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APPLICATION NUMBER:
21-299

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Paroxetine mesylate tablets
NDA 21-299

Synthon Pharmaceuticals
Chapel Hill, NC 27514

Reviewer: Iftekhar Mahmood, Ph. D.

Submission Date: September 19, 2001

Received by OCPB: September 26, 2001

Indication: Depression/panic disorder

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) in its review of May 3, 2001, had requested the Sponsor, Synthon Pharmaceuticals to adopt the following dissolution specifications for all strengths of paroxetine mesylate tablets:

~~_____~~
~~_____~~
Specification: Q = — in 30 minutes.

The Sponsor has accepted the dissolution specifications as requested by the OCPB as indicated in the Sponsor's response of September 19, 2001.

This is acceptable to OCPB..

Iftekhar Mahmood, Ph.D. _____

RD/FT initialed by Raman Baweja, Ph.D. _____

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-299, HFD-120, HFD-860 (Mahmood, Baweja, Mehta)

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BIOPHARMACEUTICS

Paroxetine mesylate tablets

Synthon Pharmaceuticals

NDA 21-299

Chapel Hill, NC 27514

Reviewer: Iftexhar Mahmood, Ph. D.

Submission Date: July 26, 2000, April 18, 2001

Received by OCPB: August 9, 2000

Indication: Depression/panic disorder

Introduction

This is 505(b)(2) submission. Currently paroxetine is manufactured by SmithKline Beecham (SKB) and is available in hydrochloride salt form at strengths of 10, 20, 30, and 40 mg immediate release tablets. The Sponsor, Synthon Pharmaceuticals, intends to manufacture paroxetine as mesylate salt and has submitted the following studies:

1. A comparative bioavailability study (10 and 40 mg tablet strengths Synthon vs SKB).
2. A comparative bioavailability study (20 mg tablet strength, European study, Synthon Czech vs SKB Germany).
3. A comparative bioavailability study (20 mg tablet strength, Australian study, Synthon Czech vs SKB Australia).
4. Single and multiple dose pharmacokinetic study (30 mg Synthon tablets).
5. In-vitro dissolution study.
6. Formulations used in the studies.
7. Analytical methods.

In addition, the Sponsor, requests in-vivo bioequivalence waiver for 10, 20 and 30 mg tablets.

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Pharmacokinetic Studies of Paroxetine mesylate:

Study #1. Comparative, randomized, 2-way crossover bioavailability study of Synthron BV 10 mg and 40 mg paroxetine mesylate tablets and SmithKline Beecham (Paxil) 10 mg and 40 mg paroxetine HCl tablets in healthy adult male and female volunteers under fasting conditions.

(Protocol # 982413) 8

Study #2. Comparative, randomized, two-period crossover bioequivalence study on paroxetine tablets 20 mg (Synthron CZ, Czech Republic) versus Aropax 20 mg tablets (SmithKline Beecham Australia Pty Ltd) in healthy volunteers (Protocol # 013/78/99). 14

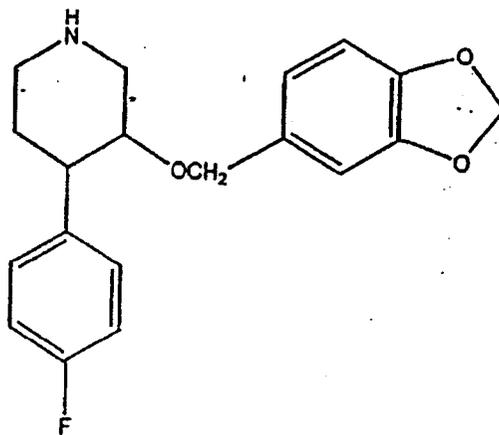
Study #3. Comparative, randomized, two-period crossover bioequivalence study on paroxetine tablets 20 mg (Synthron CZ, Czech Republic) versus Seroxat 20 mg tablets (SmithKline Beecham Pharma GmbH, Germany) in healthy volunteers (Protocol # 009/65/98). 16

Study #4. Comparative Single- and Multiple-dose Pharmacokinetic Profile of Synthron 30 mg Paroxetine Mesylate Tablets in Healthy Adult Male Subjects (protocol # CSP. POT. tab 30.001). 18

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Chemical Structure of Paroxetine Mesylate

Paroxetine; trans-(-)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine;
 $C_{19}H_{20}FNO_2$; 329.37 g/mol



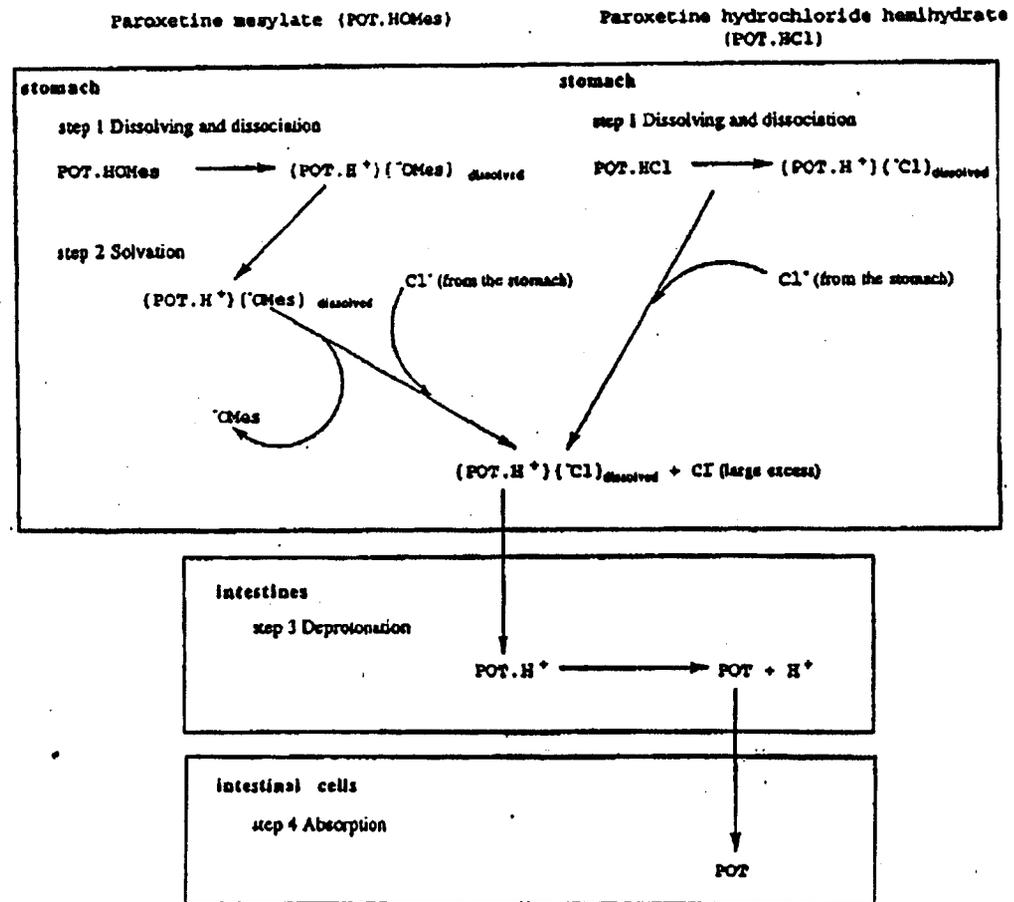
Molecular weight = 425.5 (329.4 as free base)

Solubility = 1 g/mL

Mechanism of paroxetine salt dissociation:

Synthon has developed a mesylate salt form of the paroxetine anti depressive active moiety. Paroxetine is currently marketed under the Paxil trademark by SmithKline Beecham Pharmaceuticals in the form of paroxetine hydrochloride. After disintegration of the paroxetine mesylate and paroxetine HCl in the stomach, both salt forms of the active moiety dissolve and are fully dissociated in the gastric fluid. Due to the stomach's low pH and the high pKa of 9.90 of the active moiety, both products then become protonated and are present in the form of paroxetine H^+ surrounded by an abundance of Cl^- ions. Any salt of paroxetine which is soluble in aqueous HCl solutions (i.e. gastric fluid) will follow the above route and from this point on behave in the same way. The contents of the stomach are transported to the intestines. Because of the relatively high pH in this environment, paroxetine. H^+ is deprotonated and the paroxetine free base is absorbed by the cells in the intestinal wall. Therefore, the pharmacokinetic behavior of the product is solely dependent on the kinetics of the paroxetine free base. In the case of paroxetine mesylate, there is a small amount of extra mesylate ions present in the gastric fluid which should not have any influence on the bioavailability of the paroxetine base. Figure 1 provides a schematic overview of the process.

Figure 1 A schematic overview of the transformation of paroxetine mesylate and paroxetine hydrochloride in the stomach and small intestines



6.1 Human Pharmacokinetics

Human Pharmacokinetics parameters and values for paroxetine are summarized in Table 9.

