarrhythmic rather than a pro-arrhythmic effect[15]. Indeed, some of the most potent hERG blockers, the methanesulphonamides such as class III agents like dofetilide, are used to restore sinus rhythm in atrial fibrillation.

It was suggested that drug-induced blockade of cardiac potassium channel (hERG or the potassiun current carried by the rapid delayed rectifier channel (I_{Kr})) would prolong the duration of the cardiac action potential in studies in vitro, and would prolong the QT interval in studies in vivo (and in humans)[118,81,115].

Two external studies (Rampe et al., 1997[114] IC_{50} = 44.5 nM or 6.7 nM depending on study protocol; Mohammad et al, 1997[104], IC_{50} = 6.5 nM) showed that cisapride was a potent blocker of the newly-described hERG channel, and that this provided a potential molecular mechanism for the pro-arrhythmic effect of cisapride (and of most other QT-prolonging drugs).

In addition, an external study in rabbit Purkinje fibres showed that cisapride (10 nM - 10µM) concentration-dependently prolonged the action potential duration, and induced early after depolarisations (EADs) and triggered activity[113].

Initially the Sponsor studies concentrated on isolated cardiac tissue (canine Purkinje fibers,[93] guinea-pig papillary muscles,[157]) hERG[61], and in vivo dog, pig and guinea-pig models[135,136,137,138,139,140,28]. As the work continued, and the scientific knowledge of hERG, prolongation of cardiac repolarization and QT prolongation expanded, the extensive internal studies were supplemented with external work reported in the literature, and full summaries of the electrophysiological effects of cisapride were prepared[31,32,33,34]. Attention was also paid to the effects of other hERG-blocking QT-interval prolonging agents in the models used (eg, ibutilide)[137].

In addition a series of pharmacokinetic, clinical, safety and efficacy studies were carried out by other departments of the Sponsor (Section 3.2).

2.2.2. Single Cell Studies

2.2.2.1. The Cardiac Delayed-Rectifier Potassium Current

2.2.2.1.1. I_{Kr} Cultured Cells HEK 293

A study confirmed that the inhibition by cisapride of the I_{Kr} (potassium current) in hERG transfected human embryonic kidney (HEK) cells was concentration-dependent producing 50% inhibition (IC_{50}) = 0.053 µM for inhibition of the tail current seen on repolarization to –40 mV from +60 mV for 2 sec) and largely reversible[61]. This confirmed the earlier external observations of Rampe et al., (1997) and Mohammad et al, (1997)[114,104].

In another internal study, the presence of low concentrations (0.1 to 0.4%) of human serum albumin (HSA) in the superfusate strongly reduced the inhibition of I_{Kr} by 0.1 µM cisapride (51% without HSA, 21% with 0.4% HSA[62]). This reflects the high plasma protein binding of cisapride (~98%), reducing the free concentrations acting on the cells.

In some pharmacological studies, two agents with different mechanisms of action may show synergism, where the effect of both drugs is substantially greater than the effect of either drug singly. This was examined in hERG-transfected HEK293 cells, and no synergism between the hERG blocking effects of cisapride and ketoconazole was evident[59]. In addition, the metabolite of cisapride, norcisapride, had much less blocking effect on hERG (IC_{50} ~10µM, some 166 times less than cisapride[92], and also showed no synergism with ketoconazole[59].

2.2.2.1.2. In Vitro Isolated Myocytes

In an internal study using whole-cell recordings from isolated guinea-pig ventricular myocytes (n=4-6 for each concentration and current), cisapride (0.005 to 1 µM) inhibited potassiun current carried by the inward rectifier potassium channel (I_{Kr}) in a concentration-dependent manner, IC_{50}=0.069 µM[158], but was much less potent at inhibiting I_{Ks} (IC_{50} = 0.3 µM, approximately 90%

inhibition at 1 μM). Cisapride had no relevant effect on potassiun current carried by the inward rectifier potassium channel (I_{K1})[158].

These findings confirmed and extended the external findings of Carlsson et al., (1997)[13] in rabbit myocytes and Drolet et al., (1997, 1998)[38,39] in guinea-pig ventricular myocytes.

Additionally, in isolated guinea-pig ventricular myocytes, cisapride at concentrations of $5x10^{-9}$M to $1x10^{-6}$ M reduced the fast sodium current and the L-type calcium current. Such additional ion channel effects at higher cisapride concentrations curtail a prolongation of normal repolarization induced by a blockade of the I_{Kr} current at lower concentrations of cisapride[158]. The latter findings provided an explanation for the comparatively high plasma levels of cisapride needed to affect ventricular repolarization in experimental animals in vivo, relative to the comparatively low concentrations attenuating I_{Kr} in isolated cells.

In addition, the metabolite of cisapride, norcisapride, had much less blocking effect on I_{Kr} in guinea-pig myocytes (IC_{50} ~10μM, some 166 times less than cisapride[92].

2.2.3. Other Cardiac Channels

A study with cisapride at concentrations of 5 nM to 1000 nM in isolated ventricular myocytes of the guinea-pig heart showed an inhibition of the fast sodium current I_{Na} and a reduction of the L-type calcium ($I_{Ca(L)}$) current (inhibition by 42% and 20%, respectively at 3 μM) by cisapride, which may curtail a prolongation of normal repolarisation induced by a blockade of the I_{Kr} current at lower concentrations of the compound[158].

2.2.4. Drug Interaction Studies in Single Cells

In experiments on cultured HEK cells transfected with the cloned I_{Kr} channel, hERG, cisapride did not substantially change the effect of erythromycin or ketoconazole on the I_{Kr} current[35,59]. This indicates that inhibition of I_{Kr} by cisapride and co-administered drugs such as erythromycin or ketoconazole is unlikely to be additive. In addition, similar results were obtained using the metabolite of cisapride, norcisapride[59].

2.2.5. Conclusions

The mechanism of action for the prolongation of the action potential by cisapride was identified as an attenuation of delayed rectifier potassium current (I_K) fluxes modulating the duration of the late repolarization phase in cardiac cells. Internal studies showed that the inhibition of the hERG current by cisapride is concentration dependent and largely reversible[61], and that the presence of human serum albumin (HSA) can reduce this inhibition[62]. Because of the latter finding it can be assumed that the effect of cisapride on I_{Kr} in vivo will be much smaller than anticipated from the in vitro effects in the absence of HSA.

2.3. Non-Clinical In Vivo Studies

The Sponsor also studied potential electrophysiological effects of cisapride under normal experimental conditions in studies involving dogs, guinea-pigs, and pigs.

2.3.1. Dogs

In an internal study of cisapride in 7 dogs (versus 7 with vehicle) anaesthetised with scopolamine and lofentanil, IV doses of 1.3 to 2.6 µmol/kg (median plasma C_{max} 2.3 µM after 2.6 µmol/kg) produced an increase in QT and QTc intervals (maximum change 17%), and increases in the APD_{70} and APD_{90} (maximum change 15%), but no other relevant cardiovascular effects[138]. However, at doses of 5.2-10.3 µmol/kg (median plasma C_{max} 9.5 µM), there was a slight increase in PQ and QRS intervals, indicating a slowing of ventricular and atrial conduction, and a transient depression of ventricular contractility indices[138]. A subsequent study by the Sponsor using a similar experimental design dwith lower doses demonstrated that cisapride had only minimal effects on cardio-haemodynamic parameters, although a trend towards QTc prolongation was observed, starting at 0.17 µmol/kg (median plasma C_{max} 0.3 µM) and a trend towards APD_{90} prolongation started at 0.66 µmol/kg (median plasma C_{max} 1.2 µM)[139]. Using the same model, d-sotalol (4.6 µmol/kg) had marked cardio-haemodynamic, electrophysiologic and pulmonary effects.

A single oral dose of 2.5 mg/kg cisapride was given to instrumented, conscious dogs, and followed for 4 hours[30]. Compared to solvent control, various cardiovascular parameters were affected, including an increase in heart rate and cardiac output. Although PQ-, QRS- and QT-intervals were unaffected compared to solvent, QT interval corrected for heart rate using Fredericia's formula QTcF and QTcVdW increased slightly (+8% and +4%) during the 4 hour period.

In these studies the effects of other hERG-blocking QT-interval prolonging agents were examined (eg, ibutilide[136]). The latter study demonstrated that in addition to ECG analysis, measuring the mono-phasic action potential (MAP) in the right ventricle of the anesthetized dog was a sensitive way to evaluate drug-induced effects on cardiac electrophysiology.

Another aspect of the work investigated appropriate QT correction methods for use in experimental models. It had been known since 1920 that the normal QT-interval was sensitive to heart rate, but that the use of the empirical formulae (eg, Bazett, Fridericia) was not appropriate for higher heart rates in some animal models such as the anesthetized dog. Using a variety of drugs affecting heart rate (eg, lidocaine, scopolamine) a simple linear equation, the Van de Water formula, was derived for this model[141]. This correction factor allowed more accurate examination of the effects of drugs on the QT-interval, and to this day remains one of the most-used correction factors in this model.

2.3.2. Guinea-Pigs

The anesthetized guinea-pig was known to be sensitive to the effects of hERG-blocking drugs, including cisapride[13], and is now used extensively by the Sponsor for testing early stage new compounds (eg, De Clerck et al., 2002[36]).

Again cisapride was used as a comparator compound in this model for examining potential proarrhythmic effects of other compounds[28,29].

2.3.3. Rabbits

An early non-clinical model of TdP was developed by Carlsson, following the observation that an infusion of methoxamine in the anesthetized rabbit sensitized the animal to methanesulphonamide-induced arrhythmias[12,14]. Carlsson had shown that cisapride was active in this model[13]. Cisapride (along with an experimental compound and the reference compound dofetilide) was tested[95] in the methoxamine-challenged anaesthetized rabbit. The intravenous infusion of 0.16 mg/kg/min for 60 minutes increased QT- and QTc-intervals by up to 96%, markedly increased QT dispersion, and was associated with incidences of ventricular arrhythmias.

2.3.4. Pigs

Some authors had suggested that 5-HT has a proarrythmic effect due to stimulation of 5-HT_4 receptors, and that the cardiac 5-HT_4 receptor is found only in primates and pigs (eg, Kaumann, 1994[76]). For this reason the Sponsor carried out some studies in anesthetized pigs, rather than dogs, which do not express the cardiac 5-HT_4 receptor.

Increasing intravenous doses of cisapride were administered to anaesthetized pigs[140]. Doses up to a total of 2.36 mg/kg (and plasma levels of 546.8 ng/ml) had no effect on most cardiohaemodynamic parameters, but doses of 0.08 mg/kg IV and above caused a dose-dependent increase in ventricular repolarization time.

2.3.5. Cisapride Enantiomers and Metabolites

Many compounds show stereoselectivity, where one enatiomer of a biologically active racemate is more potent than the other. Cisapride is a racemate, and both enantiomers are equipotent in their primary pharmacology[119]. From studies using isolated guinea-pig papillary muscles, the enantiomers of cisapride (R109628 and R109629) do not have differential effects on I_{Kr}[88]. Similarly, in pilot studies on transfected cells, both enantiomers are equipotent in blocking the hERG channel.

The main metabolite of cisapride is norcisapride, which has a peak plasma level of about 43% of that of cisapride[148]. Norcisapride has 2 enantiomers, (+)-norcisapride (also known as ticalopride), and (-)-norcisapride. (+)-Norcisapride has little effect on the hERG channel[63] and does not affect QT interval in vivo[135,136]. However it did prolong the action potential duration of the isolated guinea-pig papillary muscle[157]. The reason for this discrepancy is not understood.

A detailed summary of the effects of (+)-norcisapride on isolated guinea-pig myocytes was reported (Linz et al, 2001[92]). (+)-Norcisapride blocked I_{Kr} only at 10^{-5}M (52%) and 10^{-4}M (72%), but I_{Ks}, were not affected even at 10^{-4}M. Likewise, I_{Na}, I_{Ca}, and L were not affected up to 10^{-5}M. Thus the metabolite of cisapride, norcisapride, had much less blocking effect on I_{Kr} in guinea-pig myocytes (IC_{50} ~10μM, or 166 times less than cisapride[92]).

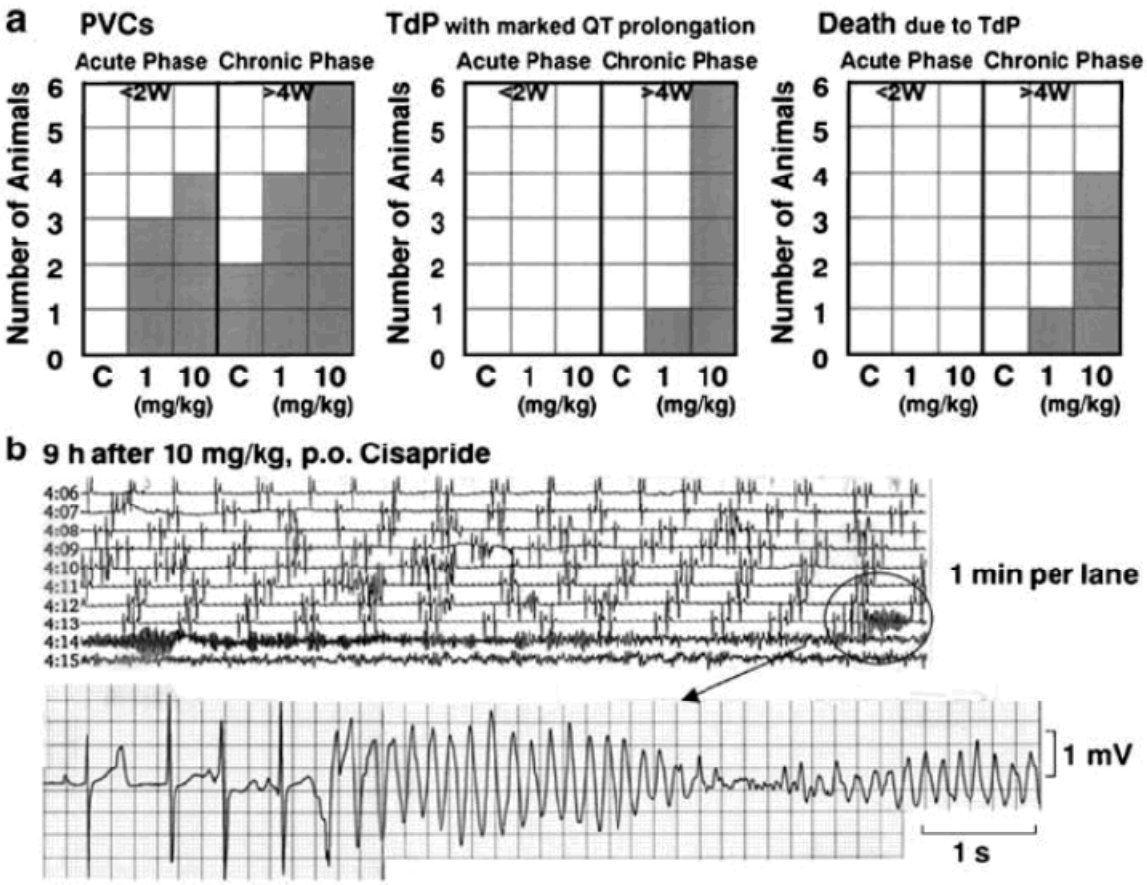
2.3.6. Cisapride and In Vivo Models of Torsades de Pointes

Because cisapride is a well-known hERG blocker and has been shown (at high plasma levels) to cause TdP in a small number of patients, cisapride has been used as a reference compound in

many external models of action potential and QT-interval prolongation. Indeed, a literature search on the Sponsor's database for "cisapride and animal and (QT or Torsades de pointes*)" retrieved 122 references (including 3 using zebrafish). TdP was only rarely reported in studies in healthy animals. In general an additional cardiac insult (eg, induction of cardiac failure, atrioventricular (AV) block, methoxamine infusion) was required to observe TdP in these studies. The most interesting are presented in Figure 2, Figure 3, Figure 4, and Figure 5.

