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Pharmacokinetics, Drug Interactions, and Tolerability of Paroxetine and Paroxetine CR

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ABSTRACT ~ The development of paroxetine hydrochloride began in the late 1970s. An abundance of data have been accumulated from clinical investigations demonstrating the efficacy of paroxetine in the treatment of major depression and anxiety disorders. The published literature contains a substantial amount of supportive data documenting the safety, tolerability, and pharmacokinetic and pharmacodynamic properties of paroxetine. The role of paroxetine in clinically significant drug-drug interactions, especially involving metabolic inhibitory effects on the substrates of cytochrome P450 2D6, has long been suspected, but only isolated cases provide any evidence. Published data for widespread patient morbidity from drug interactions with paroxetine are almost nonexistent. Considerations of the pharmacokinetic properties of paroxetine support a rationale for the development of new dosage forms that maintain the efficacy yet improve the tolerability profile of the selective serotonin reuptake inhibitors. Paroxetine controlled-release is an enteric-coated formulation with release features that may enhance clinical outcome by modifying absorption-related pharmacokinetics, improving tolerability, and maintaining therapeutic benefits. *Psychopharmacology Bulletin*. 2003;37(Suppl 1): 29-41.

INTRODUCTION

Knowledge of the pharmacology of a drug is an evolving process that begins a decade or more before the compound is first administered to human subjects. After the drug discovery process identified FG 7051 (paroxetine) as a potent inhibitor of serotonin (5-HT) reuptake, preclinical studies began in the late 1970s and demonstrated its central and peripheral serotonergic properties in rats.¹ Paroxetine was first marketed in the United States in 1993 for the treatment of major depression. During the next decade, an intensive clinical trials program demonstrated that paroxetine is also effective across the entire spectrum of major anxiety

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disorders, including generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder, panic disorder, and obsessive-compulsive disorder.²⁻⁶

Because 5-HT is involved in so many different central and peripheral functions, paroxetine and the other selective 5-HT reuptake inhibitors (SSRIs) in its class have been studied in a wide range of psychiatric disorders as well as medical illnesses. Drugs such as the SSRIs, with the potential for broad therapeutic applications, are extensively studied over a time period that often far exceeds their original patent life. Other examples of psychopharmacologic agents with multiple therapeutic uses include lithium, clozapine, and valproic acid. Because of its potential for multiple therapeutic uses, research interest in paroxetine remains high, and additional data will likely reveal new uses and suggest ways to improve current therapeutic applications.

Knowledge of the fundamental pharmacology of paroxetine continues to evolve. Ten years after it was originally brought to market, Gilmore and colleagues⁷ challenged the dogma that the therapeutic effects of paroxetine are solely a result of its 5-HT transporter inhibitor properties by showing that paroxetine had measurable effects on inhibition of norepinephrine uptake in patients with major depression. The clinical significance of this finding is currently unknown, but may ultimately translate into improved strategies for selecting antidepressants for specific patients. A small expansion of the pharmacologic profile of a drug may lead to meaningful changes in its clinical application. This concept also applies to pharmacokinetic profiles in which data regarding elimination half-life, activity of metabolites, potential drug interactions, and other aspects of disposition can greatly influence recommendations for clinical use.

The pharmacokinetic properties of the SSRIs, including their potential for involvement in drug-drug interactions, have been summarized in many reviews.⁸⁻¹¹ This article re-examines some fundamental aspects of the disposition of paroxetine and focuses on some currently relevant issues. The pharmacokinetic properties of paroxetine are important in the rationale for development of an extended, or controlled-release (CR) formulation. Published clinical trial data suggest an improved tolerability profile of paroxetine when used as the CR formulation.^{12,13} This improvement appears at least partially attributable to modification of the absorption profile of paroxetine.

PHARMACOKINETIC PROPERTIES OF PAROXETINE

Absorption

The pharmacokinetic properties of paroxetine are summarized in Table 1. Although paroxetine is rapidly and nearly completely absorbed

when taken orally as documented in a study using a C-labeled dose,¹⁴ it likely undergoes a substantial first-pass metabolism.¹⁵ Less than 2% of a dose is recovered as intact parent drug in feces.