Table 9 Pharmacokinetic Summary Table (based on current Paxil® Package insert and 2000 USP DI)

Pharmacokinetic parameter	Value/Comment
Minimum effective concentration	There is no correlation with serum concentrations and clinically efficacy
Potentially Toxic Concentration	Adverse effects do not have a direct correlation with serum concentrations
Absorption - Bioavailability - Time to peak concentration	Close to 100 % Approximately 5 hours
Distribution - Volume of distribution - Protein binding	Extensive distribution to tissues with only 1 % in systemic circulation 3.1 - 28 L/kg. Note: Breast milk concentrations are similar to plasma concentrations. The large volume of distribution is secondary to the lipophilic nature of Paroxetine 95 %
Metabolism - Metabolites - Half-life - Total body clearance	Extensive first pass effect, 85 % is oxidized to a catechol intermediate that undergoes subsequent methylation and conjugation to inactive metabolites Inactive, glucuronide and sulfate metabolites Approximately 20-24 hours, range 3-65 hours, two compartment model saturable kinetics. Prolonged in patients with severe renal or hepatic dysfunction. The half-life may also be prolonged in the elderly Greater than 95 %
Time to steady state	7 to 14 days
Elimination - Renal - Fecal - Special Populations	64 % excreted in the urine with less than 2% as unchanged drug 36 % excreted in the feces, of which less than 1% is the parent compound The half life is prolonged in patients with severe or hepatic impairment. Serum concentrations may be significantly increased in the elderly.

Absorption

Paroxetine is well absorbed, with virtual (99 %) absorption. Absorption is not influenced by the presence of food, milk, or antacids. The time to peak concentration is approximately 5 hours. By substantial first pass metabolism the absolute bioavailability is reduced to approximately 50 %.

Distribution

Paroxetine is extensively distributed into the tissues with only 1 % remaining in the systemic circulation. The volume of distribution is large secondary to the lipophilic nature of Paroxetine. Values ranging from 3-28 L/kg have been reported. Paroxetine is distributed into breast milk in concentrations similar to plasma concentrations.

Protein Binding

Paroxetine exhibits very high protein binding approximating 95 %. In Vitro studies show that other highly bound drugs such as phenytoin and warfarin are unaltered by Paroxetine.

Metabolism

Paroxetine undergoes a significant first-pass effect in the liver with at least 85 % of the Paroxetine dose being oxidized to a catechol intermediate that undergoes subsequent methylation and conjugation to clinically inactive glucuronide and sulfate metabolites. This metabolism is accomplished in part by the cytochrome P₄₅₀IID₆ (CYP2D6) system. The saturation of this enzyme at low clinical doses appears to account for the non linear Paroxetine kinetics. This has little, if any, clinical impact since there is no correlation between higher plasma concentrations of Paroxetine and toxic effects.

Elimination Half-Life

The elimination half-life of Paroxetine is approximately 20 - 24 hours with a range of 3 - 65 hours in healthy adults. The elimination half-life may be increased in the elderly. However, there is wide intersubject variability. Half-life is prolonged in patients with severe hepatic or renal function impairment. The time to steady-state concentration is achieved in 7 - 14 days for most patients, although it may take considerably longer in some patient populations.

Excretion

Paroxetine is primarily eliminated renally with approximately 64 % excreted in the urine with less than 2 % as the parent compound. In addition, 36 % is excreted in the feces with only approximately less than 1 % of Paroxetine being excreted unchanged.

Study #1

Title: Comparative, randomized, 2-way crossover bioavailability study of Synthron 10 mg and 40 mg paroxetine mesylate tablets and SmithKline Beecham (Paxil) 10 mg and 40 mg paroxetine HCl tablets in healthy adult male and female volunteers under fasting conditions. (Protocol # 982413).
Site of study: Montreal, Canada.

Test product: 40 mg Paroxetine mesylate (Batch #98G15/3; Expiry Date: July 2000); 10 mg Paroxetine mesylate (Batch #98G14/2; Expiry Date: July 2000).

Reference product: 40 mg Paroxetine HCl (Batch #937 8B13; Expiry Date: Oct 2000); 10 mg Paroxetine HCl (Batch #24 8B10; Expiry Date: Aug 2000).

Study Design

Part A (40 mg):

This was an open label, randomized, single dose, 2-way crossover study. Forty six volunteers (23 males and 23 females, 18 to 45 years) took part in this study. The subjects received a single 40 mg paroxetine tablet orally with 240 mL water either as mesylate or hydrochloride. Subjects were fasted overnight for 10 hours. The crossover period was separated by 21 days.

Part B (2 x 10 mg):

This was an open label, randomized, single dose, 2-way crossover study. Forty six volunteers (23 males and 23 females, 18 to 45 years) took part in this study. The subjects received a single 2 x 10 mg paroxetine tablet orally with 240 mL water either as mesylate or hydrochloride. Subjects were fasted overnight for 10 hours. The crossover period was separated by 21 days.

Blood sampling and pharmacokinetic analysis:

Three mL blood samples were obtained at regular intervals until 120 hours postdose. Paroxetine concentrations in plasma were determined by LC/MS/MS with a lower limit of detection of 0.2 ng/mL. Pharmacokinetic parameters such as Areas under the concentration-time curve from time

zero to infinity AUC(0-Infinity), the maximum plasma concentration (C_{max}), the time to maximum drug concentration (T_{max}), and half-life ($T_{1/2}$) were estimated.

Results

Thirty-nine volunteers for part A and forty volunteers for part B completed the study. Table 1 is the summary of the mean pharmacokinetic parameters following oral administration of 40 and 20 mg paroxetine to healthy volunteers. Following 40 mg dose, the pharmacokinetic parameters (C_{max} , T_{max} , $T_{1/2}$ and AUC(0-inf)) were comparable between the test and the reference products. A fairly high intersubject variability in the pharmacokinetic parameters of paroxetine was observed, especially the coefficient of variation (CV) for AUC was more than 100%. Despite this high intersubject variability, the 90% confidence interval for log transformed AUC(0-inf) and C_{max} were within the limits of bioequivalence criteria.

Table 1

Mean Pharmacokinetic parameters of paroxetine following 40 and 20 mg dose administered to healthy volunteers

Parameters	Synthon (Test)	SmithKline (Reference)
40 mg:		
C_{max} (ng/mL)	24.4 ± 16.2	26.7 ± 19.9
T_{max} (hrs)	6.3 ± 1.4	6.2 ± 1.1
$T_{1/2}$ (hrs)	15.3 ± 8.6	15.1 ± 8.2
AUC(0-inf) (ng*hr/mL)	644.7 ± 650.9	659.4 ± 698.2
2 x 10 mg:		
C_{max} (ng/mL)	6.4 ± 5.4	5.9 ± 5.6
T_{max} (hrs)	6.2 ± 1.5	5.8 ± 1.7
$T_{1/2}$ (hrs)	13.4 ± 8.8	12.7 ± 9.8
AUC(0-inf) (ng*hr/mL)	158.3 ± 306.2	144.9 ± 288.2

Following 20 mg dose, the pharmacokinetic parameters were comparable between the test and the reference products but intersubject variability was very high. The coefficient of variation (CV) for C_{max} and

AUC was over 80% and 200%, respectively. The 90% confidence interval for log transformed AUC(0-inf) was outside the bioequivalence limits (112.9-138.5), but C_{max} was within these limits (99.1-123.2). The failure of AUC in meeting the bioequivalence criteria may be due to high intersubject variability.

TABLE 2

The confidence intervals for paroxetine following 40 and 20 mg dose administered to healthy volunteers

Analyte	C_{max} (90% CI)	AUC (90% CI)
40 mg Paroxetine	88.0 - 101.9	92.6 - 107.5
2x10 mg Paroxetine	99.1 - 123.2	112.9 - 138.5

Discussion

The 40-mg paroxetine mesylate tablets are bioequivalent to the 40-mg paroxetine HCl tablets but the 2x10-mg paroxetine mesylate tablets fail to meet the bioequivalence criteria. It should be however, noted that the C_{max} and AUC of 2x10 mg paroxetine mesylate tablets are similar to the C_{max} and AUC of 2x10 mg paroxetine HCl tablets. Despite the fact that paroxetine is a highly variable drug, percent CVs (intersubject variability) on C_{max} and AUC for both test and reference formulations (10 and 40 mg) are comparable.

40 mg:

C_{max} = 66% (test); 74% (ref)

AUC = 100% (test); 106%(ref)

2x10 mg:

C_{max} = 84% (test); 95% (ref)

AUC = 193% (test); 199%(ref).

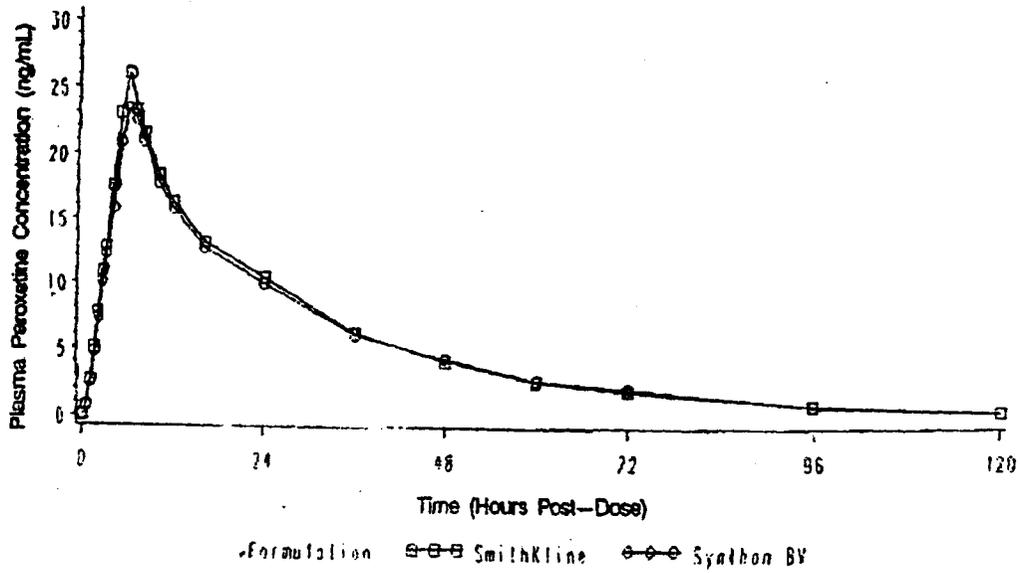
The presence of outliers in 2x10 mg tablets study was also investigated. A subject was declared outlier if the difference in AUC between the test and reference product was three times or more (arbitrary selected). There were two subjects (subjects #67 and 84) who met the criteria. The omission of these two subjects from the statistical

analysis, though, resulted in decrease in the confidence interval width (108-130 vs 113-139 all subjects included), the 2x10 mg paroxetine tablets manufactured by Synthon failed to meet the bioequivalence criteria.