AV-Blocked Dog

Figure 2: Comparison of Onset of Cisapride-Induced Torsades De Pointes (TdP) Between 0-2-Weeks and >4-Weeks Model After Atrioventricular Block. Cisapride at 1-10 Times of Clinically Relevant Maximum Daily Dose was Orally Administered in Conscious Animals in Each Model Studied. ECG was Monitored for 420 h Using Holter ECG Recording System.



(a) Summary of the results. (b) Compressed and continuous ECG image of a dog experiencing TdP[128].

AV-Blocked Primate

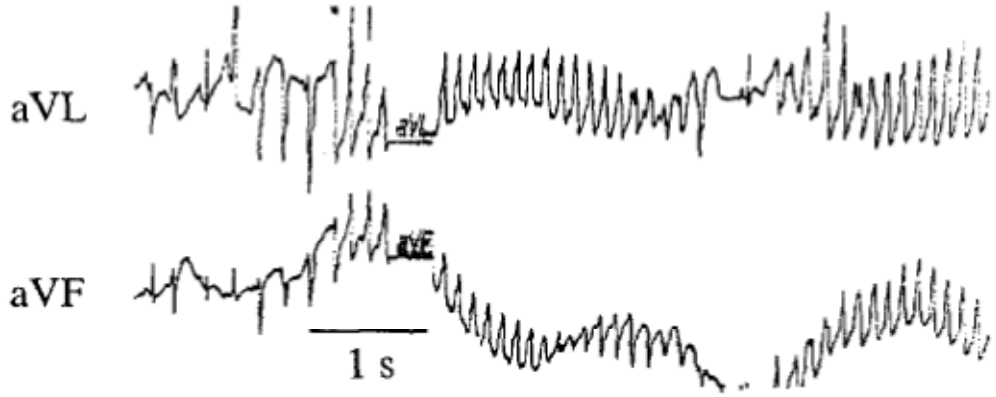
Figure 3: Summary of the Effects of a (I_{Kr}) Blocker on the ECG of the Chronic Atrioventricular Block Monkey Model. (12 Weeks After AV Block)

(C) Typical ECG tracings showing cisapride (5 mg/kg, p.o.)-induced Torsades de pointes (TdP) and its spontaneous termination.

Conscious AV-blocked monkey[129]

Rabbits with Heart Failure

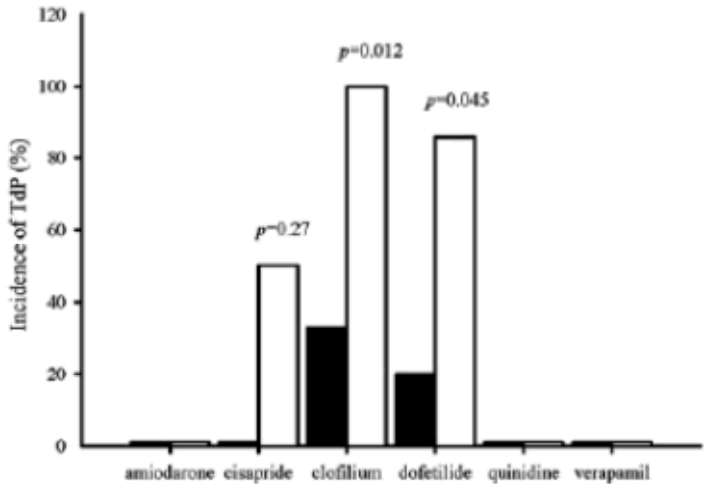
Figure 4: Electrocardiograms (leads aVL, aVF) Demonstrating Induction of Torsades De Pointes in an Anesthetized Rabbit Given Cisapride (0.3 pmol/kg/min IV). The Tachyarrhythmia was Induced After a Cumulative Dose of 1.1 pmoi/kg Cisapride.



Anesthetized rabbit with coronary occlusion-induced heart failure (4 weeks previously)[53].
Note here that cisapride induced TdP in 50% of these rabbits, as opposed to 0% of normal rabbits.

Anesthetized Rabbit with Methoxamine Infusion[13]

Figure 5: Effects of Torsadogenic Compounds (Cisapride, Clofilium, Dofetilide, Quinidine) and Non-Torsadogenic Compounds (Amiodarone, Verapamil) on the Incidence of Torsades De Pointes (TdP) in Anesthetized Rabbits Without (black) and With (white) Failing Hearts.



2.4. Platelet Aggregation

The effects of cisapride on platelet aggregation were also studied before the drug was launched. This study demonstrated the absence of anti-hemostatic effects of cisapride in man[32] (See Section 2.6 and Section 3.1 for details).

2.5. Relevance of Non-Clinical Studies of Cisapride to Clinical Use

Very few drugs are completely specific in their pharmacological action, and cisapride is no exception. Its main pharmacological action is mediated by 5-HT_4 receptor agonism (enhancing the physiological release of acetylcholine from postganglionic nerve endings of the myoenteric plexus), with 5-HT_3 antagonism, and weak dopamine D_2 antagonism.

Cisapride had the unexpected side-effect of being a potent hERG blocker, but the effects of hERG blockade in some studies are curtailed at higher concentrations by blockade of cardiac fast sodium and L-type calcium currents[158].

When examining drug side effects, it is now standard practice to calculate safety margins for the concentrations at which the side effect is observed compared to plasma concentrations achieved in therapeutic use.

Using these C_{max} plasma levels[4] for cisapride at the highest recommended dosage of 10 mg four times per day, mean peak plasma concentration is 79 ng/ml (range 38 to 192 ng/ml) (Table 3). To estimate non-clinical safety margins of in vitro studies and their potential clinical relevance, one can put the plasma levels of cisapride into perspective by using the free, unbound drug concentration of the compound in plasma. With a human plasma protein binding of around 97.5%[105,106] and a molecular weight of 465.9 daltons, 192 ng/ml maximum total level of cisapride at 192 ng/ml = 10.3 nM unbound. In addition, the plasma concentrations of the main

metabolite of cisapride, norcisapride, are 8 to 9 times lower than those of cisapride[144] (see Section 3.2.1). However, norcisapride has little blocking activity on the hERG channel[60] and therefore, does not affect the QT interval in vivo [131,132].

In the first cisapride/ketoconazole interaction clinical study, the mean C_{max} for cisapride at the recommended dosage of 10 mg four times per day was approximately 64 ng/ml, but the addition of the CYP 3A4 inhibitor ketoconazole increased this level to around 210 ng/ml [21], and caused marked increases in QTc.

Thus the maximum unbound cisapride concentrations after the highest recommended clinical doses (10.3 nM) were well below the IC_{50} for hERG blockade (53 nM), but addition of CYP 3A4 blockers such as ketoconazole markedly increased plasma concentrations to levels which could have marked hERG blockade, as seen by the prolonged QTc intervals measured in cisapride/ketoconazole interaction clinical studies.

Table 4: Cisapride Steady State Pharmacokinetics for Different Treatment Regimens

Regimen [34] (total daily dose)	C_{min} (ng/ml) mean±SD (range)	C_{max} (ng/ml) mean±SD (range)	AUC_{0-24} (ng.h/ml) mean±SD
10 mg qid (40 mg)	38.4±22.4 (14.1 – 96.1)	79.0±37.8 (37.7 – 192)	1340±664
20 mg bid. (40 mg)	38.8±23.2 (9.5 – 95.7)	101±43.2 (41.5 – 181)	1521±699
20 mg qid (80 mg)	77.3±41.6 (23.4 – 191)	135±65.8 (51.4 – 320)	2360±1195

2.6. Overview of Non-Clinical Cardiac Ischemic Events

Several non-clinical studies have examined the effects of cisapride using the isolated perfused rabbit Langendorff heart as a sensitive model to detect arrhythmias and/or pro-arrhythmic potential[69,52]. In neither case was a reduction in coronary flow (ie, a coronary constriction) found.

5-HT_4 receptors have not been reported to be involved in porcine coronary vascular contraction[24], but have been reported to be involved in the relaxation of isolated ovine pulmonary veins by serotonin[20]. In canine coronary arteries, cisapride was neither an agonist nor antagonist of serotonin-induced relaxation[24], but in porcine coronary arteries cisapride blocked serotonin-induced contraction, probably by a 5-HT_2 antagonist effect[24].

Cisapride, up to 1 x 10^{-5}M in vitro, did not significantly affect the human platelet aggregation induced by ADP, adrenaline or collagen in citrated plasma, nor the metabolism of arachidonic acid to prostaglandins and lipoxygenase products by human platelets and rat polymorphonuclear leukocytes (PMN). Production of the vasodilator prostacyclin by rat aortic rings was slightly reduced (-24%) at 1 x 10^{-5}M cisapride but not at 1 x 10^{-6}M, some 100 times the maximum free circulating levels of cisapride at the highest recommended clinical dose[32].

Kaumann's group has suggested that 5-HT_4 agonists can cause tachycardia (in pigs and humans[77]. However cisapride was only a weak inotropic partial agonist on human atrial 5-HT_4 receptors[76]. Thus cisapride has not been associated with cardiac ischemic events in non-clinical studies.

3. CLINICAL PHARMACOLOGY STUDIES

This section summarizes the Sponsor's experience and research on ventricular arrhythmia and ischemic cardiac events in clinical pharmacology studies.

3.1. Overview

The potential ECG effects of cisapride were evaluated clinically. An early study, which was neither placebo- or active-controlled, evaluated ECG in 8 healthy volunteers treated with 10 mg cispride three times daily[37]. Mean QT interval corrected for heart rate using Bazett's formula (QTcB) (2 hours post-administration) increased from 405±7 ms to 414±7 ms, but the changes were not statistically significant. Because of the natural variation in QT interval, such an interpretation (ie, "no effect") is not unexpected and due to the fact that the study was not placebo- or active-controlled. To detect the small changes in QT interval (ideally less than 5 ms) demanded by today's clinical guidelines (ICH E14[71]), modern "thorough QT studies" are now carried out under closely controlled conditions, with around 50 to 60 subjects, and in addition, use supra-therapeutic doses as well as therapeutic doses.

A later study examined the effects of high doses of cisapride in patients with digestive symptoms, up to 160 mg daily[103]. Again, no significant effects on ECG intervals were seen using the techniques available then, but the studies were conducted without inclusion of reference placebo and active control groups.

The overall conclusions from the non-clinical and clinical work carried out in the 1980's were that cisapride did not affect the ECG.

A report in 1992 associated cisapride with tachycardia[109], but a reply from the independent Drug Safety Research Unit in the United Kingdom (UK) examined data from 13,233 patients (compared with [240,381] substantially identical patients) "revealed no epidemiological support for Olsson's hypothesis"[74]. A more detailed examination confirmed this finding, and detected no unacceptable cardiovascular hazards[75]. The Sponsor examined the data regarding tachycardia and submitted the data to the FDA in December 1992 and January 1993, and subsequently added the risk of tachycardia to the package insert.

The first indications of QT prolongation with cisapride came after spontaneous reports of interactions between cisapride and the antifungal drug ketoconazole. Several articles appeared associating high doses of cisapride with (drug-induced) long QT syndrome[11,161] and Torsades de pointes[2,161]. These concerns had been initially reported to the FDA by the Sponsor in late 1994, and an "Action Plan" was submitted to the FDA in early 1995, including state of the art metabolism studies of cisapride, a cardiovascular investigation of cisapride/ketoconazole interactions in volunteers, and non-clinical investigations of the effects of cisapride and its metabolite norcisapride on isolated canine and guinea-pig ventricular tissues. A labeling change was recommended in January 1995, which was implemented 2 months later, and a "Dear Doctor" letter was sent to HCPs. A "Black Box" warning on comedication and serious cardiac adverse events was approved by the FDA in September/October 1995.

The causes and implications of QT-interval prolongation were not appreciated at this time (the first QT prolongation guideline, CPMP "Points to Consider" document was not published until December 1997[17]). However an investigation of the effects of cisapride was initiated in 1994. A clinical study carried out in 14 healthy subjects, confirmed the prolongation of the QT-interval with cisapride monotherapy and the larger prolongation with cisapride plus ketoconazole.[23] Analysis of cardiovascular safety data did not show a statistically significant change of any of the evaluated cardiovascular safety parameters after a single dose of 10 mg cisapride or after monotherapy of ketoconazole 200 mg b.i.d. The corrected QT values remained well within the normal range and within the normal within-variability, and there were no morphological changes of the ST-T segment.

One clinical report indicated that cisapride could worsen Prinzmetal angina[116], but an internal report in 1996 had revealed no association between cisapride and coronary disease[151].