Distribution and Plasma Protein Binding

The degree of plasma protein binding of paroxetine was reported as 93% to 95% at typical steady-state plasma concentrations of 100 to 400 ng/mL.¹⁵ Extensive protein binding by antidepressants has been promoted as clinically important in mediating drug-drug interactions; however, protein binding displacement interactions appear to have been overemphasized.²²⁻²⁴ An examination of the theoretical consequences of drug-protein-binding interactions concluded that the extensive binding of drugs like paroxetine that are highly extracted and metabolized during their first pass through the liver is of limited clinical significance.²⁵ Estimates of the volume of distribution of paroxetine have ranged between 3 L/kg and 28 L/kg in intravenous bolus and infusion studies,¹⁵ values that are consistent with a highly lipid-soluble drug that is widely distributed in the body. Of current interest, a recent report documented the presence of paroxetine in breast milk, but none of the 16 mother-infant-paired serum samples were found to contain paroxetine in the serum of the nursing infants.²⁶

Metabolism and Elimination

The importance of stereochemistry in the metabolism of antidepressants has been highlighted with the introduction of escitalopram, the

TABLE 1

SUMMARY OF THE MEAN (RANGE) PHARMACOKINETIC PARAMETERS FOR PAROXETINE^{8,14-21}

PARAMETER	VALUE
Bioavailability, %	>64
T _{max} , h (range)	5 (1-11)
C _{max} , ng/mL	2-20 ng/mL (single doses)
Plasma protein binding, %	93
Vd, L/kg (range)	17 (3-28)
Oral clearance/F, L/h (range)	36-167
Half-life, h (range)	18 (7-65)
Average steady-state plasma concentration, ng/mL	10-600
Urinary excretion of intact parent drug	<2%

C_{max}=maximum plasma concentration; T_{max}=time to maximum plasma concentration;
Vd = volume of distribution.

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(S)-isomer of the racemic mixture of (S)- and (R)-citalopram.²⁷ Paroxetine possesses 2 asymmetric carbon atoms in its structure and is designated as (-)-*trans*-4-(*p*-fluorophenyl)-3-[[3,4(methylenedioxy)-phenoxy]methyl]piperidine. The drug is marketed as the *trans* isomer, the more potent 5-HT uptake inhibitor.²⁸ Thus, considerations of stereospecific differences in drug disposition and pharmacologic potency are not applicable to paroxetine.

Paroxetine is highly metabolized by the liver, resulting in negligible urinary excretion of intact parent drug (<1%) following single-dose studies.¹⁵ Recovered metabolites do not possess appreciable 5-HT or norepinephrine reuptake inhibition.²⁹ One metabolite was noted to inhibit sparteine metabolism in human liver microsomes ($K_i=0.5 \mu\text{M}$) at a potency similar to that seen with paroxetine ($K_i=0.15 \mu\text{M}$).³⁰ However, no reports have been published of measurable amounts of this metabolite in human plasma.

Paroxetine undergoes nonlinear metabolism. When doses are increased from 10 to 70 mg/day, the increases in the maximum plasma concentration (C_{max}) and area under the concentration versus time curve (AUC) are greater than predicted from a proportional increase in dose.³¹ Steady-state occurs within 8 days. The mean terminal half-life of paroxetine is 18 hours (range, 7 to 65 h; Table 1), which supports once-daily dosing.

The metabolism of paroxetine is mediated by at least 2 major enzymes. The first is likely the high-affinity saturable enzyme, cytochrome P450 (CYP) 2D6, and the second pathway is a low-affinity, high-capacity enzyme.³¹ Studies of poor and extensive metabolizers have shown a longer elimination half-life and a higher steady-state plasma concentration of paroxetine in subjects whose genotype lacks CYP2D6 activity.³¹ Metabolism of paroxetine by 2 metabolic pathways provides a buffer against dramatic increases in plasma drug concentrations from the nonlinear component of elimination.³² The nonlinearity of paroxetine does not appear to be clinically important, especially because studies of steady-state plasma concentration and clinical effects have not suggested a benefit from therapeutic drug monitoring.¹⁶⁻¹⁷ As with most SSRIs, no association has been found between steady-state plasma concentrations of paroxetine and the degree of improvement in depressive symptoms. Clinical studies are consistent in these findings.¹⁶⁻¹⁹

Special Populations

Elderly patients achieve higher plasma paroxetine concentrations than younger patients given similar doses,¹⁵ which underlies recommendations for lower initial doses of paroxetine in geriatric patients. The AUC of paroxetine may increase in subjects with renal impairment as renal function declines.²⁰ In addition, the mean elimination half-life of

paroxetine is slightly longer in patients with cirrhosis of the liver compared with healthy subjects.²¹ Because plasma drug concentrations may be increased in patients with severe renal or hepatic impairment, the initial recommended dosage of paroxetine should be reduced and upward dosage titrations spaced at longer intervals.