Based on the power and sample size calculation, it was found that in the 2x10 mg group, 50 (80% power) and 62 (90% power) subjects will be required to successfully demonstrate the bioequivalence. With 37 subjects in the study, the power was only 63%. It should also be noted that the power for 40 mg tablet was 92% (n = 38).

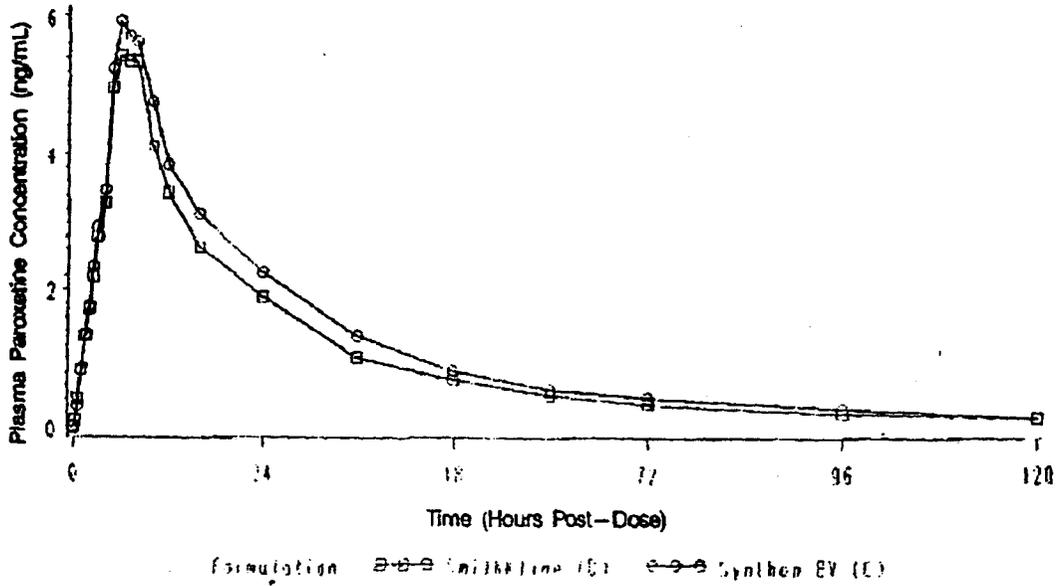
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Figure 2 Mean plasma concentration time profiles for paroxetine (test and reference) following the single dose administration of 40 mg



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Figure 3 Mean plasma concentration time profiles for paroxetine (test and reference) following the single dose administration of 2 x 10 mg



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Study #2

Title: Comparative, randomized, two-period crossover bioequivalence study on paroxetine tablets 20 mg (Synthon CZ, Czech Republic) versus Aropax 20 mg tablets (SmithKline Beecham Australia Pty Ltd) in healthy volunteers (Protocol # 013/78/99). Site of study: Prague, Czech Republic.

Test product: 20 mg Paroxetine mesylate (Batch #POT 98G14/1).

Reference product: 20 mg Paroxetine HCl (Batch #53767).

This was an open label, randomized, single dose, 2-way crossover study. Forty eight volunteers (24 males and 24 females, 18 to 45 years) took part in this study. The subjects received a single 20 mg paroxetine tablet orally with 200 mL water either as mesylate or hydrochloride. Subjects were fasted overnight for 10 hours. The crossover period was separated by 21 days. Ten mL blood samples were obtained at regular intervals until 120 hours postdose. Paroxetine concentrations in plasma were determined by LC/MS/MS with a lower limit of detection of 0.1 ng/mL. The results of the study indicated that the two products are bioequivalent. Table 3 summarizes the pharmacokinetic parameters of paroxetine mesylate and paroxetine HCl following a single 20 mg dose.

Table 3

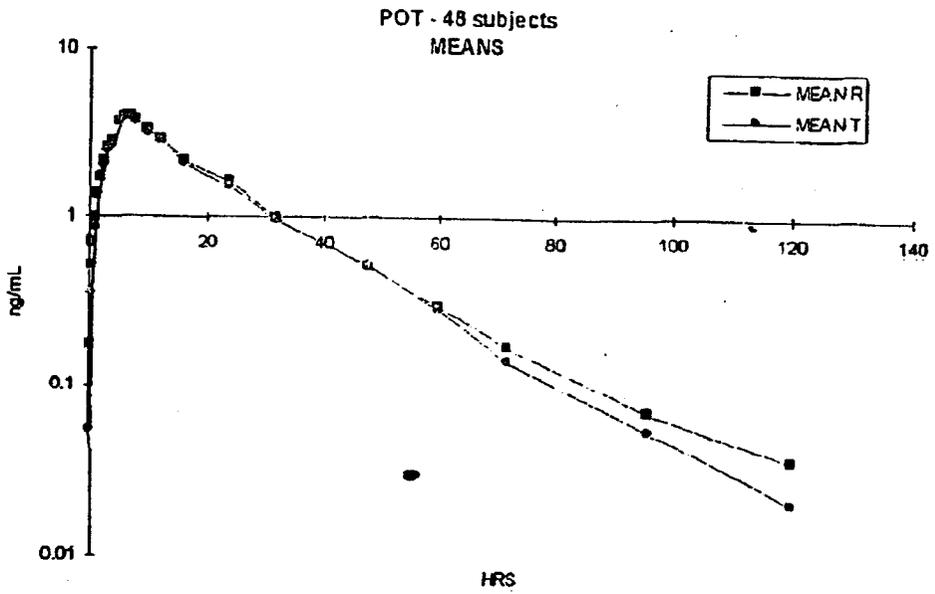
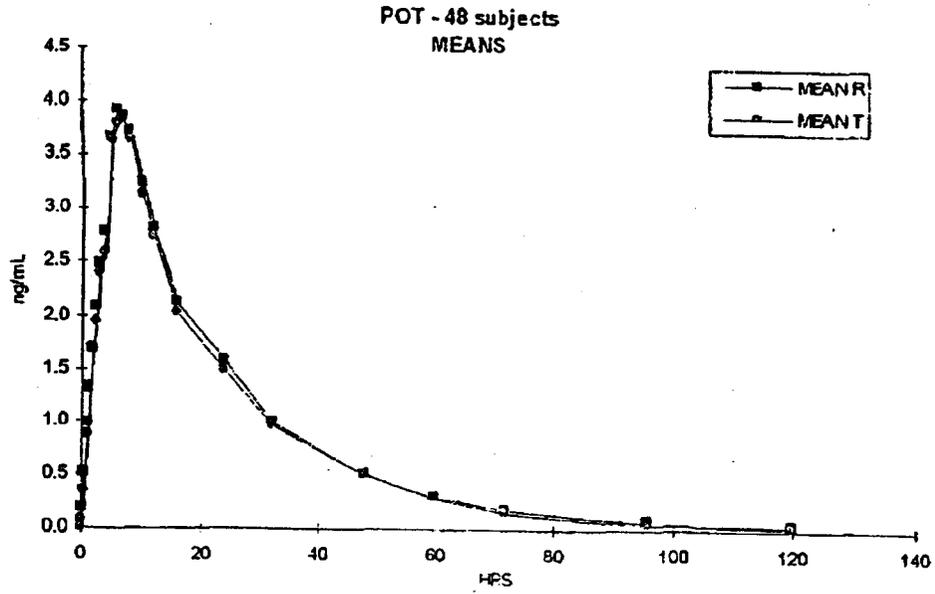
Mean Pharmacokinetic parameters of paroxetine following 20 mg dose administered to healthy volunteers

Parameters	Synthon (Test)	SmithKline (Reference)	90% CI
C _{max} (ng/mL)	4.1 ± 3.3	4.2 ± 3.5	93.3 - 107.3
T _{max} (hrs)	5.9 ± 1.5	5.7 ± 1.9	NA
T _{1/2} (hrs)	13.8 ± 6.2	13.6 ± 4.8	NA
AUC(0-inf) (ng*hr/mL)	90.6 ± 124.6	95.3 ± 131.4	93.6 - 110.2

NA = Not applicable

Ezekiel vs Austal

Summary of the Results on Paroxetine



Study #3

Title: Comparative, randomized, two-period crossover bioequivalence study on paroxetine tablets 20 mg (Synthon CZ, Czech Republic) versus Seroxat 20 mg tablets (SmithKline Beecham Pharma GmbH, Germany) in healthy volunteers (Protocol # 009/65/98). Site of study: Prague, Czech Republic

Test product: 20 mg Paroxetine mesylate (Batch #POT 98E25).