The subchronic administration of cisapride to man (10 mg orally 4 times daily for 3 days; single oral 10 mg dose 2 h before testing on the 4th day) did not significantly influence hemostatic parameters (skin bleeding time, hematocrit, platelet number, serum thromboxane B_2 levels) when compared with placebo during a double-blind, cross-over trial in 12 male volunteers. In a similar set-up, aspirin (1000 mg orally 2 h before testing) significantly prolonged the bleeding time and reduced serum thromboxane B_2 levels. This study demonstrated the absence of anti-hemostatic effects of cisapride in man[32].

3.2. Clinical Pharmacology of Cisapride

3.2.1. Summary of Results of Studies Between First-In-Human dosing and First Marketing (April 1988)

The pre-market clinical pharmacology investigations in healthy volunteers included single-dose PK and tolerability studies in the range of 2.5 to 40 mg in healthy volunteers. Repeated-dose PK and PD-studies in healthy subjects were only conducted in the assumed therapeutic dose range of 5 mg t.i.d. to 10 mg q.i.d. Based on a review of 16 studies including 173 subjects, it was concluded that "cisapride was devoid of effects on blood pressure, heart rate, ECG, respiration rate, temperature, and does not affect the blood pressure response of hypertensive patients to propanolol".[148]

Cisapride is almost completely absorbed after oral administration. Cisapride is extensively metabolized, primarily by oxidative N-dealkylation to norcisapride (43% of the dose) and aromatic hydroxylation of the fluorophenyl moiety into 2 isomeric metabolites, together accounting for 16% for the dose. Liver metabolism of cisapride is mediated through the hepatic cytochrome P-450 system. The excretion of cisapride, almost exclusively as metabolites, is about equally divided over urine and feces. Only 4% to 6% of the dose is recovered as parent drug in the feces and less than 1% in urine.

Peak plasma concentrations of cisapride are reached within 1 to 2 hours after single oral doses. Despite almost complete absorption the oral bioavailability is only 40% to 50% due to significant first-pass metabolism and absorption is highest when dosing is followed by a meal. Cisapride is

mainly bound to albumin in plasma. The human plasma protein binding is 97.5% to 98.0% and the blood/plasma ratio is 0.64. Based on in-vitro studies, cisapride is not expected to have an effect on the protein binding of other drugs.

Plasma concentrations of cisapride increase proportionally with dose for doses of 5 to 20 mg. In healthy volunteers, plasma half-lives are generally in the order of 8 to 12 hours. After repeated dosing, the pharmacokinetics profile is linear and predictable from single-dose data and the elimination half-life after the last dose is comparable to values after single dosing. The main metabolite of cisapride in the systemic circulation is norcisapride, which has a half-life of approximately 12 hours. The exposure to norcisapride in human plasma is approximately 8 to 9 times lower than parent drug.

The pharmacokinetics of cisapride are not greatly influenced by the indicated disease state or race. In elderly subjects, the rate and extent of absorption is similar to that in healthy young subjects following single dose administration, but the steady-state plasma concentrations are generally higher, due to a moderate prolongation of the elimination half-life (8 to 16 h). Therapeutic doses, however, are similar to those used in younger patients. In patients with hepatic insufficiency, the mean elimination half life is significantly prolonged (18.1 ± 10.0 h) and the mean AUC values observed after a single 10 mg dose are similar to those reported after a 20 mg dose in healthy volunteers. In patients with renal insufficiency, the pharmacokinetics of cisapride is not altered, but the elimination half-life of norcisapride is prolonged (27 ± 10 h), leading to plasma exposure of the metabolite between 30-180% of parent drug exposure. In patients with renal/hepatic insufficiency, it is recommended to halve the daily dose.

Regarding extrinsic factors that may affect the pharmacokinetics of cisapride, it was shown that cimetidine and ranitidine, relevant co-medications and known inhibitors of oxidative metabolism, increased the systemic exposure of cisapride by 45% and 25%, respectively. Concomitant administration of antacids did not affect the absorption of cisapride, whereas concomitant administration of ethanol moderately increased cisapride C_{max} by approximately 30% without affecting overall systemic exposure. Cisapride showed no clinically relevant effects on the pharmacokinetics of digoxin, propanolol, and acenocoumarol. Based on calculated antipyrin metabolic clearance, there is no indication that therapeutic doses of cisapride either inhibit or induce hepatic microsomal enzymes. Intravenously administered cisapride (8 mg) increased the peak concentrations (by 17%) and shortened the time to C_{max} (from 46 to 33 min) of oral diazepam, likely due to the effects of cisapride on gastric emptying.[107]

3.2.2. Post-Marketing Clinical Pharmacology Investigations (1988 – early 2000s)

3.2.2.1. Post-Marketing Human Metabolism and Drug Interaction Update[84,10,4]

Evolving understanding of the P450 system and additional in vitro metabolism studies with improved techniques allowed CYP3A4 to be identified as the principal cytochrome P450 enzyme involved in the metabolism of cisapride, with CYP2A6 being implicated to a minor extent in the formation of norcisapride and in an N-oxide of parent cisapride. Little contribution of other forms of the CYP3A subfamily (CYP3A3, CYP3A5) to the metabolism of cisapride was observed.

CYP3A4 is quantitatively the major cytochrome P450 form in human liver, accounting for approximately 35% of the total hepatic cytochrome P450 content, whereas CYP2A6 accounts for less than 1% of the hepatic cytochrome P450 content. CYP3A4 is quantitatively the major cytochrome in human intestinal cells, representing up to 80% of the enteric P450 content[110]. Additionally, over the concentration range of 1.1 to 30 µM, the metabolism of cisapride was linear, consistent with a single CYP enzyme being responsible. Thus, the contribution of CYP2A6 or other CYP isoforms to the metabolism of cisapride is not expected to be relevant from a clinical point of view.

The interaction between cisapride and 44 drugs likely to be co-administered with cisapride and associated with inhibition of CYP enzymes was investigated in several in vitro studies with human liver microsomes and followed up with in-vivo confirmatory studies as appropriate. These in vitro results, as shown in Table 5, allowed prediction of possible interactions that might be of clinical relevance for several classes of compounds that are notable CYP3A4 inhibitors: azole-antimycotics (ketoconazole, itraconazole, fluconazole), protease inhibitors (ritonavir, indinavir), mibefradil, troleandomycin, nefazodone. Potent inhibitors of other CYP forms, including CYP2C (omeprazole) and CYP2D6 (fluoxetine, quinidine) were predicted <u>not</u> to inhibit cisapride metabolism. The in vivo results, as displayed in Table 6, were generally in line with the in-vitro results, except for an apparent discrepancy for the predicted interaction potential of erythromycin and clarithromycin, which seemed to be underestimated in the experiments using human liver microsomes, likely due to mechanism-based inactivation of these macrolide antibiotics.

On the basis of these continued non-clinical and clinical pharmacology investigations, the concomitant use of cisapride with the potently to moderately CYP3A4 inhibiting imidazoles ketoconazole, itraconazole, miconazole and fluconazole, and the macrolide antibiotics troleandomycin, erythromycin and clarithromycin, was contraindicated in subsequent updates of product labels worldwide. In addition, nefazodone and protease inhibitors such as ritonavir were contraindicated on the basis of in vitro studies only.[3]

Table 5: Inhibition of Cisapride Metabolism in Human Liver Microsomes

Compounds tested	IC_{50} >nor-cisapride (µg/mL)	IC_{50} overall metabolism (µg/mL)	IC_{50}/C_{ss}*
Alprazolam	>15.4 (2)	>15.4 (8)**	>275
Amiodarone	>32.3 (29)	>32.3 (26)	>13
Astemizole	13.8	15.0	3125
Azithromycin	>375 (-6)	>375 (-2)	>>940
Cimetidine	>12.6 (9)	>12.6 (7)	>>5.2
Clarithromycin	69	84.6	24
Clindamycin	>300 (46)	>300 (31)	>17.9
Desmethylastemizole	14.5	16.6	4500
Diazepam	>14.2 (30)	>14.2 (28)	>7
Diltiazem	>3 (9.7)	>3 (4.7)	>12.5
Diltiazem + pre-incubation	>3 (28.7)	>3 (20.9)	>12.5
Erythromycin	88.0	81.8	21
Fluconazole	20.6	20.8	1.1
Fluoxetine	>15.5 (19)	>15.5 (23)	>>388
Fluvoxamine	>15.9 (3)	>15.9 (11)	>>53
Furosemide	>16.5 (11)	>16.5 (1)	>>8
Hydroxy-itraconazole	0.47	0.47	0.12
Indinavir	0.29	0.14	0.02
Itraconazole	0.63	0.49	0.21
Josamycin	20.7	24.2	5
Ketoconazole	0.16	0.12	0.02
Lincomycin	>1000 (31)	>1000 (31)	>10.3
Metronidazole	>85.6 (0)	>85.6 (0)	>>4
Mibefradil	0.14	0.17	0.21
Miconazole	0.80	0.84	0.09
Midazolam	3.95	4.72	18
Naringenin	74.7	136	N.A.
Nefazodone	1.06	1.01	0.44
Nifedipine	1.49	2.02	17
Norfluoxetine	>15 (34)	>15 (17)	>30
Ofloxacin	>100 (0	>100 (0)	>13.3
Omeprazole	>17.3 (22)	>17.3 (33)	>5
Paroxetine	60.1	99.5	663
Quinidine	59.8	39.1	8
Quinine	91.3	87.3	22
Ranitidine	>15.7 (-12)	>15.7 (-8)	>>2.8
Ritonavir	0.051	0.065	<0.01
Roxithromycin	129	207	20.5
Saquinavir	3.3	3.3	12.8
Sertraline	>10 (44)	>10 (39)	>40
Terbinafine	>30 (5.1)	>30 (5.1)	>10
Terfenadine	>23.6 (34)	>23.6 (49)	>18000
Troleandomycin	0.90	0.81	0.41
Warfarin	>15.4 (19)	>15.4 (13)	>>10

(*)IC_{50}/C_{ss}: represents the ratio between the IC_{50} value for the metabolism of cisapride and the therapeutic
plasma concentration of the inhibitor at steady state.

(**) Values in brackets indicate the percentage inhibition obtained at the highest concentration studied.

Table 6: Effect of Metabolic Interactions on the Pharmacokinetics of Cisapride

Perpetrator drug	IC_{50}/C_{ss} (*)	Cisapride treatment	Effect on Cisapride PK Expressed as ratio PK parameter		
			C_{min}	C_{max}	AUC
Azole antifungals					
Ketoconazole (200 mg b.i.d.)	0.02	10 mg single dose	-	2.59	7.90
		10 mg q.i.d. (ss)	4.63	3.27	4.02
Fluconazole (400 mg o.d.)	1.1	10 mg q.i.d. (ss)	-	2.18	2.55
Macrolides					
Clarithromycin (500 mg b.i.d.)	24	10 mg q.i.d. (ss)	4.29	2.73	3.16
Erythromycin (500 mg q.i.d.)	21	10 mg q.i.d. (ss)	-	1.97	2.05
SSRI's					
Fluoxetine (20 mg o.d.)	>>388	10 mg q.i.d. (ss)	0.77	0.84	0.84
Proton Pump inhibitors					
Omeprazole (20 mg o.d.)	>>5	10 mg q.i.d. (ss)	1.16	0.97	1.02
Other					
Grapefruit Juice (200 mL q.i.d.)	N.A.	10 mg q.i.d. (ss)	1.50	1.46	1.49

(*) Ratio of IC_{50} for perpetrator drug on cisapride metabolism in human liver microsomes, divided by its steady state plasma concentrations.
References: [23,64,65,66,67,21,83,152] and aggregate table from Atsma et al.[4]

3.2.2.2. Post-Marketing Human CV-Safety Update in Healthy Volunteer Studies

The new findings on cisapride's I_{Kr}-blocking properties and intrinsic potential for prolonging QTc, as well as its potential for metabolic drug-drug interactions as predicted from in vitro models, led to the execution of post-approval pharmacokinetic- and drug-interaction studies that included standardized cardiovascular safety assessments.

The Sponsor performed DDI studies with cardiovascular safety assessments with the following known CYP-inhibitors: ketoconazole, fluconazole, clarithromycin, erythromycin, fluoxetine, omeprazole, and grapefruit juice. In that same period, other groups reported on their DDI studies with cardiovascular safety assessments (eg, grapefruit, pantoprazole). Table 7 summarizes the effect upon the QTc interval duration in these studies.

Co-administration of ketoconazole, fluconazole, clarithromycin, erythromycin, potent to moderate inhibitors of CYP3A4, may lead to clinically relevant QTc prolongations. In addition, potent inhibitors of other CYPs (fluoxetine, omeprazole) neither increased the systemic exposure, nor the QTc, after combination treatment with cisapride.

Table 7: Summary of Effects of Cisapride and of the Combination of Cisapride With Metabolic Inhibitors on the QTc Interval

Co-administered drug	Cisapride treatment	N	QTc (msec) Mean ± SD		
			Baseline	Cisapride alone	Combination treatment
Azole antifungals					
Ketoconazole (200 mg b.i.d.)	10 mg single dose 10 mg q.i.d. (ss)	14 14	385 ± 7[#] 396 ± 7[#]	405 ± 7[#,*] 410 ± 6[#]	423 ± 5[#,*] 442 ± 7[#,*]
Fluconazole (400 mg o.d.)	10 mg q.i.d. (ss)	12	394 ± 7	399 ± 11	405 ± 13
Macrolides					
Clarithromycin (500 mg b.i.d.)	10 mg q.i.d. (ss)	12	400 ± 19	406 ± 18*	425 ± 20*
Erythromycin (500 mg q.i.d.)	10 mg q.i.d. (ss)	12	399 ± 12	406 ± 13	413 ± 21
SSRI's					
Fluoxetine (20 mg o.d.)	10 mg q.i.d. (ss)	12	407 ± 14	412 ± 14*	417 ± 13
Proton Pump inhibitors					
Omeprazole (20 mg o.d.)	10 mg q.i.d. (ss)	15	411 ± 22	404 ± 19	406 ± 22
Pantoprazole (40 mg t.i.d.)	10 mg q.i.d. (ss)	16	403 ± 25	407 ± 12	406 ± 15
Other					
Grapefruit Juice (200 mL q.i.d.)	10 mg q.i.d. (ss)	14	423 ± 30	422 ± 32[$] 429 ± 24[£]	423 ± 23[$] 443 ± 20[£]
Grapefruit Juice (200 mL t.i.d.)	10 mg single dose	10	389 ± 19	407 ± 24	405 ± 20

#: SEM (standard errof of the mean)
SD = standard deviation
*: $p<0.05$
$: steady state Day 6, before morning dose
£: steady state Day 6, 1 hour after 3rd dose
ss: steady state
References: Ferron GM et al. 1999[47], Ferron; GM et al. 1999[82] and aggregate table from Atsma et al.[4]

Of note are the 2 cardiovascular safety PK- and PD-studies in adult volunteers which the Sponsor performed after initial submission/approval:

- A steady-state, double-blind (DB), 3-period cross-over study to assess the effects of different doses of cisapride (10 mg q.i.d., 20 mg b.i.d. and 20 mg q.i.d. for 6 days) on ECG-changes in 24 male volunteers. These doses correspond to the recommended therapeutic dose (10 mg q.i.d.) and maximum approved dose (20 mg q.i.d.) of cisapride. This study ran from September to November 1996.[64]
  - Apart from a high level of daily variability in QTc intervals observed, there were small but statistically significant increases for all doses in QTc interval. Compared to a baseline Day 0, mean increases in QTc,avg (average QTc of 18 ECGs during 24 h period) during cisapride treatment at 10 mg q.i.d., 20 mg b.i.d. and 20 mg q.i.d. were 4 msec (p=0.035), 5 msec (p=0.009), and 4 msec (p=0.004), respectively. A statistically significant difference was also observed in the change from baseline in QTc,max (maximum QTc observed during 24 h period) for the 20 mg b.i.d. group (9 msec, p=0.05), but not for the 10 and 20 mg q.i.d. groups. There was no statistically significant or clinically relevant correlation between dose and frequency or magnitude of QTc prolongation. There was no correlation between cisapride plasma concentrations and absolute QTc intervals as well as changes from baseline at doses of up to 80 mg per day in these subjects. Importantly, it should be noted that this study did not include placebo or active control.