DRUG-DRUG INTERACTIONS

The potential for paroxetine to be involved in drug-drug interactions has been assessed by an extensive battery of *in vitro* studies and clinical pharmacokinetic trials. Premarketing studies documented few effects of paroxetine on a standard battery of drugs with low therapeutic indices or drugs used as prototypes for extensive hepatic metabolism or renal elimination. Paroxetine does not appear to interact with haloperidol, lithium, digoxin, propranolol, or terfenadine, or potentiate the depressant effects of alcohol, benzodiazepines, or antihistamines.^{15,33-37} Combining paroxetine with tryptophan or monoamine oxidase inhibitors could result in a serotonin syndrome.^{38,39} Rare reports of adverse events of combining an SSRI with sumatriptan merit a precaution if this drug is used in conjunction with paroxetine.⁴⁰ A pharmacodynamic interaction may occur with paroxetine and warfarin. Mild, but clinically significant, bleeding has occurred in subjects who did not demonstrate concurrent changes in prothrombin times.³⁶

Interactions between paroxetine and hepatic enzyme inducers and inhibitors have been studied. The plasma concentrations of paroxetine are decreased with concomitant administration of phenytoin or phenobarbital and increased with concomitant administration of cimetidine.³⁴ Dosage adjustment of paroxetine may be necessary in these situations, but treatment should be guided by individual patient response.

The greatest concern about drug interactions involving paroxetine has been the recognition of its ability to inhibit CYP2D6. The initial observation by Crewe and colleagues³⁰ that various SSRIs could inhibit CYP2D6 in human liver microsomes led to a series of studies, most of which were conducted in healthy volunteers, demonstrating that fluoxetine and paroxetine could elevate the plasma concentration of CYP2D6 substrates, such as imipramine and desipramine.⁴¹⁻⁴⁹ This effect suggests the need for caution when paroxetine is coadministered with CYP2D6 substrates such as the type 1C antiarrhythmics (propafenone, flecainide, encainide), some β -blockers (alprenolol, timolol), tricyclic antidepressants, codeine, oxycodone, and some antipsychotics (thioridazine, perphenazine, fluphenazine).

Despite the demonstration of drug-drug interactions between paroxetine and CYP2D6 substrates in *in vitro* studies and in healthy volunteers, there is a marked paucity of reports of clinically significant interactions.

In fact, more data for healthy volunteers than patients have appeared in the literature. We conducted a postmarketing surveillance program during a 4-year period to prospectively detect pharmacokinetic interactions involving the SSRIs in 170 patients.⁵⁰ Plasma drug concentrations in the presence and absence of treatment with an SSRI served as the primary assessment variable. In combination with drugs known to have a CYP2D6 component to their metabolism (risperidone, propranolol, nortriptyline, imipramine, trazodone, metoprolol), evidence for a metabolic interaction caused by paroxetine was found only for trazodone and imipramine, and in these patients, without consequences on tolerability.

Some potential reasons for a lack of predictability between the results of volunteer pharmacokinetic studies and documentation of morbidity from paroxetine interactions could include the use of dosage titration from low initial starting doses, the presence of multiple pathways of elimination, or patient noncompliance. Certainly, continuing medical education in psychiatry has contributed to an increased awareness by prescribers of the potential for drug-drug interactions. The outcome may be an appropriate avoidance of potentially interacting drug combinations. Also, it should be remembered that pharmacokinetic interactions are not necessarily predictive of pharmacodynamic consequences. In summary, rare, but fatal drug interactions can and do occur in medicine and psychiatry.⁵¹⁻⁵³ In the case of paroxetine, the combined weight of published data and clinical experience offers compelling evidence that pharmacokinetic interactions do occur on occasion, but clinically important drug-drug interactions are rare.