Reference product: 20 mg Paroxetine HCl (Batch #828).

This was an open label, randomized, single dose, 2-way crossover study. Forty eight volunteers (25 males and 23 females, 18 to 41 years) took part in this study. The subjects received a single 20 mg paroxetine tablet orally with 200 mL water either as mesylate or hydrochloride. Subjects were fasted overnight for 10 hours. The crossover period was separated by 21 days. Ten mL blood samples were obtained at regular intervals until 120 hours postdose. Paroxetine concentrations in plasma were determined by LC/MS/MS with a lower limit of detection of 0.2 ng/mL. The results of the study indicated that the two products are bioequivalent. Table 4 summarizes the pharmacokinetic parameters of paroxetine mesylate and paroxetine HCl following a single 20 mg dose.

Table 4

Mean Pharmacokinetic parameters of paroxetine following 20 mg dose administered to healthy volunteers

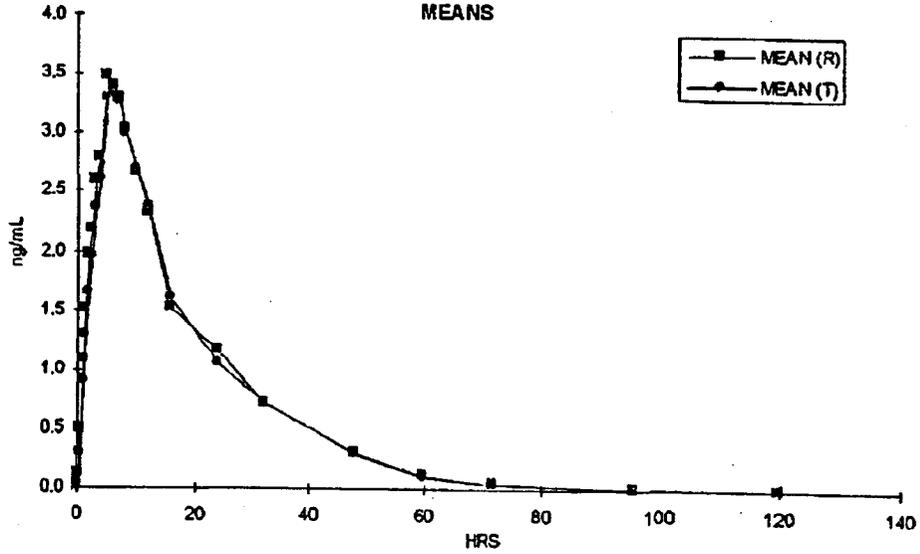
Parameters	Synthon (Test)	SmithKline (Reference)	90% CI
C _{max} (ng/mL)	3.7 ± 2.7	3.9 ± 3.0	87.4 - 103.0
T _{max} (hrs)	5.4 ± 1.8	5.2 ± 2.1	NA
T _{1/2} (hrs)	13.7 ± 5.3	13.3 ± 4.2	NA
AUC(0-inf) (ng*hr/mL)	71.6 ± 59.7	72.5 ± 62.7	91.6 - 106.1

NA = Not applicable

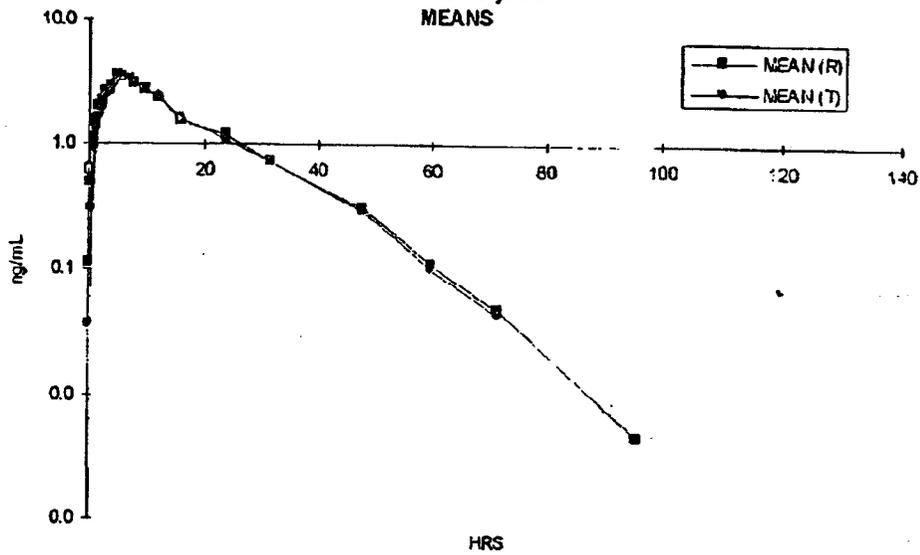
Czech vs German

Summary of the Results on Paroxetine

POT - 48 subjects
MEANS



POT - 48 subjects
MEANS



Study #4

Title: Comparative Single- and Multiple-dose Pharmacokinetic Profile of Synthron 30 mg Paroxetine Mesylate Tablets in Healthy Adult Male Subjects (protocol # CSP. POT. tab 30.001). Site of study: Prague. Czech Republic.

Study Design

This was an open-label, non-randomized, single and multiple dose study. The study was conducted in 25 healthy, non-smoking, adult male subjects (18 to 45 years of age). All the subjects received a single oral dose (1 x 30 mg, Batch #98G14/1) and then a 30 mg dose given once daily for 24 days. The subjects were fasted for 10 hours prior to the administration of the first dose. On Day 1 (dose #1), all subjects received an oral, single 30 mg dose starting at 8:00 AM. Blood samples were collected frequently till 96 hours. On Days 6-28, the subjects received an oral 30 mg dose of Paroxetine mesylate (dose #2 - 24) on 23 consecutive mornings (starting at 8:00 AM). Blood samples were collected before the administration of each dose to determine the time of steady state. On Day 29, after a 10 hour fast, all subjects received an oral single 30 mg dose (dose # 25) and blood samples were collected till 96 hours. Paroxetine plasma concentrations were analyzed using a LC/MS/MS method. The limit of quantification (LOQ) for the method was —

Results

Twenty two subjects completed the study. Table 5 summarizes the pharmacokinetic parameters of paroxetine mesylate following single and multiple administration of 30 mg oral dose. In this Table, pharmacokinetic data of paroxetine mesylate have also been compared with the pharmacokinetic data of paroxetine HCl (paxil, historical data). Please note that paroxetine HCl was given for 30 days as compared to 24 days for paroxetine mesylate

TABLE 5

Mean Pharmacokinetic parameters of paroxetine mesylate or paroxetine HCl following 30 mg single and multiple doses to healthy volunteers

Parameter	Single dose		Multiple dose	
	Par. mesylate	Par. HCl	Par. mesylate	Par. HCl
C _{max} (ng/mL)	13.0 ± 8.3	13.7 ± 11.9	81.3 ± 33.7	61.7 ± 27.8
AUC(0-24)	176 ± 130	175 ± 161	1509 ± 660	1021 ± 510
C _{min} (ng/mL)	NA	NA	43.2 ± 22.6	30.7 ± 20.6
T _{max} (hrs)	5.6 ± 1.2	4.8 ± 1.2	8.1 ± 4.5	5.2 ± 0.5
T _{1/2} (hrs)	23.5 ± 12.4	9.8 ± 2.5	33.2 ± 17.3	21.0 ± 6.7
AR	NA	NA	14.96 ± 13.0	11.8

Unit of AUC is ng*hr/mL. NA = Not applicable.

AR (Accumulation Ratio) = AUC_{ss}(0-24)/AUC(0-24) single dose.

The pharmacokinetic parameters (C_{max}, T_{max} and AUC(0-24)) of paroxetine mesylate were comparable to historical single dose estimates for paroxetine HCl. The mean elimination half-life, was 23.5 hrs for paroxetine mesylate and was at least 2 fold higher than paroxetine HCl (9.84 hrs). Following multiple administration of paroxetine mesylate, the C_{max}, C_{min}, AUC(0-24) and T_{1/2} were 1.3, 1.4, 1.5 and 1.6 times higher than paroxetine HCl, respectively.

C_{min} levels were obtained starting from Study Days 6 to 28 (corresponding to Doses #2 to 24) to assess the attainment of steady state. The last dose was administered on Day 29 (corresponding Dose #25). Visual inspection of the trough concentrations indicated that steady state was achieved between dose #13 and dose #20 and maintained up to dose #24 just prior to the last dose (dose #25). Predose concentrations for dose #25 decreased unexpectedly and the cause of this decrease was investigated. It was noted that the predose samples for dose #25 were collected using a heparin lock rather than venipuncture (EDTA). It was found that the decreased plasma concentrations were attributed to heparin displacement of paroxetine from plasma to red blood cells. The details of this investigation conducted by the Sponsor follows after the conclusions.