- A randomized, double-blind, placebo-controlled, dose-escalating study in 24 male and female volunteers to assess the cardiovascular safety of single doses of 10, 20, 40, 80, 130 and 200 mg cisapride, which eventually completed at the dose of 130 mg. This study ran from October to November 2000 and did not include an active comparator arm.[64]
  - This study showed no clinically relevant changes in ECG and other parameters or other observations for placebo and the approved 10- and 20-mg doses of cisapride.
  - A pattern of statistically significant increases in QTc across correction approaches were observed in doses of 40 mg and higher, with consistent, statistically significant and clinically meaningful increases at multiple time points for doses of 80 mg and higher. A statistically significant increase in QTc (Bazett) was seen from 1 hour to approximately 6 to 12 hours after administration, with peak changes at 1.5 hours after administration of 37.2, 30.1 and 44.9 msec for 40, 80 and 130 mg cisapride, respectively (all $p<0.05$). Compared with run-in, mean HR was somewhat higher after all treatments with no relevant differences between placebo, run-out and cisapride 10 and 20 mg
  - A statistically significant relationship between cisapride plasma concentration and changes in the corrected QT intervals was observed. A population pharmacokinetic-pharmacodynamic modeling approach was applied: the pharmacokinetic model included a two-compartment disposition and sequential zero- and first-order absorption with a lag time; the pharmacodynamic model consisted of a QT-correction submodel, a diurnal variation submodel and a drug effect submodel (in the form of a sigmoid E_{max} model). The baseline value of QT was typically shorter in men (380 msec) than in women (392 msec). The mean model-estimated maximum change was 7.57%, ie, 29.8 msec in females and 28.8 msec in males. Females (estimated EC_{50} 118 ng/mL) were somewhat more sensitive to cisapride QT prolonging effects than males (estimated EC_{50} 154 ng/mL).[48,147]

3.2.2.3. Summary of Effects on the Cardiovascular System

Single-doses of 20 mg cisapride or less do not induce a clinically significant change in the QTc interval duration. At single doses of 40 mg or higher, a dose- and concentration-dependent prolongation of the QTc interval has been observed of which the magnitude depends on the method used to correct the QT interval for changes in heart rate. Multiple-dose treatment with cisapride 10 mg and 20 mg q.i.d. (ie, 40 and 80 mg/day) as monotherapy does not appear to evoke clinically significant changes in the QTc interval. Nevertheless, cisapride has the potential to prolong the QT interval, as evident from its pharmacological I_{Kr}-blocking profile, especially when used at high doses or in circumstances that could lead to higher than expected cisapride plasma concentrations. Dose-dependent QTc-increases have only been observed when cisapride plasma concentrations are above the normal therapeutic range, for example following high single doses of 40 to 130 mg. Increases in QTc may become clinically significant when cisapride is given with drugs that inhibit CYP3A4, or with drugs that themselves prolong the QTc interval.

4. Pre-Approval Clinical Trials

The NDA for cisapride presented safety information from clinical trials for 979 adult patients in the United States and 3,081 patients in controlled studies in countries outside the US. In addition, the safety data from 294 healthy volunteers and patients exposed to cisapride on an acute basis in US clinical pharmacology studies, as well as the findings from 698 patients from 27 non-US

studies reported in the literature and conducted by Janssen affiliates were reported in the NDA. The overall safety results from more than 1014 patients given cisapride on a compassionate use basis in the US also were evaluated.

The overall conclusion from the safety review of the NDA by the FDA medical officer was that "no clinically relevant changes in blood pressure, heart rate, ECG, respiration rate or temperature were observed in healthy subjects at doses up to 40 mg QID for five days, or in constipated patients or patients with diabetes mellitus after single oral doses of up to 40 mg, repeated oral doses up to 10 mg TID for 12 weeks or single IV doses up to 10 mg".

5. Cummulative Review of Cases Retrieved From the Company Safety Database for Cisapride

Ventricular tachyarrhythmia-related events are well characterized in the United States Prescribing Information (USPI).

A cumulative, aggregate evaluation of all spontaneously reported, clinical study, post-marketing study, or registry (including limited access programs, compassionate use programs) cases reporting ventricular tachyarrhythmia-related events with the use of cisapride received through 25 July 2011 and entered into the Global Medical Safety (GMS) safety database was conducted at the request of the FDA. No new safety signals were identified in this review.

Cardiac ischemia-related events have not emerged as a safety signal. A cumulative, aggregate evaluation of all spontaneously reported, clinical study, post-marketing study, or registry cases (including limited access programs, compassionate use programs) reporting cardiac ischemia-related events with the use of cisapride received through 25 July 2011 and entered into the GMS safety database was conducted. This review did not identify a role for cisapride in the development of cardiac ischemia-related events.

6. LIMITED ACCESS PROGRAM (LAP) – UNITED STATES

The sponsor was requested by the FDA to discuss its experience from the US. Cisapride Limited Access Program (LAP). Following the voluntary marketing discontinuation of cisapride, a limited access program was established in the United States in July 2000. The objective of the LAP is to allow physicians the use of cisapride for patients with a critical need for the drug and a favorable benefit/risk ratio. Because of the known risks associated with the use of cisapride, patients who are eligible for enrollment in the LAP have failed standard treatments, and cannot be managed by other available therapy. In these patients, the lack of therapeutic alternatives would result in significant discomfort, adverse health consequences, or surgical intervention.

Protocol CIS-USA-154 enrolls adult outpatients with GERD, gastroparesis, intestinal pseudo-obstruction, or severe chronic constipation to be screened for entry.

A second protocol, CIS-USA-156, is designed for pediatric outpatients who have either signs and symptoms secondary to GERD (failure to thrive, asthma, recurrent pneumonia, colicky behavior, esophagitis), or acute, life-threatening signs and symptoms secondary to GERD (bradycardia, apnea, respiratory distress), pseudo-obstruction, gastroparesis, or severe chronic constipation.

Because the indications for use of cisapride in these protocols are not encompassed by existing product labeling in the US, the 2 protocols are conducted under the Sponsor's Investigational New Drug (IND) application for cisapride. All physician investigators must receive Institutional Review Board approval in order to screen patients for entry in the program.

Patients are assessed for eligibility with a baseline screening and diagnostic evaluation that includes a complete history and physical examination, cardiologist interpreted ECG, appropriate endoscopy/radiology, and laboratory tests to rule out contraindicating risk factors. Patients participating in the program are counseled by their physician regarding risks and benefits.

For adults, therapy is initiated at 10 mg q.i.d, and if necessary, the dose can be increased to 20 mg q.i.d. after 6 weeks of treatment. For children administered the suspension, therapy is initiated at 0.1 mg/kg/dose given 3 or 4 times per day and the dose can be increased to 0.2 mg/kg/dose given 3 or 4 times per day if necessary, with a maximum dose not exceeding 0.2 mg/kg/dose or 10 mg q.i.d., whichever is lower.

Patients are required to undergo clinical re-evaluation at regular intervals, including ECG, laboratory tests to monitor for the development of risk factors (e.g. QTc prolongation beyond protocol-specified limits or a new medical condition) that would contraindicate continued participation, and to ensure ongoing patient benefit.

US physicians may potentially obtain cisapride through single-patient INDs to treat patients not eligible for the LAP. Safety reporting to FDA for these single-patient INDs is the responsibility of the physician investigators.

Safety data for the LAP are regularly provided to the FDA. Cisapride-related cardiac adverse events observed in the LAP have primarily been QTc prolongation, with no reported cases of Torsades de pointes, ventricular tachycardia or fibrillation, or sudden cardiac death. Cardiac ischemia has not emerged as a safety signal.

Steady annual enrollment in the LAP program suggests a continued unmet medical need in children with GERD and in adults with gastroparesis. Future development of prokinetics should include investigation of a broad spectrum of disorders in children and adults.

PART II SUMMARIES AND CONCLUSIONS OF LITERATURE REVIEWS ON VENTRICULAR ARRHYTHMIA AND ISCHEMIC EVENTS AS REQUESTED BY FDA

1. Introduction and Methods

Literature searches of non-clinical and clinical use of cisapride and for cisapride and cardiac ischemia were performed and the results of these searches were reviewed and are presented below.

1.1. Ventricular Arrhythmias Related to Cisapride

1.1.1. Non-Clinical Use

Because cisapride is a well-known hERG blocker, and has been shown (at high plasma levels) to cause TdP in a small number of patients, cisapride has been used as a reference compound in many non-clinical studies trying to establish or validate models of action potential prolongation and QT-interval prolongation. Indeed, a literature search of PubMed as well as the Sponsor's internal database of publications about Janssen products for "cisapride and animal and (QT or torsade*)" retrieved 122 references (including 3 using zebrafish). Some of the earlier literature has been summarised in Sections 2.2.1 and 2.3.6 in Part I. The following literature review summarizes the earliest seminal studies, and quotes some more recent papers.

Two original studies showed that cisapride was a potent blocker of the newly-described hERG channel, and that this provided a molecular mechanism for the occasional pro-arrhythmic effect of cisapride (and of most other QT-prolonging drugs) (Rampe et al., 1997[114] IC_{50} = 44.5 nM or 6.7 nM depending on study protocol; Mohammad et al[104] 1997, IC_{50} = 6.5 nM)

A study in rabbit Purkinje fibres showed that cisapride (10 nM to 10µM) concentration-dependently prolonged the action potential duration, and induced early after depolarisations (EADs) and triggered activity[113].

Cisapride was active in an early model of TdP[12], following the observation that an infusion of methoxamine in the anesthetized rabbit sensitized the animal to methanesulphonamide-induced arrhythmias. The intravenous infusion of 0.16 mg/kg/min for 60 minutes increased QT- and QTc-intervals by up to 96%, markedly increased QT dispersion, and was associated with the occurrance of ventricular arrhythmias.[13]

In a study on the isolated Langendorff heart cisapride was found to prolong the action potential duration (APD) concentration-dependently, and concentrations of 300 nM and above were associated with instability, triangulation, reverse use dependence, EADs and TdP in some hearts (Hondeghem, 2003)[70]. Very similar results were found in studies by Lawrence et al. (2006)[85] and Steidl-Nichols et al., (2008)[126], using the same model.

Two large, multi-laboratory studies ("ILSI-HESI", and "PRODACT") examined the effects of a series of torsagagenic drugs (including cisapride) on:

1. hERG currents, Purkinje fiber repolarization, and in vivo QT studies in conscious telemeterized dogs[54].

2. in vitro guinea pig papillary muscle action potential recordings and in vivo ECG recordings in unanesthetized or anesthetized beagle dogs, cynomolgus monkeys and miniature pigs[56].

hERG channel mutants have been used to gain insights into the individual amino acids responsible for binding cisapride (and other hERG blockers)[46].

The effects of cisapride on hERG with single nucleotide polymorphisms, rather than Caucasian "wild type" (WT) were examined. The SNPs used in this study are found in individuals with normal QT intervals in the absence of hERG-blocking drugs (ie, they are not SNPs leading to the congenital form of long QT), although some of them have been linked with drug-induced long QT syndrome. The results showed that cisapride potencies defined using the Caucasian WT sequence were, at least in this in vitro system, representative of potencies for these relatively common SNPs[99].

Findings not directly connected to hERG channel blockade show that, in contrast to torsadogenic drugs such as pentamidine or arsenic trioxide which block hERG trafficking (the post-expression processing and transport of the channel to the membrane), cisapride had no effect on hERG trafficking[156]. In contrast, higher concentrations of cisapride were able to "rescue" the surface expression of the hERG channel trafficking mutations which cause certain clinical long QT (LQT) syndromes[162,102].

Cisapride, as a potent hERG blocker, inhibited the growth of gastric cancer cells (which express hERG) by altering distribution of the cell cycle and inducing apoptosis. Similarly cisapride induced strong antiproliferative and antimigratory effects in melanoma cells.[122]

There have been more than 100 reports of cisapride effects on hERG, action potential duration, and QT interval. In general, the studies show inhibition of hERG, action potential prolongation, and QT prolongation. Overt TdP was only rarely reported in these studies in healthy animals or tissues from healthy animals: an additional insult (eg, cardiac failure, AV block, methoxamine infusion) was required to observe TdP in these studies (see Section 2.3.6 in Part I).

1.1.2. Effects on the Human Cardiovascular System

1.1.2.1. Adults

Up to 1999, 2 publications described cisapride-related cases of QT interval prolongation, serious ventricular arrhythmia, including Torsades de pointes, and sudden death, from consolidated spontaneous adverse event reports.