SAFETY AND TOLERABILITY

The safety and tolerability of paroxetine have been demonstrated repeatedly in clinical trials. Comparisons of the tolerability of paroxetine with the other SSRIs have not revealed any dramatic and consistent differences. Occasional reports of differences in sexual dysfunction or weight gain all document a large patient variability in the expression of adverse events. There is a clear-cut class effect for adverse events associated with the SSRIs, which consists of headache, nausea and other gastrointestinal disturbances, sleep disturbances, and sexual dysfunction.⁵⁴ Gastrointestinal side effects, mostly nausea, are common, although tolerance quickly develops to this effect during the first several weeks of treatment in most patients. Nausea and other gastrointestinal disturbances have been implicated as the adverse events that most often cause early nonadherence with antidepressant therapy.⁵⁵

The cardiovascular safety of drugs continues to be a relevant issue in psychiatry. This was highlighted with the recent addition to the labeling of a black-box warning about QTc prolongation with thioridazine, a drug

that has been in common use for nearly 40 years.⁵⁶ The cardiovascular effects of paroxetine have been evaluated in patients with ischemic heart disease. Roose and colleagues⁵⁷ compared the efficacy, cardiovascular effects, and safety of a 6-week course of paroxetine or nortriptyline in 81 depressed outpatients. Both agents were equally effective antidepressants. Paroxetine had no sustained effects on heart rate, rhythm, or heart rate variability. In contrast, patients treated with nortriptyline had a sustained 11% increase in heart rate and a statistically significant ($P < .001$) reduction in heart rate variability. In another study, platelet activation factors were measured in patients with ischemic heart disease.⁵⁸ Beta-thromboglobulin and platelet factor 4 both significantly decreased from their elevated baseline values within 1 week of treatment with paroxetine and remained low at 3- and 6-week measurements. These results suggest that paroxetine may reduce platelet aggregation in vivo and provide potential benefits for patients with ischemic heart disease apart from their clinical antidepressant efficacy. Previous studies found no inotropic effect, positive or negative, in depressed patients receiving paroxetine, further indicating that paroxetine is an antidepressant free from significant cardiovascular side effects.⁵⁹

In summary, paroxetine hydrochloride during a 10-year period of widespread clinical use as an immediate-release (IR) dosage formulation has accumulated an impressive safety and tolerability record. The adverse events that commonly occur are characteristic of the SSRI class. Nevertheless, modifications to the rate of delivery of paroxetine to the gastrointestinal tract may further enhance its tolerability.

RATIONALE FOR DEVELOPMENT OF CONTROLLED-RELEASE DOSAGE FORMULATIONS

There are several reasons for controlling the rate and location of drug absorption after oral administration (Table 2). Some of the purposes are interrelated and have the desired outcome of improving tolerability and medication adherence, 2 of the major problems encountered during pharmacotherapy of psychiatric disorders.

The rate at which a drug enters the systemic circulation is slowed by extending the period during which an oral dosage form releases drug for dissolution into solution and subsequent gastrointestinal absorption. This delays the C_{\max} and diminishes its magnitude compared with an IR formulation (Figure 1). When the extent of drug absorption is similar between different dosage forms, no difference in systemic exposure, as measured by the AUC, should be apparent. One important benefit of an extended-release formulation is that the time during which plasma drug concentrations exceed some minimum threshold for producing an adverse event may be decreased, which may translate into marked improvement in tolerability.

PAROXETINE CR (CONTROLLED RELEASE)

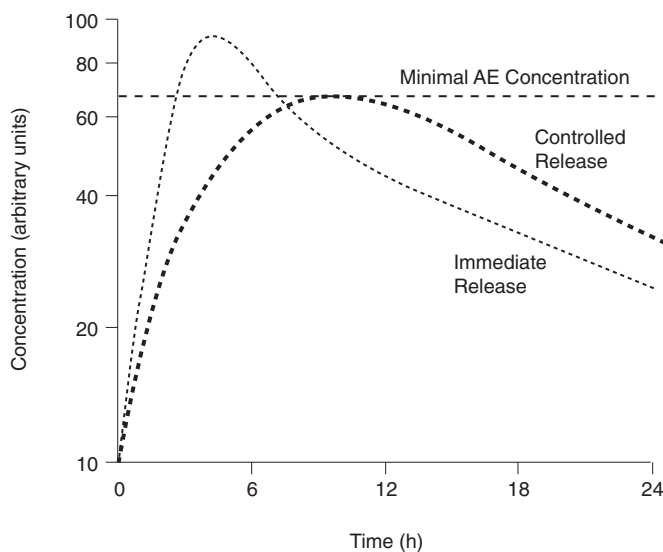
The favorable pharmacokinetic and pharmacologic profile of paroxetine underlies the rationale for formulating this compound into an extended-release dosage form. Nausea is the most frequently reported adverse event associated with SSRI treatment.⁵⁴ Its occurrence is thought to be partially