In terms of accumulation, the ratio of the areas under the plasma concentration-time curve over 24 hr dosing interval on study days 1 and 29 for paroxetine mesylate was approximately 14.96. The accumulation ratio was widely variable among subjects (range: 3-58). Exclusion of the highest accumulation ratio (58) from the calculation, the accumulation ratio in remaining subjects is reduced to 12.9. The accumulation ratio reported for Paxil was 11.8. Literature reports have indicated that the accumulation of paroxetine following multiple dosing is probably due to the saturation of CYP2D6 enzymes.

Conclusions

The pharmacokinetic parameters of paroxetine mesylate were comparable with paroxetine HCl following a single dose, whereas following multiple dosing these parameters were higher at least by 1.3 times. It appeared that steady-state plasma levels were achieved by dose #13 - #20 and were maintained until dose #24, just prior to the last dose. In vitro experiments demonstrated that the observed decrease in plasma paroxetine concentrations on Day 29 was caused by a displacement of the drug from plasma into red blood cells. The accumulation ratio for paroxetine mesylate was approximately 15 (paxil 11.8), indicating significant accumulation following multiple dosing probably due to the saturation of metabolic processes.

Additional in vitro experiments to determine the unexpected drop of predose trough concentration on day 29 (dose #25):

Based on the observed predose trough concentrations obtained via venipuncture during Day 6-28 (Doses 2-24), the accumulation of plasma exhibited an increase in trough level and attainment of steady-state. However, the predose trough level on Day 29 (Dose #25) exhibited an unexpected drop in concentrations for almost all of the subjects. The drop of concentration was approximately 66% and was consistent with all subjects. An extensive investigation was performed to evaluate this phenomena. The following reasons were speculated and examined:

1. Missing dose on Day 28 and/or Day 29: This reason is extremely unlikely since missing such a great extent (i.e., missing a dose in every subject) is highly improbable. In addition, the dose given on Day 29 was the last dose. The 24-hr postdose levels for the last dose (Dose #25) for almost all subjects returned to the predose trough concentration of Day 28 (one dose prior to the last dose) indicating that missing the dose on Day 28 and/or Day 29 is highly unlikely. In addition, the drug accountability records indicated that all subjects had received their doses.

2. Effect of using heparin lock instead of venipuncture: Due to the extensive blood sampling on day 29 (Dose #25), a heparin lock was used instead of venipuncture as done during Days 6- 28. The predose trough level on Day 29 (Dose #25) was the first sample obtained using a heparin lock during the multiple dosing. It should be noted that a heparin lock was also used for the first dose (single dose). The heparin lock was removed after the 16 hour postdose sample for almost all subjects. If the heparin lock system had some effect on the plasma concentration determination, it may explain why the 24-hr postdose levels (via venipuncture) for almost all subjects returned to the predose trough concentration of Day 28 (one dose prior to the last dose).

Possible explanations for the drop of plasma concentration via heparin lock:

If the heparin lock exerted some effects on the plasma paroxetine concentration determination then the following explanations are possible:

1. Dilution effect of heparin solution in the heparin lock system (cannula):

This is highly unlikely since the void volume of the heparin lock system is merely 0.3 mL. The dilution of 0.3 mL of heparin solution in 7 mL of blood from the draw cannot explain almost 66% predose trough plasma paroxetine concentration on Day 29.

2. Binding of paroxetine to the components (including syringe and cannula) used in the heparin lock system:

In order to investigate this phenomena, an in vitro experiment was carried out.

Two stock paroxetine solutions 15 and 150 ng/mL) with and without heparin were used in the study. The results indicated that drug absorption to the heparin lock system (cannula and syringe) is not significant and can

not explain the drop of the predose trough plasma paroxetine concentrations on Day 29.

3. Heparin in the cannula displaced the drug from plasma to red blood cell (RBC) or somehow heparin in the cannula interacted with the EDTA in the vacutainer tube and drug from plasma to RBC before plasma was harvested by centrifugation:

In order to investigate this phenomena, an in vitro experiment was carried out. Six mL of freshly obtained blood was added to open tubes containing EDTA, 0.1 mL of paroxetine solution, and 0.85 mL of either water, 10U heparin/mL, or 100U heparin/mL. The final paroxetine concentration was approximately 75 and 150 ng/mL (corresponding to the steady state plasma concentration observed in the PK study). The blood sample was gently mixed and allowed to sit for 10 minutes before centrifugation to harvest the plasma. Six replicates were performed for each drug concentration and three heparin concentrations (total $N = 6 \times 3 \times 2 = 36$). The plasma drug concentrations were determined using the same LC/MS/MS procedures as described in the PK study. The ratios between paroxetine and the deuteriated paroxetine (D-paroxetine) were used to determine the effect of drug displacement in plasma to blood. The results indicated that heparin drastically decreased the plasma concentration (ratio of paroxetine and D-paroxetine) of paroxetine as compared to the situation when heparin was not used in the study (zero heparin). Compared to the blood without heparin added, the ratios of paroxetine and D-paroxetine dropped to 68.82 % and 66.84%, respectively, for the blood samples containing 150 ng paroxetine/mL and spiked with 0.85 mL of 10U heparin/mL and 100U heparin/mL. For the corresponding 75 ng paroxetine/mL blood samples, the paroxetine and D-paroxetine ratios dropped to 47.03% and 49.04%, respectively.

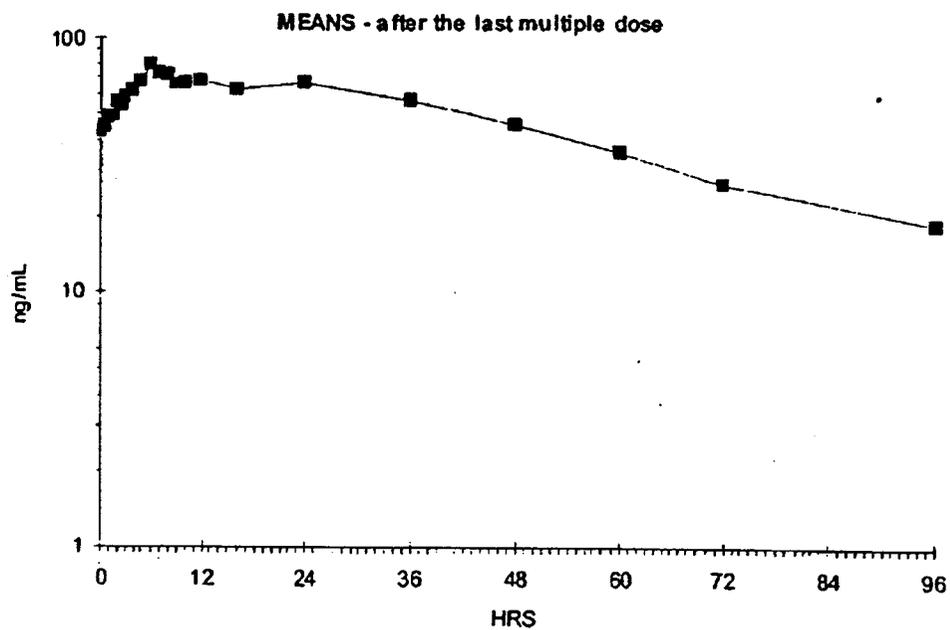
The above experiments hypothesized that the drug that normally binds to plasma was displaced by heparin and subsequently increased penetration of the drug into the RBC. Therefore, drug plasma concentration dropped as compared to the drug plasma concentration without heparin. However, because of the experiment using a total of 0.95 mL of solution (0.1 mL of drug stock solution and 0.85 mL of water or heparin solution), the effect of 0.95 mL of solution on drug distribution can not be excluded. It should be noted that the harvested plasma samples were clear and no

hemolysis was observed. To reconfirm the above experiment and exclude the effect of 0.95 mL of water, the experiment was repeated. The experimental details are essentially the same as Experiment 2 with the exception that a lesser volume and more concentrated heparin solutions were used (0.1 mL of 100U and 1000U heparin/mL instead of 0.85 mL of 10U and 100U heparin/mL solutions). Therefore, a total of only 0.2 mL solution was used instead of 0.95 mL used in Experiment 2. In addition, one more concentration of paroxetine (30 ng/mL, in addition to 75 and 150 ng/mL) was used in Experiment 3. In this experiment, the ratios of paroxetine and D-paroxetine again reduced to approximately 80% (range 83.91 to 89.30%) as compared to ratios without heparin.

The in vitro experiments described above demonstrated that the drop of plasma paroxetine concentrations was caused by heparin displacing the drug in plasma into RBC before the plasma was harvested as in the case of using heparin lock system in collecting blood samples. This unexpected artifact can decrease the plasma concentration as compared to blood collection situation where heparin was not used such as venipuncture. The anticoagulant, EDTA, used in the vacutainer tube did not have the same drug displacement effect as demonstrated in these in vitro experiments.