Wysowski et al[160] described 117 cases of QT prolongation, 107 cases of Torsades de pointes, 16 cases of polymorphic ventricular tachycardia, 18 cases of ventricular fibrillation, 27 cases of ventricular tachycardia, 25 cases of cardiac arrest, 16 cases of serious arrhythmia and 15 cases of sudden death. Of the 341 cases, 207 (61%) were cases in women, which could be explained by a

preponderance of female users. The median time from initiation of cisapride to onset of the event was 14 days for 215 patients without concomitant use of enzyme inhibitor drugs. The authors concluded that there is a close temporal relationship between onset of cisapride treatment and the cardiac event.

Barbey et al[5] reviewed 574 reported adverse event cases of which 391 cases were reports of QT prolongation and 305 cases were reports of QT prolongation plus polymorphic ventricular arrhythmia or Torsades de pointes. Recognized risk factors were identified in 262 (67%) of the 391 cases, and other labeled conditions in an additional 51 cases (13%). Most common risk factors include the combination of cisapride with medication that inhibits cytochrome P450 3A4 (110 cases [42%]), hypokalemia and/or hypomagnesemia (83 cases [32%]); and co-administration of other QT prolonging drugs (75 cases [29%]). Bradycardia was reported in 47 cases (18%); pre-existing and presumably congenital QT prolongation in 31 cases (12%), and cisapride overdose in 32 cases (12%). Recognized co-factors were present in 82.1% of 119 cases.

1.1.2.2. Neonates, Premature Neonates, Infants and Children

The literature search revealed clinically relevant findings on the cardiac side effects of cisapride in preterm infants. Forty-six preterm infants with a mean birth weight of 1,350 g and mean post conceptional age (PCA) of 31 weeks were investigated.[19] The results showed that intrauterine growth retardation could be an important risk factor for cisapride-induced QT prolongation in preterm infants. Chronic malnutrition associated with intrauterine growth retardation may induce an altered pattern of cardiac electric activity in response to different stimuli, including cisapride, during early postnatal life.

An investigation in 10 preterm neonates, (mean gestational age [GA] at birth 30.6 weeks, range of 26.6 to 33.4 weeks), treated at a mean postnatal age of 21.7 days (range 5 to 51 days) found that the QTc interval increased significantly from 423 msec to 461 msec after 72 hours of treatment with cisapride (dose 0.76 to 0.89 mg/kg/day; mean 0.80 mg/kg/day). The change in QTc interval was inversely related to postnatal age ($p=0.02$), but not with gestational age or cisapride plasma levels. Mean (±SD) trough and peak cisapride plasma levels in the 10 premature neonates were 104.8±32.1 ng/mL and 114.9±31.4 ng/mL, respectively.[86]

In contrast, a subsequent study of 31 premature infants receiving cisapride 0.8 mg/kg/day as either an every 6-hour regimen (0.2 mg/kg/dose) or an every 3-hour regimen (0.1 mg/kg/dose), demonstrated a weak, but positive, correlation between prolongation of QT with Bazett correction method and cisapride serum concentration ($R^2=0.20$; $p=0.015$).[58] However, a potential increase in heart rate (and, therefore, shortening of the RR interval) associated with cisapride is not accounted for in this publication. Bazett's method overcorrects QT at higher heart rates, confounding the putative correlation. In addition, during this study, ECGs were measured at different sites and by different methods for each of the two dosing regimens (0.2 mg/kg/dose: digital display; 0.1 mg/kg/dose: printed paper). Thus, the reported relationship between QTc prolongation and cisapride serum concentration could have resulted from systematic bias, that is, those with higher cisapride concentrations (0.2 mg/kg/dose) may have had higher delta QTc values because of the digital measurements.

Clinical observations regarding the effects of cisapride on the electrocardiogram in neonates, infants, and children are summarized here. Four reports describe the effects of cisapride ≤0.8 mg/kg/day on QTc interval. The remaining publications address the use of cisapride doses above the recommended maximum daily dose.

Semama reported on the effects of 0.8 mg/kg/day cisapride on the QTc interval before and during (time points included 48 hours and Days 7 and 15) therapy in 21 at-term neonates (GA 39 weeks).[121] Mean QTc interval increased from 397 msec before therapy to 418 msec at 48 hours (n=21; p<0.01), 431 msec at Day 7 (n=14), and 447 msec at Day 15 (n=7). Of the 21 neonates, 6 developed a QTc ≥450 msec; 3 at 48 hours, 1 at Day 7 and 2 at Day 15.

In a prospective study,[40] 25 neonates (all ≤34 weeks GA; 18 preterm neonates <32 weeks GA) admitted for reflux were treated with cisapride 0.1 mg/kg every 6 hours initially; the dose was increased to 0.8 mg/kg/day maximum only if clinically indicated. A baseline ECG was performed 24 hours before initiation of cisapride and follow-up ECGs were taken after 30 to 60 hours of therapy and again after a dose increase. Eight of the 25 neonates (32%) developed a QTc prolongation of ≥450 msec. All 8 patients were ≤32 weeks GA; in 6 patients, the QTc prolongation occurred while on 0.1 mg/kg/day (a total of 13 neonates received 0.1 mg/kg/day) and in 2 patients while on 0.2 mg/kg/day (a total of 12 neonates received 0.2 mg/kg/day). The mean QTc of the 18 preterm neonates (<32 weeks GA) was prolonged from 0.41±0.02 sec at baseline to 0.44±0.02 sec during cisapride therapy (p <0.05); mean QTc of the 7 term neonates was 0.40±0.02 sec at baseline and 0.42±0.02 sec during therapy (not significantly different).

To investigate the effect of cisapride 0.8 mg/kg/day on QTc over a 14-day period, China et al studied a prospective cohort of 50 infants (44 preterm, 6 term neonates).[16] At the start of cisapride therapy, mean PCA was 34.5±7.5 weeks; PCA ranged from 30.3±3.1 weeks for 11 subjects born at ≤26 weeks GA to 43.5±4.6 for 6 subjects born at term, ≥37 weeks GA. ECGs were obtained on Days 3, 5, 7 and 14 of treatment. Fifteen infants (30%) developed a prolonged QTc interval, ie, ≥450 msec. There was no correlation between QTc prolongation and GA and only a weak correlation between QTc and PCA at the initiation of cisapride (r=0.285; p=0.045). In 13 of the 15 infants, the QTc interval normalized without discontinuation of cisapride therapy. Infants, who on Day 3 of cisapride therapy had a QTc interval ≥441 msec, ie, 2 standard deviations above the mean baseline, were more likely to develop a prolonged QTc interval (p <0.0001).

Levine et al investigated the effects of cisapride on QT interval before and after a 1-month treatment with 0.2 mg/kg q.i.d. cisapride in 38 patients, of which 12 were premature neonates.[89] Results for 30 subjects were reported (including 10 premature neonates at 3.6±2.5 weeks PCA; GA 25-36 weeks) and 20 infants and children with a mean age of 8.4±5.5 years. In the premature neonates, mean baseline QTc was 380±30 msec compared with 371±20 msec after 1 month of therapy. In the children, mean QTc was 390±20 msec at baseline and 394±30 msec after 1 month of therapy. In both groups, the differences in QTc interval between baseline and 1 month were not statistically significantly different.

Summarizing these case studies, it may be that cisapride, at doses ≤0.8 mg/kg/day, is associated with prolongation of the QTc interval. A relationship between cisapride plasma levels and QTc was not convincingly established at the recommended treatment dose. It is possible that preterm neonates are more susceptible to QTc prolongation.[22,78,58,16] None of these 4 case series included a placebo group as reference, therefore it is difficult to assess the clinical relevance of the observation that in up to 30% of neonates in these studies, the QTc interval exceeded 450 msec Two studies suggest that QTc normalizes under continuation of cisapride treatment at Day 14[16] or at 1 month.[89] No arrhythmias were reported and the clinical consequence of the reported QTc changes (using Bazett's correction for heart rate) in young neonates is unclear.

Several publications, including those in which cisapride doses well exceeded the recommended total dose of 0.8 mg/kg/day, describe statistically significant differences in QTc interval in neonates and infants treated with various cisapride regimens. Tahiri reported electrocardiographic findings from a cohort of 259 referrals: 80 neonates were on cisapride therapy (mean dose 0.97 mg/kg/day, range: 0.6 to 2.35 mg/kg/day) and 179 were not (controls). A statistically significant ($p<0.002$) difference in QTc interval was observed between cisapride-treated subjects (399 msec) and controls (389 msec).[130] A second publication by the same authors describes 368 neonatal infants (mean age of 3.8 months, including 15 premature neonates) referred to the cardiology unit for evaluation between April 1 and December 31, 1996. Of these, 121 patients were treated with cisapride (mean dose 0.96 mg/kg/day, [range: 0.5 to 2.35 mg/kg/day]) and 247 served as untreated infants.[131] The study found a significant difference ($p<0.0001$) in QTc interval between cisapride-treated patients (mean 403±30 msec; range 332 to 495) and the untreated patients (mean 389±25 msec; range 332 to 495). QTc prolongation (>440 msec) was seen in 19 subjects: 12 patients on cisapride and 7 untreated infants. Of the patients receiving the recommended dose of cisapride (≤0.8 mg/kg/day), 94% had a normal QTc, whereas 6% and 11.5% of patients treated with doses above the recommended dose had QTc >440 msec.

The QTc results of these two observational studies seem to be consistent with two prospective case reports: one in neonates and one including infants and older children. In an open-label, prospective study, Bernardini treated 51 neonates (mean PCA 12.4±9.7 days with a range of 1 to 43 days; GA range 25 to 41 weeks) with cisapride 0.42 to 1.6 mg/kg. ECGs were assessed before therapy and between Days 2 and 6 of cisapride therapy. A significant ($p<0.0001$) increase was noted in mean QTc interval between baseline (395 msec; range 356 to 446 msec) and the follow-up assessment (418; range 371 to 504 msec).[9] Another case series described 30 subjects with a median age of 3.6 months (range 17 days to 12.5 years) for whom mean QTc interval increased from 393.9±27.0 msec at baseline to 409.4±30.0 msec ($p<0.002$) after 2 to 5 days of cisapride 0.6 to 1.2 mg/kg/day.[79,117]

A case-control study included 202 infants born at term: 84 patients undergoing cisapride therapy for at least 4 days and 118 untreated controls. Subjects were divided into three groups according to age: <3 months, 3 to 6 months, and >6 months.[129] Mean dosages of cisapride were 0.80 mg/kg/day (range: 0.38-1.55 mg/kg/day); 0.80 mg/kg/day (range: 0.23 to 1.38 mg/kg/day), and 0.72 mg/kg/day (range: 0.32-1.41 mg/kg/day) in the three age groups respectively. The infants underwent polysomnography for 8 hours overnight, including a continuous bipolar limb

lead I, starting 40 to 60 minutes after cisapride administration. From the polysomnography recording, QTc intervals were assessed hourly, taking three cycles each time; therefore, for each subject, the QTc value was an average of 24 cycles. Differences in QTc between cisapride-treated and control subjects were seen only in the youngest age group. In the youngest age group, mean QTc was significantly ($p<0.001$) prolonged in the cisapride-treated (434.6±14.9 msec; n=64) subjects, compared with controls (411.1±14.6 msec; n=55) Two neonates in the age group <3 months had QTc values over 500 msec. In a separate publication of this same somnography study, cisapride plasma concentrations in these two subjects were >115 ng/mL. Two other subjects with plasma concentrations >115 ng/mL had QTc intervals of less than 470 msec.[130] The results of this study suggest that infants under 3 months of age may be more susceptible to developing QT prolongation as a result of overdosing ie, cisapride administration above the recommended total of 0.8 mg/kg/day, and consequently increased cisapride plasma levels.

Several authors hypothesized that infants under 3 months of age exhibit more variable and higher cisapride plasma concentrations for the same mg/kg dose than older children, related to the lower, more variable and rapidly changing amount of CYP3A4 in the neonatal liver during the first days, weeks and months after birth.[7,78,22,163]

Bedu suggested that a reduction in the dosage of cisapride to 0.8 mg/kg/day may reduce the risk of QTc prolongation[6]; and many reports confirm that QT prolongation is fully reversible when cisapride therapy is stopped.[9,6,57,97,111]

Case reports of QT prolongation often describe neonates, infants, or children exceeding the maximum recommended cisapride dose (0.8 mg/kg/day), cases where contraindicated co-medication is involved or other risk factors for cardiac-rhythm disturbances have to be taken into account.[91,111,45,51,55,60,68,80,90,100,101,108,120,125,132,133,155] A case-control study in 35 children (age 0.4 to 18 years) with GERD receiving an average cisapride dosage of 0.67 mg/kg/day (range 0.30 to 1.68 mg), compared ECG results with those from a control group of 1,000 healthy children.[68] No significant difference between groups was found with respect to mean QTc interval (430±37 msec for cisapride versus 420±20 msec for controls). Nevertheless, 11 of the 35 (31%) treated patients had a prolonged QTc interval (≥450 msec). Of the 11 children with prolonged QTc interval, 2 had documented Torsades de pointes ventricular tachycardia. Both of these patients were taking cisapride (dosage not reported) concomitantly with a macrolide antibiotic.[68]

A retrospective survey of academic neonatal intensive care units in the US[155] including >11,000 preterm neonates treated with cisapride (typically 0.1 to 0.2 mg/kg per dose repeated every 6 to 8 hours), reported three non-fatal arrhythmias. No deaths attributable to cisapride were reported. In two patients, bradycardic arrhythmia requiring resuscitation was observed in association with 10-fold dosing errors, ie, doses of 2 mg/kg rather than 0.2 mg/kg. A third patient developed a transient bradycardic arrhythmia during co-treatment with erythromycin, a macrolide antibiotic that reduces the metabolism of cisapride.[87]

The cardiac side effects of cisapride were investigated in 46 pre-term infants with a mean birth weight of 1,350 g and mean post conceptional age of 31 weeks.[19] This study was not blinded, however, all measurements were taken by the same pediatric cardiologist, who was unaware of the treatment each patient received. Thirty-one of the infants were appropriate for gestational age (AGA) and 15 were small for gestational age (SGA). Cisapride was randomly administered at a dose of 0.3 mg/kg/day or 0.6 mg/kg/day. The control group comprised 50 pre-term new born infants with a mean birth weight of 1,300 g and post-conceptional age of 30.5 weeks who were not treated with cisapride. Fifteen patients were SGA and 35 were AGA.

The monitoring of infants treated with cisapride compared to those not treated with cisapride was similar. During a 15-month period, in both cisapride and control groups, a pretreatment baseline ECG and a second one during the treatment period (2 to 7 days interval), was performed to measure the QTc.