TABLE 2**RATIONALE FOR CONTROLLING THE RATE AND LOCATION OF ORAL DRUG ABSORPTION**

- Improve medication adherence by decreasing the number of total daily doses
- Blunt peak serum concentrations and maintain minimally effective concentrations over a longer period of time
- Reduce adverse events from local or systemic drug effects
- Minimize variability and influence of presystemic administration (first-pass effects)
- Minimize effects of food, antacids, or other physical barriers to absorption
- Prolong systemic exposure or elimination half-life
- Minimize effects of drug-drug interactions
- Minimize abuse liability of a drug

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DeVane CL. *Psychopharmacology Bulletin*. Vol. 37. Suppl. 1. 2003.**FIGURE 1****IDEALIZED EFFECT OF DECREASING THE RATE BUT NOT COMPLETENESS OF ORAL ABSORPTION OF A DRUG BY USE OF A CONTROLLED-RELEASE FORMULATION**

Maximum plasma concentration (C_{\max}) is diminished and occurs later, but the area under the concentration vs time curve (AUC), as well as the rate of elimination, are similar between the 2 dosage forms.

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mediated by 5-HT₃ and other 5-HT receptor subtypes located in the upper gastrointestinal tract, in addition to a centrally mediated effect.^{60,61} One possibility for minimizing SSRI-associated nausea would be to delay drug absorption by physical means, such as administration of paroxetine with food or antacid. Traditionally, drug administration with food has been advocated for medications such as lithium, aspirin, and potassium chloride to avoid local irritation and to improve tolerability. In healthy volunteers, the absorption of paroxetine was unaffected by the presence of food, fat content of the diet, or concomitant antacid administration.¹⁴ An alternative is to delay or prolong the release of drug from the oral dosage formulation (Figure 1). Recent advances in pharmaceutical technology have allowed a wide degree of flexibility in controlling drug release from oral dosage forms.

Paroxetine CR contains a degradable polymeric matrix that controls the rate of drug release in vivo in 2 stages.¹⁴ First, an enteric coating delays drug release until the dosage form has progressed beyond the acidic environment of the stomach. Second, a degradable polymeric matrix controls the dissolution rate of paroxetine during a period of approximately 4 to 5 hours, effectively slowing the rate of absorption. Ultimately, once absorption is complete, the elimination of drug proceeds based on its intrinsic clearance by the liver apart from any effect of the dosage form.³² The elimination half-life is minimally affected. The half-life from administration of paroxetine CR is 15 to 20 hours,¹⁴ similar to results obtained with paroxetine IR formulation (Table 1). Approximately 20% of the drug content of paroxetine CR tablets is not absorbed, and is eliminated unchanged. Therefore, in terms of systemic bioavailability, AUC at steady-state, and hence, doses, paroxetine CR 25 mg/day corresponds to paroxetine IR 20 mg/day, and paroxetine 12.5 mg/day corresponds to paroxetine IR 10 mg/day.

Compared with the conventional IR formulation, the rate of paroxetine absorption is approximately 25% lower after paroxetine CR administration. This results in a delayed time to maximum plasma concentration (T_{max}) (6-10 h for paroxetine CR versus 5 h for paroxetine IR) and, more significantly, a marked reduction in C_{max} . As shown in Figure 2, C_{max} at each paroxetine CR dose is markedly lower than C_{max} at the corresponding paroxetine IR dose. As a result, the degree of circadian fluctuation between peak and trough plasma concentrations at steady-state is 20% lower with paroxetine CR.^{14,62}