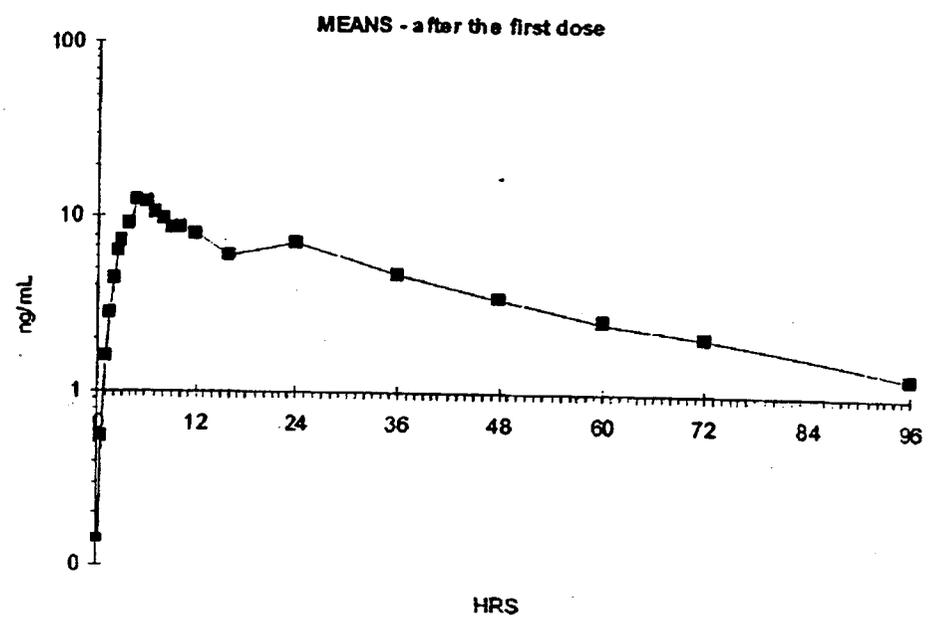
It should also be noted that the majority of blood samples on Days 1 and 29 were drawn using the heparin lock system. Therefore, comparing dose #1 and dose #25 (Day 29) and the calculation of an accumulation ratio is still valid in this study.

Figure 6 Mean Plasma Concentration-Time Profile on Day 29 for Paroxetine Mesylate following multiple 30 mg doses (semilogarithmic scale)



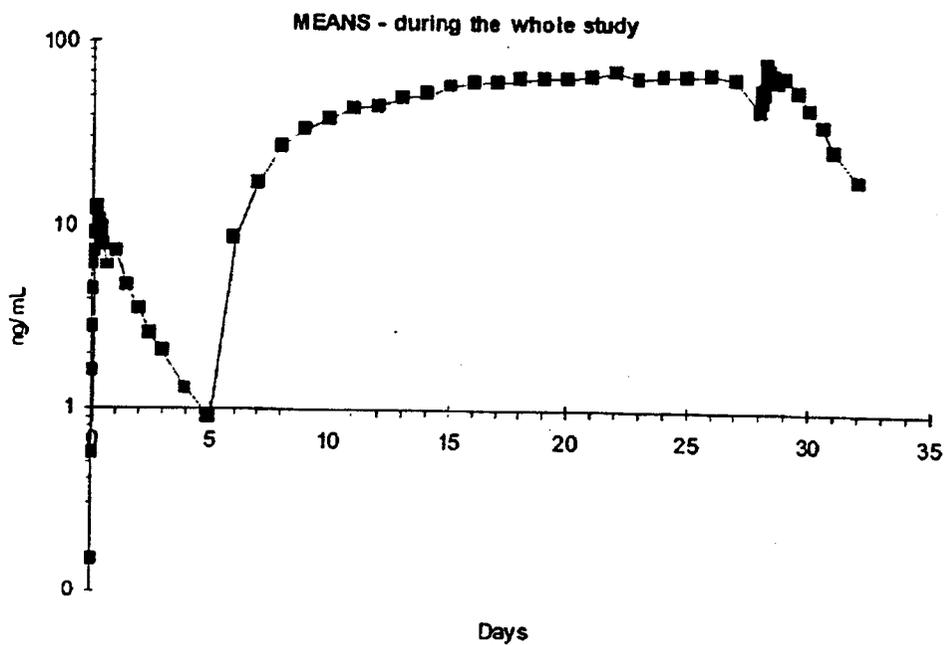
**APPEARS THIS WAY
ON ORIGINAL**

Figure 2 Mean Plasma Concentration-Time Profile for Paroxetine Mesylate from a 30 mg dose on Day 1 (semi-logarithmic scale)



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ON ORIGINAL

Figure 4 Mean Plasma Concentration-Time Profile for Paroxetine Mesylate following single and multiple 30 mg doses (semilogarithmic scale)



**APPEARS THIS WAY
ON ORIGINAL**

Dissolution

Based on its developmental studies, Synthon is proposing the following dissolution testing method for its **paroxetine mesylate** tablets:

Sponsor's Specification: Q = _____ in 30 minutes.

Based on the evaluation of individual tablet data for all strengths biobatches, following is the FDA's dissolution specification for paroxetine mesylate tablets.

FDA's Specification: Q = _____ in 30 minutes

Dissolution specifications for **paroxetine HCl** tablets:

Sponsor's Specification: Not less than _____, in _____ minutes

Synthon initially proposed the _____ method at a _____ speed of _____. However, the FDA informed Synthon during the pre-NDA meeting that the _____ speed may be too fast. Therefore, Synthon proceeded to develop an alternative method that used a slower _____ speed. That development work was complicated by the fact that Synthon's tablets tended to stick to the _____ walls and a cone of undissolved excipients were formed at the bottom of the _____. The sticking and coning problems resulted in data that was inconsistent and an inaccurate representation of the dissolution of the product.

Synthon conducted the following dissolution studies in its attempt to find an appropriate dissolution method: _____

_____ Of those methods, only the _____, and the _____ provided satisfactory results. Dissolution profiles and individual dissolution data _____ are attached.

Table 8 Proposed Product Dissolution Method

	Apparatus Type	Media	Volume	Speed

Table 19 Qualitative comparison between Synthon and SmithKline Beecham's product

Excipient	Synthon:	SmithKline Beecham:
	Paroxetine (as mesylate) tablets	Paroxetine (as hydrochloride) tablets
CaHPO ₄ dihydrate	-	+
CaHPO ₄	+	-
Sodiumstarchglycolate	+	+
Magnesiumstearate	+	+
HPMC	+	+
HPC	+	-
PEG	-	+
PEG	-	+
Polysorbate 80	-	+
Titaniumdioxide	+	+
Colouring agents	+	+

Figure 9 Cone formation of Synthon's tablets after 30 minutes, using a speed of _____ as dissolution medium



Figure 10

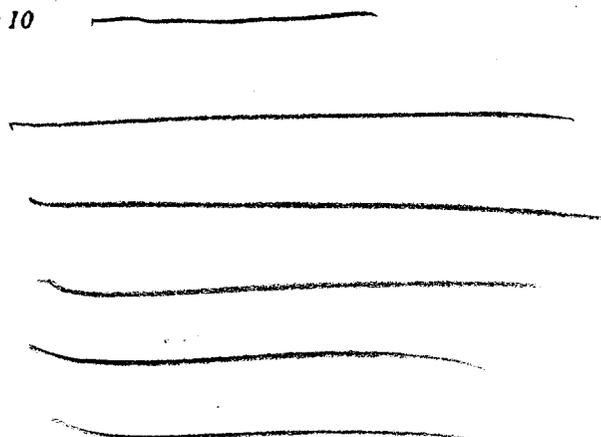


Figure 11 Dissolution profile comparison of the GMP-batches of the 10 mg strength

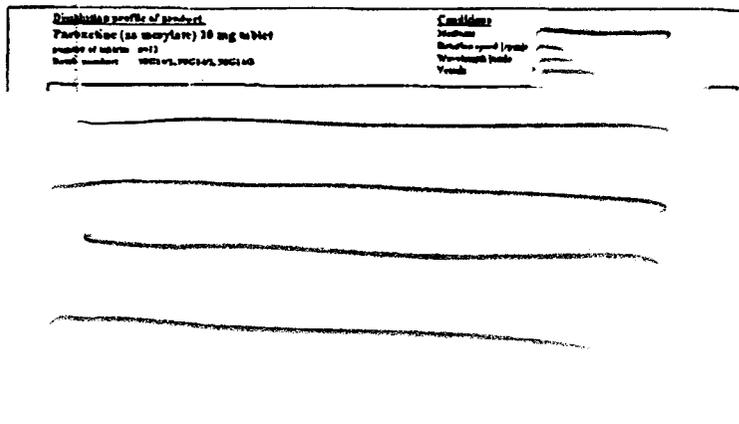


Table 20 Statistical dissolution profile comparison of the GMP batches of the 10 mg strength

	10 mg 98G142	10 mg 98G143
10 mg batch 98 G142	F ₁ = 3 F ₂ = 84	F ₁ = 5 F ₂ = 75

Paroxetine (as mesylate) 10 mg tablet, batch 98G142

Dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
	%	%	%	%	%	%	%	%	%	%
Mean (%)	0	8	32	43	51	56	69	73	82	88
Stdev	0	2	6	5	5	6	5	5	5	4
RSD (%)	0	27	14	11	10	8	8	7	6	5

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Paroxetine (as mesylate) 10 mg tablet, batch 98G14/2 ✓
3 batches

Dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
Mean (%)	0	4	43	68	78	86	94	99	100	100
Stdev	0	2	10	10	9	7	5	3	3	3
RSD (%)	0	48	23	15	11	8	5	3	3	3

Paroxetine (as mesylate) 10 mg tablet, batch 98G14/3

Dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
Mean (%)	0	5	47	69	81	87	95	100	102	102
Stdev	0	4	11	10	9	9	7	5	4	4
RSD (%)	0	73	24	15	12	10	7	5	4	4

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Figure 12 Dissolution profile comparison of the batches of the 20 mg strength