Before starting treatment no patients had significant alterations of electrolytes, hepatic or renal indices, or were receiving drugs known to enhance cisapride toxicity. In the cisapride treatment group overall, mean post-treatment QTc (400 ms) was significantly longer than the pretreatment QTc (390 ms); p=0.0001. In the SGA group of patients treated with cisapride, mean post-treatment QTc (410 ms range 360 to 500 ms) was significantly longer than in the AGA group (396 ms; range 370-420 ms); p=0.02. In contrast, in the control group, the mean QTc at the second reading was not significantly different between SGA and AGA infants. Mean QTc lengthening during cisapride treatment was also significantly higher in the SGA group compared with the AGA group (p=0.041). Three infants in the SGA group showed an increase in QTc >440 ms following cisapride treatment but no infants in the AGA group. There was no significant correlation between either birth weight or gestational age and changes in QTc values during cisapride treatment among AGA pre-term babies.

In conclusion, the results of the electrocardiographic studies suggested that infants, less than 3 months of age and small for gestation age infants, may be at higher risk of developing QTc prolongation, when exposed to cisapride, although QTc prolongation was generally seen only in infants who received cisapride doses well above the recommended maximum (≤0.8 mg/kg/day). It is possible, however, that after an initial lengthening of the QT interval, normalization follows with continued administration of cisapride.[16,89]

The assessment of what constitutes a normal or acceptable QTc interval in newborns and young infants is hindered by our lack of understanding of the natural development of this parameter in early life. “Normal” QT has been reported as 451 msec on Day 4, 454 msec at 2 months, 451 msec at 4 months and 442 msec at 6 months of age.[120] Apart from the question of the applicability of Bazett’s correction in early preterm neonates, it is unclear what value a given QTc interval has in predicting risk of serious VA and Torsades de pointes.

Reports of serious VA and Torsades de pointes are mostly associated with cisapride overdose or the administration of contraindicated concomitant medication eg, macrolide antibiotics, interfering with the CYP 3A4 metabolism of cisapride.[117,155]

1.1.2.3. Elderly

There have been few clinical studies specifically investigating the effect of cisapride on cardiac function.

There is no evidence that age greater than 65 years is a risk factor for QT prolongation in patient taking cisapride. However, there are no prospective data confirming this and it is reasonable, therefore, to advise caution given that the elderly may have a relevant medical history.

1.1.2.4. Organ Impaired Population

Little information is available on the relationship between cisapride plasma levels and QT intervals in patients with organ impairment. Two recent communications discussed the effect of cisapride on QTc in patients with end-stage renal disease.[60,80] Discontinuation of cisapride led to a statistically significant reduction in QTc interval and in QTc dispersion in nine patients. These patients had abnormally long QTc intervals even off cisapride, suggesting a predisposition towards QTc prolongation. However, in 23 other patients, discontinuation of cisapride caused only a 2-msec reduction in mean QTc interval. In this study, prolonged QTc was seen in four patients. There was no significant difference in the number of hospital admissions per month for cisapride patients compared to those not receiving cisapride.

1.1.2.5. Diabetic Patients

The association between QT-interval prolongation and diabetic autonomic neuropathy has been investigated because cardiorespiratory arrest and sudden death have been reported in patients with diabetes mellitus and clinical evidence of autonomic neuropathy. While the relationship between these events and diabetic neuropathy is unknown, it has been suggested that QT-interval prolongation predisposes diabetic patients to ventricular arrhythmia and sudden death.[149]

The EURODIAB IDDM Complication Study evaluated the prevalence of QT-interval prolongation and its relation with diabetic complications. This study involved 3,250 insulin-dependent diabetic patients attending 31 centers in 16 European countries.[150] The prevalence of an abnormally prolonged QTc was 16% in the whole diabetic patient population. For male patients, the prevalence was 11% compared to 21% for female patients ($p<0.001$). Mean QTc was 412 msec for male and 422 msec for female patients ($p<0.001$). QTc interval prolongation was independently associated with age, hemoglobin A1c and blood pressure. QTc prolongation was correlated with ischemic heart disease and nephropathy, and this relationship appeared stronger in male than female patients. Also, a higher mean adjusted QTc interval was found for male patients with neuropathy or impaired heart rate variability or both compared to male patients without this complication. The relationship between QTc-interval prolongation and autonomic neuropathy was not observed for female patients. Other, smaller studies confirm the association of QTc-interval prolongation with the presence of neuropathy in patients with diabetes.[125,132]

The clinical consequence of prevalent QT prolongation in diabetics, as observed specifically in patients with major diabetic autonomic neuropathy, with respect to treatment with cisapride, ie, the potential for excess cardiac risk, is unknown.

Summary of Effects on the Cardiovascular System

Single-doses of 20 mg cisapride or less do not induce a clinically significant change in the QTc interval duration. At single doses of 40 mg cisapride or higher, a dose- and concentration-dependent prolongation of the QTc interval has been observed of which the magnitude depends on the method used to correct QT interval for changes in heart rate. Multiple-dose treatment with cisapride 10 mg and 20 mg q.i.d. as monotherapy do not appear to evoke clinically significant changes in QTc interval. Nevertheless, cisapride is a drug with potential for prolonging the QT interval, as evident from its pharmacological I_{Kr}-blocking profile, especially when used at high doses or in circumstances that could lead to higher than expected cisapride plasma levels.

Cisapride is associated with a mean increase in QTc in several study populations. Dose-dependent QTc increases have only been observed when cisapride plasma levels are well above the normal therapeutic range, for example following high single doses of 40 to 130 mg. QTc increases may become clinically significant when cisapride is given with drugs that inhibit CYP 3A4, or with drugs that independently prolong the QTc interval. In general, an increased QTc does not occur in all subjects, the increases in QTc are rarely clinically significant, and clinically significant increases are almost always asymptomatic.

All patients with, or suspected of having risk factors for ventricular arrhythmia should be carefully evaluated prior to administration of cisapride. In particular, patients with the following should be evaluated:

- a history of significant cardiac disease, including:
  - serious ventricular arrhythmia
  - second or third degree atrioventricular block
  - sinus node dysfunction
  - congestive heart failure, ischemic heart disease
- family history of sudden death
- chronic dialysis and kidney failure
- other risk factors for electrolyte disturbances, ie, hypokalemia or hypomagnesemia, because of
  - potassium-wasting diuretics
  - the administration of insulin in acute settings
  - persistent vomiting and/or diarrhea
- significant chronic obstructive pulmonary disease and respiratory failure
- known congenital long-QT interval or family history of congenital long-QT syndrome

An ECG and an assessment of serum electrolytes (potassium and magnesium) and renal function should be performed in every patient before and during cisapride treatment. Due to the significant inter- and intra-patient variability in QT interval,[8] it often is unclear whether a given QTc prolongation observed during treatment with cisapride constitutes a meaningful degree of excess risk for serious VA to an individual patient.[108] Cisapride should not be prescribed to patients with a baseline QTc interval of >450 msec or to those with uncorrected electrolyte disturbances. Cisapride should be withheld upon the detection of a prolonged QTc interval and contributing factors evaluated.

The treatment in premature neonates should be restricted to specialized critical care units and cisapride should be administered only under constant cardiac monitoring.

1.1.2.6. Pharmaco-Epidemiology Studies

Following spontaneous reports of suspected adverse reactions classified as prolonged QT interval, serious ventricular arrhythmia, or sudden cardiac death associated with the use of cisapride, retrospective pharmaco-epidemiological studies were conducted to explore the nature and frequency of these adverse reactions as a consequence of cisapride use in the general population.

In the Prescription Event Monitoring study, which included over 13,000 patients, the incidence of cardiac rhythm disorders was similar between cisapride, 2.8 events per 1,000 patients, and thirty-three other medications, including ten cardiovascular drugs (3.3 per 1,000). All cause mortality also was no higher among cisapride users (2.9%) than among the entire cohort (5.5%).[153] Limitations of this work include: the recorded adverse events may be either new onset or recurrent; the outcome tabulation is substantially broader (any disorder of cardiac rhythm) than the outcome of primary interest (serious VA); the reporting of events is voluntary; and the results are not adjusted for age, sex, comorbidity or concurrent medication.

The relationship between cisapride and serious VA was assessed using two validated population databases; the General Practice Research Database in the UK and the Saskatchewan Health Database in Canada.[155] More than 37,000 cisapride users were evaluated in a combined evaluation. Fifty-two serious VAs were reported, of which 18 were associated with recent cisapride use, ie, within a 56-day window following drug dispensing. There were no cases among subjects aged less than 15 years. The age and sex standardized rates of arrhythmic events was 1.1 per 1,000 person-years for recent use of cisapride versus 0.6 events per 1,000 person-years for non-use, resulting in an odds ratio of 1.6 (95% CI: 0.9 to 2.9). With adjustment for clinical history, use of CYP3A4 inhibitors, and use of drugs that prolong the QT interval, the odds ratio for cisapride and cardiac outcomes was 1.0 (95% CI: 0.3 to 3.7). There was no identifiable increase in risk when cisapride was dispensed at about the same time as QT-prolonging drugs or CYP3A4 inhibitors. QT- prolonging agents were associated with a 2.5-fold increase in the risk of arrhythmic events (95% CI: 1.1 to 5.8). The authors concluded that serious rhythm disorders were not associated with cisapride use, although the upper confidence bounds do not rule out an increase in risk.[154]

These findings were confirmed in an observational study using a large US database of 28,078 patients under the age of 65 years with no history of antiarrhythmia treatment who received cisapride between 1993 and 1998 (United Health Care research database).[43] Rates of events were calculated for time on and off cisapride. There were 23 cases of serious VA: 10 during periods of cisapride use in the primary definition of exposure, ie, within a 56-day window after drug dispensing, and 13 during periods of non-use. The adjusted rate ratio of serious VA events for cisapride use versus non-use time was 1.60 (95% CI: 0.67 to 3.82) in the 56-day window. The rate ratio of 1.19 (95% CI: 0.44 to 3.17) was observed in a more stringent, 28-day exposure window after drug dispensing. A dose-response relationship between the dosage of cisapride and the risk of an arrhythmic event could not be established. There was little evidence for an interactive effect between cisapride and concomitant use of contraindicated medication. The rate ratio identified for QT-interval-prolonging drugs (other than cisapride) was 1.60 (95% CI: 0.65-3.98) in the 56-day exposure window and 3.02 (95% CI: 1.22 to 7.49) in the 28-day window. The authors concluded that "The evidence for an increased risk of SVAs associated with cisapride was equivocal after taking observation time on and off cisapride into account, and adjusting for risk factors, though we cannot exclude the possibility of a 3.8-fold increased risk. Overall, the plausible risks of cisapride were similar to those of other QT-prolonging drugs.[43]"

Also using the United Health Care research database, the incidence of SIDS was investigated in 3,082 evaluable infants who received cisapride between January 1, 1993, and June 30, 1998. Of 14 confirmed deaths, 2 were deemed possible SIDS. The SIDS risk for each infant in the cohort was derived from a review of national statistics and calculated by summing the observation-time-weighted risks across sex and prematurity/birth weight strata. The observed (2 cases) to expected (1.80 cases) ratio of SIDS was 1.1 (95% CI 0.24, 7.2) in the population of infants who had used cisapride: thus, no increase or decrease of SIDS was identified in the cisapride-treated compared with the general infant population.[41]

A retrospective mail survey involved 105 neonatology training-program directors.[155] More than 58,000 premature neonates of <36 weeks gestation were admitted to the 46 responding institutions. Of these premature neonates, 11,149 (19.1%) were treated with cisapride. No deaths were attributable to cisapride. Three patients with non-fatal arrhythmias were reported: two were observed in association with 10-fold dosing errors; and one patient developed a transient bradycardic arrhythmia during co-treatment with erythromycin.

Summary of Pharmacoepidemiology Studies

The risk of serious VA during cisapride use is very low. The reviews of the combined UK General Practice Research Database/Saskatchewan Health Database study, the United Health Care research database study, and the other observational studies presented, essentially arrive at the same conclusion, ie, they do not establish a relationship between serious rhythm disorders and cisapride. Nevertheless, these studies also did not rule out a possible increase in serious VA from the (very low) background risk.

1.2. Ischemic Cardiac Events Related to Cisapride

A total of 102 articles were identified from the literature search. All of these articles lacked relevant cardiac ischemia/ischemic safety information or did not include data from clinical trials (eg, they were review articles, case studies, retrospective or epidemiological studies).

Therefore, no clinical trial data with relevant information about cardiac ischemia were identified in the literature over the past 19 years.

PART III

1. Points to Consider Based on Experience With Cisapride

The following is a summary of the points to consider in response to the FDA's request to provide an overview of the cisapride experience to provide the agency with recommendations for pre-market clinical development programs necessary for the evaluation of CV safety for 5-HT_4 agonists.

1.1. Non-Clinical

Testing pre-clinically for ventricular tachyarrhythmia potential:

- 5HT4 agonists blockade on the hERG channel is not a class effect
- If any hERG inhibition or QT prolongation is observed, identify the safety margins with regard to maximum Cmax plasma levels measured with recommended doses, and supra-therapeutic doses.
- Identify if there are likely drug-drug interactions with other commonly used/prescribed drugs.
- Use the appropriate species (eg, pig) when evaluating atrial, atrio-ventricular and ventricular conduction.

For identifying risks of cardiovascular ischemia and 5-HT_4 agonists:

- Characterize the general receptor/enzyme/ion channel binding profile.
- Check agonist/antagonist functional profiles for any other 5-HT receptor hits (eg, 5-HT2B agonism causes valvulopathy).
- Evaluate for coronary vasoconstriction (eg, 5-HT1B and 5-HT2A agonism).
- Identify if there are any vascular structure effects in toxicology, particularly in coronary beds.
- Since 5-HT2a receptors are present on platelets and facilitate platelet aggregation there should be an examination of hemostasis, coagulation/ fibrinolysis, platelet effects and/or interference with eicosanoid synthesis.
- 5-HT4 receptors: In humans and pigs (but not dogs,) hydroxytryptamine causes tachycardia via activation of atrial 5-HT4 receptors.