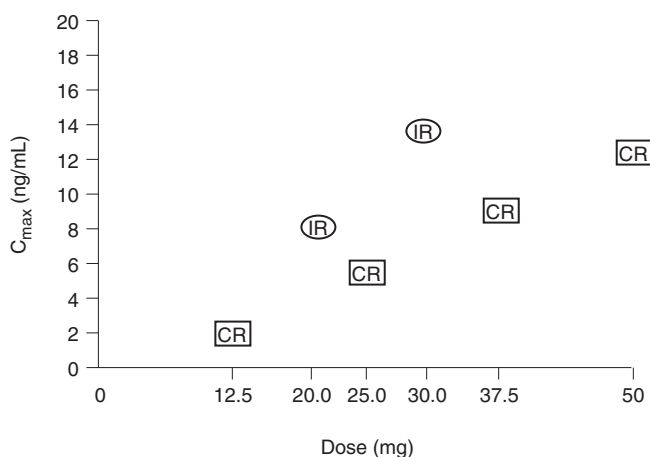
The hypothesis that the use of paroxetine CR could result in differences in tolerability was tested in 2 studies of patients with major depressive disorder^{12,13} and in an unpublished analysis of the paroxetine clinical trials database. In the combined analysis of the 2 studies, 622 adults were treated with paroxetine CR (25-62.5 mg/d), paroxetine IR (20-50 mg/d),

or placebo for a 6-week period. Rates of nausea were significantly lower for paroxetine CR (14%) than for paroxetine IR (23%; $P < .05$) during the first week of the trial. As expected, patients in both groups reported less nausea with each subsequent evaluation. By the conclusion of the trial, no difference existed between active treatments or placebo, and all were less than 5%. Although other adverse events (eg, somnolence, dizziness, diarrhea, sweating, tremor) were similar between active treatment groups, fewer patients receiving paroxetine CR dropped out of the study (10%) compared with patients receiving the IR formulation (16%), and the dropout rate from adverse events for paroxetine CR was similar to that for placebo (6%).¹²

The efficacy and tolerability of paroxetine CR have also been evaluated in a randomized, double-blind, 12-week study of 319 elderly outpatients with major depression.¹³ Patients were randomized to receive paroxetine CR (up to 50 mg/d), paroxetine IR (up to 40 mg/d), or placebo. Both active treatments were effective, with mean end point Hamilton Rating Scale for Depression (HAM-D) total scores of 10. Remission was defined as a HAM-D total score ≤ 7 , and 43% of patients in the paroxetine CR group ($P = .009$ vs placebo), 44% of patients in the paroxetine IR group ($P = .01$ vs placebo), and 26% of placebo patients achieved full remission at study end point. Paroxetine CR also was well tolerated; 12.5% of patients

FIGURE 2

RATES OF ABSORPTION FOR PAROXETINE IR AND PAROXETINE CR



The maximum mean concentration of paroxetine achieved in plasma following single oral doses of 20 mg and 30 mg of the paroxetine immediate-release (IR) formulation and between 12.5 mg and 50 mg of the paroxetine controlled-release (CR) formulation.^{14,62}

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in the paroxetine CR group withdrew from the study because of adverse events, and 16% and 8.3% of paroxetine IR or placebo patients, respectively, withdrew.

The rates of premature study withdrawal because of adverse events have been assessed in an analysis of the paroxetine CR clinical trials database. Data from more than 1400 patients with major depression were pooled and analyzed from 4 studies. Treatment with either paroxetine CR (N=617) or placebo (N=466) resulted in low rates of study withdrawal due to adverse events (7% and 6%, respectively).¹⁴ A similar pooling of all available depression trials data demonstrated withdrawal rates from adverse events of 20% for paroxetine IR and 9% for placebo.⁶³

CONCLUSION

Paroxetine has proven to be a broadly useful drug for the treatment of both major depression and anxiety disorders. During more than a decade of use as an IR formulation, paroxetine has accumulated a substantial record of safety and tolerability. The pharmacokinetic profile of paroxetine is well defined. The delivery system of paroxetine has been significantly refined with the development of the CR dosage form. Evidence from clinical trials indicates that the changes in absorption kinetics associated with paroxetine CR result in improved tolerability (ie, lower rates of nausea) in the early weeks of treatment, while clinical effectiveness is preserved. ❖

DISCLOSURE

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