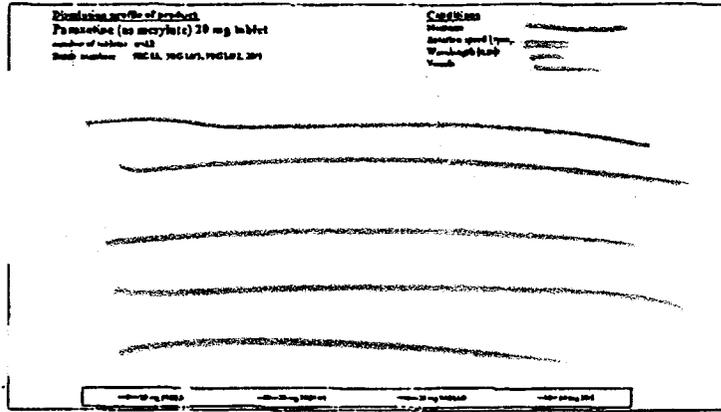


Table 21 Statistical dissolution profile comparison of the batches of the 20 mg strength

	20 mg 98G13	20 mg 20/L	20 mg 98 G14/2
20 mg batch 98 G14/1 <i>Batch 1</i>	F ₁ = 8 F ₂ = 67	F ₁ = 6 F ₂ = 71	F ₁ = 19 F ₂ = 51

Paroxetine (as mesylate) 20 mg tablet, batch 98G13

Dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	16 min	20 min	30 min	45 min	60 min
	%	%	%	%	%	%	%	%	%	%
1	0	1	38	66	82	89	95	99	100	100
2	0	1	10	10	10	9	8	3	2	2
3	0	60	27	16	12	10	7	3	2	2
4	0	1	38	66	82	89	95	99	100	100
5	0	1	10	10	10	9	8	3	2	2
6	0	60	27	16	12	10	7	3	2	2
7	0	1	38	66	82	89	95	99	100	100
8	0	1	10	10	10	9	8	3	2	2
9	0	60	27	16	12	10	7	3	2	2
10	0	1	38	66	82	89	95	99	100	100
11	0	1	10	10	10	9	8	3	2	2
12	0	60	27	16	12	10	7	3	2	2
Mean (%)	0	1	38	66	82	89	95	99	100	100
Stdev	0	1	10	10	10	9	8	3	2	2
RSO (%)	0	60	27	16	12	10	7	3	2	2

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Paroxetine (as mesylate) 20 mg tablet, batch 99C14/1 ✓

Dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
	%	%	%	%	%	%	%	%	%	%
Mean (%)	0	2	34	60	76	85	94	98	99	100
Stdev	0	1	11	12	11	9	7	3	1	1
RSD (%)	0	70	32	20	15	11	7	3	1	1

Paroxetine (as mesylate) 20 mg tablet, batch 99C14/2

Dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
	%	%	%	%	%	%	%	%	%	%
Mean (%)	0	2	47	71	85	91	95	99	99	99
Stdev	0	2	8	8	8	7	5	2	2	2
RSD (%)	0	65	17	11	9	7	5	2	2	2

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Paroxetine (as mesylate) 20 mg tablet, batch 2071

Dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
	%	%	%	%	%	%	%	%	%	%
1	0	1	36	65	81	90	96	98	98	98
2	0	1	16	13	10	8	3	3	2	2
3	0	47	45	20	12	7	3	3	2	3
4	0	1	36	65	81	90	96	98	98	98
5	0	1	16	13	10	8	3	3	2	2
6	0	47	45	20	12	7	3	3	2	3
7	0	1	36	65	81	90	96	98	98	98
8	0	1	16	13	10	8	3	3	2	2
9	0	47	45	20	12	7	3	3	2	3
10	0	1	36	65	81	90	96	98	98	98
11	0	1	16	13	10	8	3	3	2	2
12	0	47	45	20	12	7	3	3	2	3
13	0	1	36	65	81	90	96	98	98	98
14	0	1	16	13	10	8	3	3	2	2
15	0	47	45	20	12	7	3	3	2	3
16	0	1	36	65	81	90	96	98	98	98
17	0	1	16	13	10	8	3	3	2	2
18	0	47	45	20	12	7	3	3	2	3
19	0	1	36	65	81	90	96	98	98	98
20	0	1	16	13	10	8	3	3	2	2
21	0	47	45	20	12	7	3	3	2	3
22	0	1	36	65	81	90	96	98	98	98
23	0	1	16	13	10	8	3	3	2	2
24	0	47	45	20	12	7	3	3	2	3
25	0	1	36	65	81	90	96	98	98	98
26	0	1	16	13	10	8	3	3	2	2
27	0	47	45	20	12	7	3	3	2	3
28	0	1	36	65	81	90	96	98	98	98
29	0	1	16	13	10	8	3	3	2	2
30	0	47	45	20	12	7	3	3	2	3
31	0	1	36	65	81	90	96	98	98	98
32	0	1	16	13	10	8	3	3	2	2
33	0	47	45	20	12	7	3	3	2	3
34	0	1	36	65	81	90	96	98	98	98
35	0	1	16	13	10	8	3	3	2	2
36	0	47	45	20	12	7	3	3	2	3
37	0	1	36	65	81	90	96	98	98	98
38	0	1	16	13	10	8	3	3	2	2
39	0	47	45	20	12	7	3	3	2	3
40	0	1	36	65	81	90	96	98	98	98
41	0	1	16	13	10	8	3	3	2	2
42	0	47	45	20	12	7	3	3	2	3
43	0	1	36	65	81	90	96	98	98	98
44	0	1	16	13	10	8	3	3	2	2
45	0	47	45	20	12	7	3	3	2	3
46	0	1	36	65	81	90	96	98	98	98
47	0	1	16	13	10	8	3	3	2	2
48	0	47	45	20	12	7	3	3	2	3
49	0	1	36	65	81	90	96	98	98	98
50	0	1	16	13	10	8	3	3	2	2
51	0	47	45	20	12	7	3	3	2	3
52	0	1	36	65	81	90	96	98	98	98
53	0	1	16	13	10	8	3	3	2	2
54	0	47	45	20	12	7	3	3	2	3
55	0	1	36	65	81	90	96	98	98	98
56	0	1	16	13	10	8	3	3	2	2
57	0	47	45	20	12	7	3	3	2	3
58	0	1	36	65	81	90	96	98	98	98
59	0	1	16	13	10	8	3	3	2	2
60	0	47	45	20	12	7	3	3	2	3
61	0	1	36	65	81	90	96	98	98	98
62	0	1	16	13	10	8	3	3	2	2
63	0	47	45	20	12	7	3	3	2	3
64	0	1	36	65	81	90	96	98	98	98
65	0	1	16	13	10	8	3	3	2	2
66	0	47	45	20	12	7	3	3	2	3
67	0	1	36	65	81	90	96	98	98	98
68	0	1	16	13	10	8	3	3	2	2
69	0	47	45	20	12	7	3	3	2	3
70	0	1	36	65	81	90	96	98	98	98
71	0	1	16	13	10	8	3	3	2	2
72	0	47	45	20	12	7	3	3	2	3
73	0	1	36	65	81	90	96	98	98	98
74	0	1	16	13	10	8	3	3	2	2
75	0	47	45	20	12	7	3	3	2	3
76	0	1	36	65	81	90	96	98	98	98
77	0	1	16	13	10	8	3	3	2	2
78	0	47	45	20	12	7	3	3	2	3
79	0	1	36	65	81	90	96	98	98	98
80	0	1	16	13	10	8	3	3	2	2
81	0	47	45	20	12	7	3	3	2	3
82	0	1	36	65	81	90	96	98	98	98
83	0	1	16	13	10	8	3	3	2	2
84	0	47	45	20	12	7	3	3	2	3
85	0	1	36	65	81	90	96	98	98	98
86	0	1	16	13	10	8	3	3	2	2
87	0	47	45	20	12	7	3	3	2	3
88	0	1	36	65	81	90	96	98	98	98
89	0	1	16	13	10	8	3	3	2	2
90	0	47	45	20	12	7	3	3	2	3
91	0	1	36	65	81	90	96	98	98	98
92	0	1	16	13	10	8	3	3	2	2
93	0	47	45	20	12	7	3	3	2	3
94	0	1	36	65	81	90	96	98	98	98
95	0	1	16	13	10	8	3	3	2	2
96	0	47	45	20	12	7	3	3	2	3
97	0	1	36	65	81	90	96	98	98	98
98	0	1	16	13	10	8	3	3	2	2
99	0	47	45	20	12	7	3	3	2	3
100	0	1	36	65	81	90	96	98	98	98

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Figure 13 Dissolution profile comparison of the GMP-batches of the 30 mg strength

Disintegration results of testing: Paroxetine (as mesylate) 30 mg tablet number of tablets: n=12 Batch number: 98G14/1, 98G14/2, 98G14/3	Conditions: Medium: _____ Apparatus used: _____ Water through funnel: _____ Volume: _____
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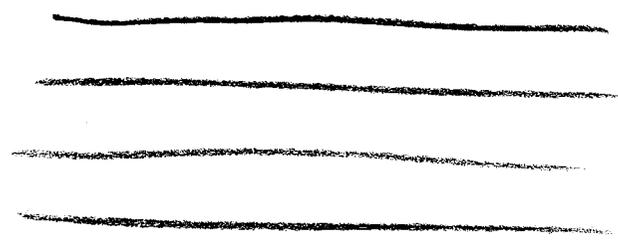