1.2. Clinical

- Characterize the main drug clearance pathways and identify the intrinsic and extrinsic factors that could affect plasma concentrations to a clinically relevant extent.
- Validate potential or predicted drug interactions with appropriately designed clinical pharmacology studies.
- Investigate safety and tolerability of multiples of the anticipated clinical dose-range, sufficiently high to account for increases in plasma exposure based on knowledge of these factors that may lead to increased systemic exposure.

1.3. Post-Approval Safety Surveillance

- Post-approval safety surveillance identified ventricular tachyarrhythmia-related events as a safety signal.
- No safety signal emerged from post-approval safety surveillance or from the medical literature to suggest an association between cisapride and cardiac ischemia-related events.
- Additional strategies to consider for post-approval monitoring of rare events include the use of registries, electronic health records, and administrative claims databases.

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SUPPORTING DATA

Attachment 1: Cisapride United States Package Insert

JANSSEN
Pharmaceutica

PROPULSID®
(cisapride)
TABLETS/SUSPENSION
Rx only
Professional Package Insert

Warning: Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking PROPULSID®. From July 1993 through May 1999, more than 270 such cases have been spontaneously reported, including 70 fatalities. In approximately 85% of these cases the events occurred when PROPULSID® was used in patients with known risk factors. These risk factors included the administration of other drugs which caused QT prolongation, inhibited the cytochrome P450 3A4 enzymes that metabolize cisapride, or depleted serum electrolytes; or the presence of disorders that may have predisposed patients to arrhythmias. In approximately 0.7% of these cases, the events occurred in the absence of identified risk factors; in the remaining cases, risk factor status was unknown. Because the cases were reported voluntarily from a population of unknown size, estimates of adverse event frequency cannot be made. (See **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS** and **Drug Interactions**.)

Numerous drug classes and agents increase the risk of developing serious cardiac arrhythmias. PROPULSID® is contraindicated in patients taking certain ***macrolide antibiotics*** (such as clarithromycin, erythromycin, and troleandomycin), certain ***antifungals*** (such as fluconazole, itraconazole, and ketoconazole), ***protease inhibitors*** (such as indinavir and ritonavir), ***phenothiazines*** (such as prochlorperazine and promethazine), ***Class IA and Class III antiarrhythmics*** (such as quinidine, procainamide, and sotalol); ***tricyclic antidepressants*** (such as amitriptyline); certain ***antidepressants*** (such as nefazodone and maprotiline); certain ***antipsychotic medications*** (such as sertindole), as well as ***other agents*** (such as bepridil, sparfloxacin, and grapefruit juice). (See **PRECAUTIONS: Drug Interactions**.) **The preceding list is not comprehensive.**

QT prolongation, torsades de pointes (sometimes with syncope), cardiac arrest and sudden death have been reported in patients taking PROPULSID® without the above-mentioned contraindicated drugs. Most patients had disorders that may have predisposed them to arrhythmias with PROPULSID®. These include history of prolonged electrocardiographic QT intervals or known family history of congenital long QT syndrome; history of ventricular arrhythmias, ischemic or valvular heart disease; other structural heart defects; cardiomyopathy; congestive heart failure; clinically significant bradycardia; sinus node dysfunction; second or third degree atrioventricular block; respiratory failure; or conditions that result in electrolyte disorders (hypokalemia, hypocalcemia, and hypomagnesemia), such as severe

dehydration, vomiting, or malnutrition; eating disorders; renal failure; or the administration of potassium-wasting diuretics or insulin in acute settings. PROPULSID® is contraindicated in patients with these conditions.

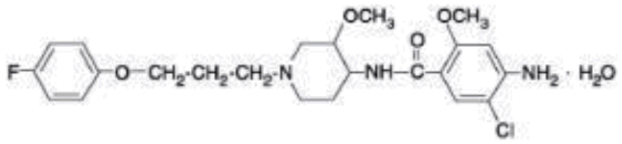
A 12-lead ECG should be performed prior to administration of PROPULSID®. Treatment with PROPULSID® should not be initiated if the QTc value exceeds 450 milliseconds. Serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed prior to administration of PROPULSID® and whenever conditions develop that may affect electrolyte balance or renal function. (See **DOSAGE AND ADMINISTRATION**.)

If syncope, rapid or irregular heartbeat develop, patients should immediately stop taking PROPULSID® and seek the attention of a physician.

Recommended doses of PROPULSID® should not be exceeded.

DESCRIPTION

PROPULSID® (cisapride) Tablets and Suspension contain cisapride as the monohydrate, which is an oral gastrointestinal agent chemically designated as (±)-cis-4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrate. Its empirical formula is $C_{23}H_{29}ClFN_3O_4 \cdot H_2O$. The molecular weight is 483.97 and the structural formula is:



Cisapride as the monohydrate is a white to slightly beige odorless powder. It is practically insoluble in water, sparingly soluble in methanol, and soluble in acetone. Each 1.04 mg of cisapride as the monohydrate is equivalent to one mg of cisapride.

PROPULSID® is available for oral use in tablets containing cisapride as the monohydrate equivalent to 10 mg or 20 mg of cisapride and as a suspension containing the equivalent of 1 mg/mL of cisapride. The inactive ingredients in the tablets are colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, povidone, and starch (corn). The 20 mg tablets also contain FD&C Blue No. 2 aluminum lake. The inactive ingredients in the suspension are hydroxypropyl methylcellulose, methylparaben, microcrystalline cellulose and carboxymethylcellulose sodium, polysorbate 20, propylparaben, sodium chloride, sorbitol, and water. The 1 mg/mL suspension also contains artificial cherry cream flavor and FD&C Red No. 40.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Cisapride is metabolized mainly via the cytochrome P450 3A4 enzyme. PROPULSID® (cisapride) is extensively metabolized; unchanged drug accounts for less than 10% of urinary and fecal recovery following oral administration. Norcisapride, formed by N-dealkylation, is the principal metabolite in plasma, feces and urine. PROPULSID® is rapidly absorbed after oral administration; peak plasma concentrations are reached 1 to 1.5 hours after dosing. The absolute bioavailability of PROPULSID® is 35-40%. When gastric acidity was reduced by high dose histamine H_2 receptor blocker and sodium bicarbonate in fasting subjects, there was a decrease in the rate, and to a lesser degree the extent, of PROPULSID® tablet absorption. (This has not been established for the suspension.) PROPULSID® binds to an extent of 97.5-98% to plasma proteins, mainly to albumin. The volume of distribution of PROPULSID® is about 180 L, indicating extensive tissue distribution.

The plasma clearance of PROPULSID® is about 100 mL/min. The mean terminal half-life reported for PROPULSID® ranges from 6 to 12 hours; longer half-lives, up to 20 hours, have been reported following intravenous (IV) administration.

There was no unusual drug accumulation due to time-dependent or non-linear changes in pharmacokinetics. After cessation of the repeated dosing, the elimination half-lives (8 to 10 hr) were in the same order as after single dosing. The degree of accumulation of PROPULSID® and/or its metabolites may be somewhat higher in patients with hepatic or renal impairment and in elderly patients compared to young healthy volunteers, but the differences are not consistent. Dose adjustments are recommended in patients with hepatic impairment. (See **DOSAGE AND ADMINISTRATION**.)

The pharmacokinetics of cisapride in pediatric patients are not well characterized. Therefore, it is unknown if the dose-response relationship in the adult population can be extrapolated to the pediatric population. (See **PRECAUTIONS: Pediatric Use**.)

Pharmacodynamics

The onset of pharmacological action of cisapride is approximately 30 to 60 minutes after oral administration.

Cisapride promotes gastric motility. The mechanism of action of cisapride is thought to be primarily enhancement of release of acetylcholine at the myenteric plexus. Cisapride does not induce muscarinic or nicotinic receptor stimulation, nor does it inhibit acetylcholinesterase activity. It is less potent than metoclopramide in dopamine receptor-blocking effects in rats. It does not increase or decrease basal or pentagastrin-induced gastric acid secretion.

In vitro studies have shown that cisapride is a serotonin-4 (5-HT_4) receptor agonist.

Electrophysiological studies in *in vivo* anesthetized guinea pig and rabbit models and *in vitro* isolated rabbit Purkinje fibers and ventricular papillary muscle and isolated rabbit ventricular myocyte models, have shown that cisapride prolonged cardiac repolarization without slowing conduction by selectively blocking the rapid component of the delayed rectifying K^+ current (I_{kr}) which leads to a lengthening of the action potential (QT Syndrome).

Esophagus: Twenty milligrams oral cisapride given once to healthy volunteers increased lower esophageal sphincter pressure (LESP), starting 45 minutes after dosing, with a peak response at 75 minutes. The full duration of the effect was not monitored, and doses smaller than 20 mg were ineffective. Ten milligrams oral cisapride, administered 3 times daily for several days to patients with gastroesophageal reflux disease (GERD), resulted in a significant increase in LESP, and an increased esophageal acid clearance.

Stomach: Cisapride (single 10 mg doses or 10 mg given orally 3 times daily up to six weeks) significantly accelerated gastric emptying of both liquids and solids. Acceleration of gastric emptying, measured over a four hour period following a radio-labeled test meal given at lunch time, was greatest when 10 mg cisapride was given both in the morning and again before the test meal, intermediate when 20 mg was given as a single administration in the morning and least when only 10 mg was given on the morning of the test meal. The increases in gastric emptying were proportional to the plasma levels of cisapride measured in these subjects over the same 4 hours that the gastric emptying test was conducted.

Clinical Trials

Clinical trials have shown that cisapride can reduce the severity of symptoms of nocturnal heartburn associated with gastroesophageal reflux disease. Two placebo-controlled studies, one using a dose of 10 mg q.i.d., the other both 10 and 20 mg q.i.d., showed effects on nighttime heartburn, although the 10 mg dose in the second study was only marginally effective. There were no consistent effects on daytime heartburn, symptoms of regurgitation, or histopathology of the esophagus. Use of antacids was only infrequently affected and slightly decreased. In a third controlled trial of similar design to the others, neither 10 mg nor 20 mg taken 4 times daily was superior to placebo. In these clinical trials cisapride did not show a significant effect on LESP.

In a clinical trial comparing 10 mg cisapride to placebo, pH probe evaluation, in a relatively small number of patients, did not reveal a significant difference in pH.

INDICATIONS AND USAGE

PROPULSID® (cisapride) is indicated for the symptomatic treatment of adult patients with nocturnal heartburn due to gastroesophageal reflux disease. Because of the risk of serious, and sometimes fatal, ventricular arrhythmias (see **Boxed Warning**), PROPULSID® should generally be reserved for patients who do not respond adequately to lifestyle modifications (See **PRECAUTIONS: Information for Patients** and **Medication Guide**), antacids and gastric acid reducing agents.

CONTRAINDICATIONS

Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking PROPULSID® (cisapride) with other drugs that inhibit cytochrome P450 3A4 or that prolong the QT interval. Some of these events have been fatal. Concomitant oral or intravenous administration of these drugs with PROPULSID® is contraindicated. PROPULSID® is also contraindicated for patients with disorders that may predispose

them to arrhythmias. (See **Boxed Warning, WARNINGS, PRECAUTIONS** and **Drug Interactions**.)

PROPULSID® should not be used in patients in whom an increase in gastrointestinal motility could be harmful, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

PROPULSID® is contraindicated in patients with known sensitivity or intolerance to the drug.

WARNINGS
PROPULSID® (cisapride) undergoes metabolism mainly by the hepatic cytochrome P450 3A4 isoenzyme. Drugs which inhibit this enzyme can lead to elevated cisapride blood levels. (See **PRECAUTIONS** and **Drug Interactions**.)

Numerous cases of serious cardiac arrhythmias, including ventricular arrhythmias and torsades de pointes associated with QT prolongation, have been reported in patients taking PROPULSID® alone or with the drugs listed above, or with disorders that may have predisposed them to arrhythmias. Some of these patients did not have cardiac disease; however, most had been receiving multiple other medications and had pre-existing cardiac disease or risk factors for arrhythmias. Some of these cases have been fatal. (See **Boxed Warning**.)

PRECAUTIONS
General: Potential benefits should be weighed against risks prior to administration of PROPULSID® (cisapride) to patients who have conditions that could predispose them to the development of serious arrhythmias, such as multiple organ failure, COPD, apnea and advanced cancer. (See **CONTRAINDICATIONS**.)

Information for Patients: Patients should be warned against concomitant use of promethazine (Phenergan®), bepridil (Vascor®), quinidine (such as Quinidex®, Cardioquin®, Quinaglute®), procainamide (Procanbid®), sotalol (Betapace®), erythromycin (such as E.E.S.®, E-Mycin®, Ilotycin®, Pediazole®), clarithromycin (Biaxin®), troleandomycin (TAO®), sparfloxacin (Zagam®), amitriptyline (Elavil®), maprotiline (Ludiomil®), nefazodone (Serzone®), fluconazole (Diflucan®), itraconazole (Sporanox®), ketoconazole (Nizoral®), prochlorperazine (Compazine®), sertindole, indinavir (Crixivan®), ritonavir (Norvir®) and warfarin (Coumadin®). (See **Drug Interactions**.) **The preceding list is not comprehensive.**

Recommended doses should not be exceeded.

Patients should be advised to stop PROPULSID® and seek medical attention if they faint or become faint, dizzy, experience an irregular heartbeat or pulse, or any other unusual symptoms while using PROPULSID®.

Patients should be questioned about concomitant medication use. Patients taking PROPULSID® should also be advised to inform their physician when new medications are prescribed.

Patients should be advised to refrain from consuming grapefruit juice for the duration of their PROPULSID® therapy.

Although PROPULSID® does not affect psychomotor function nor does it induce sedation or drowsiness when used alone, patients should be advised that the sedative effects of benzodiazepines and of alcohol may be enhanced by PROPULSID®.

Patients should be advised that generally the following lifestyle changes should be tried before using any drug for nighttime heartburn, including PROPULSID®: avoiding alcohol, quitting/decreasing cigarette smoking, elevating the head of the bed, avoiding large meals/meals just before bedtime, losing weight, avoiding fatty foods, chocolate, caffeine, or citrus.

Patients should be given the Medication Guide for additional information.

Drug Interactions: Cisapride is metabolized mainly via the cytochrome P450 3A4 enzyme. In some cases where serious ventricular arrhythmias, QT prolongation, and torsades de pointes have occurred when PROPULSID® was taken in conjunction with one of the cytochrome P450 3A4 inhibitors, elevated blood cisapride levels were noted at the time of the QT prolongation.

Antibiotics: *In vitro* and/or *in vivo* data show that **clarithromycin, erythromycin** and **troleandomycin** markedly inhibit the metabolism of PROPULSID®, which can result in an increase in plasma cisapride levels and prolongation of the QT interval on the ECG.

Anticholinergics: Concurrent administration of certain anticholinergic compounds, such as belladonna alkaloids and dicyclomine, would be expected to compromise the beneficial effects of PROPULSID®.

Anticoagulants (oral): In patients receiving oral anticoagulants, the coagulation times were increased in some cases. It is advisable to check coagulation time within the first few days after the start and discontinuation of PROPULSID® therapy, with an appropriate adjustment of the anticoagulant dose, if necessary.

Antidepressants: *In vitro* data indicate that **nefazodone** inhibits the metabolism of PROPULSID®, which can result in an increase in plasma cisapride levels and prolongation of the QT interval on the ECG.

Antifungals: *In vitro* and/or *in vivo* data indicate that **fluconazole**, **itraconazole** and **oral ketoconazole** markedly inhibit the metabolism of PROPULSID®, which can result in an increase in plasma cisapride levels and prolongation of the QT interval on the ECG. Human pharmacokinetic data indicate that oral ketoconazole markedly inhibits the metabolism of cisapride, resulting in a mean eight-fold increase in AUC of cisapride. A study in 14 normal male and female volunteers suggests that coadministration of PROPULSID® and ketoconazole can result in prolongation of the QT interval on the ECG.

Diuretics: Drugs such as furosemide and the thiazides are associated with depletion of electrolytes which may result in PROPULSID®-induced cardiac arrhythmias. Serum electrolytes should be assessed in diuretic-treated patients before initiating PROPULSID® therapy and periodically thereafter. PROPULSID®-treated patients to whom diuretic therapy is added should undergo careful electrolyte monitoring after diuretic initiation.

H_2 receptor antagonists: **Cimetidine** coadministration leads to an increased peak plasma concentration and AUC of PROPULSID®; there is no effect on PROPULSID® absorption when it is coadministered with **ranitidine**. The gastrointestinal absorption of cimetidine and ranitidine is accelerated when they are coadministered with PROPULSID®.

Protease inhibitors: *In vitro* data indicate that **indinavir** and **ritonavir** markedly inhibit the metabolism of PROPULSID® which can result in an increase in plasma cisapride levels and prolongation of the QT interval on the ECG.

Other: Co-administration of grapefruit juice with PROPULSID® increases the bioavailability of cisapride by an average of 50%. Patients on PROPULSID® should refrain from consuming grapefruit juice for the duration of their PROPULSID® therapy.

PROPULSID® should not be used concomitantly with other drugs known to prolong the QT interval: certain antiarrhythmics, including those of Class IA (such as quinidine and procainamide) and Class III (such as sotalol); tricyclic antidepressants (such as amitriptyline); certain tetracyclic antidepressants (such as maprotiline); certain antipsychotic medications (such as sertindole); bepridil, and sparfloxacin. **The preceding lists are not comprehensive.**

The acceleration of gastric emptying by PROPULSID® could affect the rate of absorption of other drugs. Patients receiving narrow therapeutic ratio drugs or other drugs that require careful titration should be followed closely; if plasma levels are being monitored, they should be reassessed.

Carcinogenesis, mutagenesis, impairment of fertility: In a twenty-five month oral carcinogenicity study in rats, cisapride at daily doses up to 80 mg/kg was not tumorigenic. For a 50 kg person of average height (1.46 m^2 body surface area), this dose represents 50 times the maximum recommended human dose (1.6 mg/kg/day) on a mg/kg basis and 7 times the maximum recommended human dose (54.4 mg/m^2) on a body surface area basis. In a nineteen month oral carcinogenicity study in mice, cisapride at daily doses up to 80 mg/kg was not tumorigenic. This dose represents 50 times the maximum recommended human dose on a mg/kg basis and about 4 times the maximum recommended human dose on a body surface area basis.

Cisapride was not mutagenic in the *in vitro* Ames test, human lymphocyte chromosomal aberration test, mouse lymphoma cell forward mutation test, and rat hepatocyte UDS test and *in vivo* rat micronucleus test, male and female mouse dominant lethal mutations tests, and sex linked recessive lethal test in male *Drosophila melanogaster*.

Fertility and reproductive performance studies were conducted in male and female rats. Cisapride was found to have no effect on fertility and reproductive performance of male rats at

oral doses up to 160 mg/kg/day (100 times the maximum recommended human dose on a mg/kg basis and 14 times the maximum recommended human dose on a mg/m^2 basis). In the female rats, cisapride at oral doses of 40 mg/kg/day and higher prolonged the breeding interval required for impregnation. Similar effects were also observed at maturity in the female offspring (F_1) of the female rats (F_0) treated with oral doses of cisapride at 10 mg/kg/day or higher. Cisapride at an oral dose of 160 mg/kg/day also exerted contragestational/pregnancy disrupting effects in female rats (F_0).

Pregnancy: Teratogenic effects: Pregnancy category C: Oral teratology studies have been conducted in rats (doses up to 160 mg/kg/day) and rabbits (doses up to 40 mg/kg/day). There was no evidence of a teratogenic potential of cisapride in rats or rabbits. Cisapride was embryotoxic and fetotoxic in rats at a dose of 160 mg/kg/day (100 times the maximum recommended human dose on a mg/kg basis and 14 times the maximum recommended human dose on a mg/m^2 basis) and in rabbits at a dose of 20 mg/kg/day (approximately 12 times the maximum recommended human dose on a mg/kg basis) or higher. It also produced reduced birth weights of pups in rats at 40 and 160 mg/kg/day and adversely affected the pup survival. There are no adequate and well-controlled studies in pregnant women. Cisapride should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the mother and the fetus.

Nursing Mothers: Cisapride is excreted in human milk at concentrations approximately one twentieth of those observed in plasma. Caution should be exercised when PROPULSID® is administered to a nursing woman, and particular care must be taken if the nursing infant or the mother is taking a drug that might alter PROPULSID®'s metabolism in the infant. (See **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS** and **Drug Interactions**.)

Pediatric Use: Safety and effectiveness in pediatric patients under the age of 16 years have not been established for any indication. Although causality has not been established, serious adverse events, including death, have been reported in infants and children treated with PROPULSID®. Several pediatric deaths were due to cardiovascular events (third degree heart block and ventricular tachycardia). Pediatric deaths have been associated with seizures and there has been at least one case of “sudden unexplained death” in a 3-month-old infant. Other unlabeled potentially serious events which have been reported in pediatric patients include: antinuclear antibody (ANA) positive, anemia, hemolytic anemia, methemoglobinemia, hyperglycemia, hypoglycemia with acidosis, unexplained apneic episodes, confusion, impaired concentration, depression, apathy, visual changes accompanied by amnesia, and severe photosensitivity reaction. (See **OVERDOSAGE**.)

Geriatric Use: Steady-state plasma levels are generally higher in older than in younger patients, due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults.

The rate of common adverse experiences in patients greater than 65 years of age in clinical trials was similar to that in younger adults.

ADVERSE REACTIONS

In the U.S. clinical trial population of 1728 patients (comprising 506 with gastroesophageal reflux disorders, and the remainder with other disorders) the following adverse experiences were reported in more than 1% of patients treated with PROPULSID® (cisapride) and at least as often on PROPULSID® as on placebo.

System/Adverse Event	**PROPULSID® N=1042**	**Placebo N=686**
Central & Peripheral Nervous Systems		
Headache	19.3%	17.1%
Gastrointestinal		
Diarrhea	14.2	10.3
Abdominal pain	10.2	7.7
Nausea	7.6	7.6
Constipation	6.7	3.4
Flatulence	3.5	3.1
Dyspepsia	2.7	1.0
Respiratory System		
Rhinitis	7.3	5.7
Sinusitis	3.6	3.5
Coughing	1.5	1.2
Resistance Mechanism		
Viral infection	3.6	3.2
Upper respiratory tract infection	3.1	2.8
Body as a Whole		
Pain	3.4	2.3
Fever	2.2	1.5
Urinary System		
Urinary tract infection	2.4	1.9
Micturition frequency	1.2	0.6
Psychiatric		
Insomnia	1.9	1.3
Anxiety	1.4	1.0
Nervousness	1.4	0.7
Skin & Appendages		
Rash	1.6	1.6
Pruritus	1.2	1.0
Musculoskeletal System		
Arthralgia	1.4	1.2
Vision		
Abnormal vision	1.4	0.3
Reproductive, Female		

Vaginitis	1.2	0.9

The following adverse events also reported in more than 1% of PROPULSID® patients were more frequently reported on placebo: dizziness, vomiting, pharyngitis, chest pain, fatigue, back pain, depression, dehydration and myalgia.

Diarrhea, abdominal pain, constipation, flatulence and rhinitis all occurred more frequently in patients using 20 mg of PROPULSID® than in patients using 10 mg.

Additional adverse experiences reported to occur in 1% or less of patients in the U.S. clinical studies are: dry mouth, somnolence, palpitation, migraine, tremor and edema.

In other U.S. and international trials and in postmarketing experience, there have been rare reports of seizures and extrapyramidal effects. Also reported have been tachycardia, elevated liver enzymes, hepatitis, thrombocytopenia, leukopenia, aplastic anemia, pancytopenia and granulocytopenia. The relationship of PROPULSID® to the event was not clear in these cases.

Cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation, in some cases resulting in death, have been reported. (See **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS** and **Drug Interactions**.)

Ongoing Postmarketing Surveillance: Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking PROPULSID®. From July 1993 through May 1999, more than 270 such cases have been spontaneously reported, including 70 fatalities. In approximately 85% of these cases the events occurred when PROPULSID® was used in patients with known risk factors. These risk factors included the administration of other drugs which caused QT prolongation, inhibited the cytochrome P450 3A4 enzymes that metabolize cisapride, or depleted serum electrolytes; or the presence of disorders that may have predisposed patients to arrhythmias. In approximately 0.7% of these cases, the events occurred in the absence of identified risk factors; in the remaining cases, risk factor status was unknown. Because the cases were reported voluntarily from a population of unknown size, estimates of adverse event frequency cannot be made. (See **Boxed Warning, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS** and **Drug Interactions**.) PROPULSID®-induced serious ventricular arrhythmias and death may not correlate with the degree of drug-induced prolongation of the QT interval detected by 12-lead ECG.

In addition to the cardiovascular adverse events, the following events have been identified during post-approval use of PROPULSID® in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion in this insert due to a combination of their seriousness, frequency of reporting, or potential causal connection to PROPULSID®: allergic reactions, including bronchospasm, urticaria, and angioedema; possible exacerbation of asthma; psychiatric events, including confusion, depression, suicide attempt, and hallucinations; extrapyramidal effects including akathisia, Parkinson-like

symptoms, dyskinetic and dystonic reactions; gynecomastia, female breast enlargement, urinary incontinence, hyperprolactinemia and galactorrhea.

The following events were specifically reported in the pediatric population: antinuclear antibody (ANA) positive, anemia, hemolytic anemia, methemoglobinemia, hyperglycemia, hypoglycemia with acidosis, unexplained apneic episodes, confusion, impaired concentration, depression, apathy, visual changes accompanied by amnesia, and severe photosensitivity reaction.

There have been rare cases of sinus tachycardia reported. Rechallenge precipitated the tachycardia again in some of those patients.

OVERDOSAGE

With overdose, rare cases of QT prolongation and ventricular arrhythmia have been reported.

A one-month-old male infant received 2 mg/kg of cisapride four times per day for 5 days. The patient developed third degree heart block and subsequently died of right ventricular perforation caused by pacemaker wire insertion.

In instances of overdose, patients should be evaluated for possible QT prolongation and ventricular arrhythmias, including torsades de pointes. Treatment should include gastric lavage and/or activated charcoal, close observation and general supportive measures.

Reports of overdosage with PROPULSID® (cisapride) also include an adult who took 540 mg and for 2 hours experienced retching, borborygmi, flatulence, stool frequency and urinary frequency.

Single oral doses of cisapride at 4000 mg/kg, 160 mg/kg, 1280 mg/kg and 640 mg/kg were lethal in adult rats, neonatal rats, mice, and dogs, respectively. Symptoms of acute toxicity were ptosis, tremors, convulsions, dyspnea, loss of righting reflex, catalepsy, catatonia, hypotonia and diarrhea.

DOSAGE AND ADMINISTRATION

5 mL (1 teaspoon) suspension = 5 mg.

A 12-lead ECG should be performed prior to administration of PROPULSID® (cisapride). Treatment with PROPULSID® should not be initiated if the QTc value exceeds 450 milliseconds. Serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed prior to administration of PROPULSID® and whenever conditions develop that may affect electrolyte balance or renal function.

Adults: Initiate therapy with one 10 mg tablet of PROPULSID® or 10 mL of the suspension 4 times daily at least 15 minutes before meals and at bedtime. In some patients the dosage will need to be increased to 20 mg, given as above, to obtain a satisfactory result.

Caution must be exercised in elderly patients since there is a significant proportion who have conditions or use other drugs which contraindicate the use of PROPULSID®. A 12-lead ECG and serum electrolyte measurement should be performed prior to treatment with PROPULSID®. In elderly patients, steady-state plasma levels are generally higher due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults.

It is recommended that the daily dose be halved in patients with hepatic insufficiency.

The minimum effective dose of PROPULSID® should be used. Recommended doses should not be exceeded. PROPULSID® should be discontinued if relief of nocturnal heartburn does not occur.

HOW SUPPLIED

PROPULSID® (cisapride) Tablets are provided as scored white tablets debossed "Janssen" and P/10 containing the equivalent of 10 mg of cisapride in blister packages of 100 (NDC 50458-430-01) and in unit of use bottles of 120 (NDC 50458-430-12). PROPULSID® is also provided as blue tablets, debossed "Janssen" and P/20, containing the equivalent of 20 mg cisapride in blister packages of 100 (NDC 50458-440-01) and in unit of use bottles of 60 (NDC 50458-440-06).

PROPULSID® Suspension is provided as a bright pink homogeneous suspension containing the equivalent of 1 mg/mL of cisapride in 16 oz. unit of use bottles containing 450 mL (NDC 50458-450-45).

Unit of use bottles should be dispensed as an intact unit. The Medication Guide should be dispensed with the product.

Store at 15°-25°C (59°-77°F). Protect the tablets from moisture. The 20 mg tablets should also be protected from light.

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