Table 22 Statistical dissolution profile comparison of the GMP batches of the 30 mg strength

	30 mg 98G14/1	30 mg 98 G14/2
30 mg batch 98 G14/3	F ₁ = 12 F ₂ = 58	F ₁ = 5 F ₂ = 78

Paroxetine (as mesylate) 30 mg tablet, batch 98G14/1

Disolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
	%	%	%	%	%	%	%	%	%	%
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean (%)	0	1	34	66	82	91	98	100	101	101
Stdev	0	1	8	7	6	5	3	2	2	2
RSD (%)	0	80	23	11	8	5	3	2	2	2

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Paroxetine (as mesylate) 30 mg tablet, batch 89G14/3

Dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
	%	%	%	%	%	%	%	%	%	%
Mean (%)	0	1	28	57	74	85	93	98	100	100
Stdev	0	1	8	8	7	6	4	2	1	1
RSD (%)	0	69	20	13	9	7	5	2	1	1

Paroxetine (as mesylate) 30 mg tablet, batch 89G14/2

Dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
	%	%	%	%	%	%	%	%	%	%
Mean (%)	0	1	25	54	70	80	87	95	97	98
Stdev	0	1	9	11	12	11	10	8	6	5
RSD (%)	0	64	38	20	17	14	11	8	6	5

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Figure 14 Dissolution profile comparison of the GMP-batches of the 40 mg strength

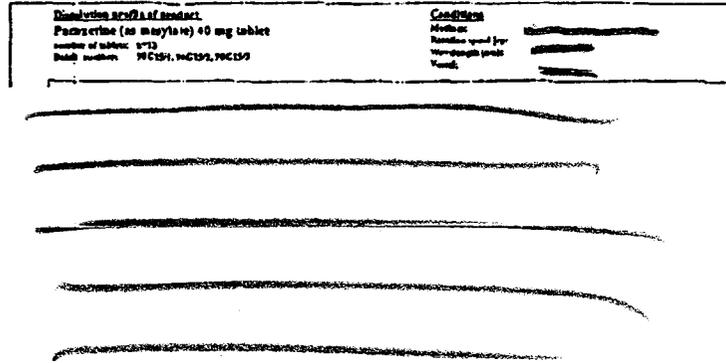


Table 23 Statistical dissolution profile comparison of the GMP batches of the 40 mg strength

	40 mg 98G15/1	40 mg 98 G15/2
40 mg batch 98 G15/3	F ₁ = 4 F ₂ = 81	F ₁ = 5 F ₂ = 77

Paroxetine (as mesylate) 40 mg tablet, batch 98G15/1

Un-dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
	%	%	%	%	%	%	%	%	%	%
1	0	1	27	37	74	86	85	100	101	101
2	0	1	9	7	5	4	4	2	2	2
3	0	98	33	12	7	5	4	2	2	2
4	0	1	27	37	74	86	85	100	101	101
5	0	1	9	7	5	4	4	2	2	2
6	0	98	33	12	7	5	4	2	2	2
7	0	1	27	37	74	86	85	100	101	101
8	0	1	9	7	5	4	4	2	2	2
9	0	98	33	12	7	5	4	2	2	2
10	0	1	27	37	74	86	85	100	101	101
11	0	1	9	7	5	4	4	2	2	2
12	0	98	33	12	7	5	4	2	2	2
Mean (%)	0	1	27	37	74	86	85	100	101	101
Stdev	0	1	9	7	5	4	4	2	2	2
RSD (%)	0	98	33	12	7	5	4	2	2	2

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Paroxetine (as mesylate) 40 mg tablet, batch 98G16/3 ✓

Dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
	%	%	%	%	%	%	%	%	%	%
Mean (%)	0	1	27	55	71	82	92	98	99	99
Stdev	0	1	8	9	9	8	7	4	3	2
RSD (%)	0	87	29	17	12	10	8	4	3	2

Paroxetine (as mesylate) 40 mg tablet, batch 98G16/2

Dissolved amount paroxetine at different sampling times in % (corrected for tablet mass)

Samples	0 min	3 min	6 min	9 min	12 min	15 min	20 min	30 min	45 min	60 min
	%	%	%	%	%	%	%	%	%	%
Mean (%)	0	2	23	57	74	85	93	98	98	99
Stdev	0	4	11	10	10	9	7	4	3	3
RSD (%)	0	199	48	18	14	11	7	4	3	3

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The results of the execution of the dissolution profile comparison using _____ as dissolution medium are presented in the following figure and table.

Figure 15 Dissolution profile comparison of the lower strengths to the 40 mg strength using _____ as dissolution medium

Dissolution profile of product	Conditions
Paracetamol (as trihydrate) 10, 20, 30 and 40 mg tablets number of tablets: 6-12 Batch number: _____	Medium: _____ Rotation speed (rpm): _____ Waterbath (mm): _____ Vessel: _____



Dissoln.
(biobatch)

Table 24 Statistical dissolution profile comparison to the 40 mg strength using _____ as dissolution medium

	10 mg	20 mg	30 mg
Difference factor f_1	16	9	4
Similarity factor f_2	52	67	83

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3.3 Formulations Used in Studies

Synthon has developed a mesylate salt form of the paroxetine antidepressive active moiety as 10 mg, 20 mg, 30 mg, and 40 mg tablets. Paroxetine is currently marketed under the Paxil® trademark by SmithKline Beecham Pharmaceuticals ("SB") in the form of paroxetine hydrochloride in the US. Synthon is seeking approval for the 10 mg, 20 mg, 30 mg, and 40 mg strengths of paroxetine (as mesylate) tablets. In order to fulfill the regulatory requirements necessary for a 505(b)(2) application, Synthon performed four comparative bioavailability studies and one steady-state pharmacokinetic study in healthy volunteers. The formulation development summary, detailing the formulations used in comparative bioavailability studies and in the steady-state pharmacokinetic study is presented in table 2. The composition and batch numbers of reference tablet formulations used in these studies are presented in table 3 and table 4, respectively. The reference formulations were manufactured by SmithKline Beecham and are marketed in the US, Europe, and Australia as Paxil®, Seroxat®, and Aropax™, respectively.

Table 2 Drug Product Formulation Development Summary

Study Number	Lot. No.	Strength/ Dosage form	Batch size	Formulation or significant manufacturing change (if any) and reason for change	Effect of change
982413	98G15/3	40 mg tablet	_____	No change	N.A.
CPR-PA5	98G14/1	30 mg tablet	_____	No change	N.A.
982413B	98G14/2	10 mg tablet	_____	No change	N.A.
009/65/98	98E25	20 mg tablet	_____	No change	N.A.
013/78/99	98G14/1	20 mg tablet	_____	No change	N.A.

Table 3 Comparison of Reference Tablet Formulations

Qualitative Composition		
Paxil® 20mg (U.S.)	Seroxat® 20mg (Europe)	Aropax™ 20mg (Australia)
Dibasic calcium phosphate dihydrate	_____	_____
Sodium starch glycolate	_____	_____
Magnesium stearate	_____	_____
Polysorbate 80	_____	_____
Polyethyleneglycols	_____	_____
Titanium dioxide	_____	_____

Table 4 Comparison of Reference Tablet Mass

Product	Batch	Average Mass (mg)
Paxil® 20mg (U.S.)	418 8B11	357.1
Seroxat® 20mg (Europe)	828	354.5
Atopax™ 20mg (Australia)	53411	355.7

Paroxetine mesylate is currently manufactured at _____

_____ Table 5 presents the tablet composition of the four tablet strengths. Table 6 presents the manufacturing formula for the production runs of 10 mg, 20 mg, 30 mg, and 40 mg paroxetine (as mesylate) tablets.

Table 5 Tablet composition expressed in percentage of total tablet weight

Ingredient	10 mg (%)	20 mg (%)	30 mg (%)	40 mg (%)
Paroxetine (as Mesylate)	_____	_____	_____	_____
Dibasic calcium phosphate	_____	_____	_____	_____
Sodium starch glycolate	_____	_____	_____	_____
Magnesium stearate	_____	_____	_____	_____
Hydroxypropyl methylcellulose*	_____	_____	_____	_____
Hydroxypropyl cellulose*	_____	_____	_____	_____
Titanium dioxide*	_____	_____	_____	_____
Ferric oxide yellow (CI 77492)*	_____	_____	_____	_____
Ferric oxide red (CI 77491)*	_____	_____	_____	_____

Proportional Formulation

All Synthon tablet strengths, 10 mg, 20 mg, 30 mg and 40 mg, are proportional in active and inactive ingredients as depicted in the table below.

Table 18 *Quantitative composition of Paroxetine (as mesylate) tablets*

Ingredients	10 mg (mg)	20 mg (mg)	30 mg (mg)	40 mg (mg)	Function
Core:					
Paroxetine mesylate					Drug Substance
Dibasic calcium phosphate (anhydrous)					
Sodium starch glycolate					
Magnesium stearate					
Mass cores					
Coating:					
Hydroxypropyl methylcellulose					
Hydroxypropyl cellulose					
Titanium dioxide					
Ferric oxide yellow (C.I. 77492)					
Ferric oxide red (C.I. 77491)					
Purified water ¹					
Mass coating					
Total mass					

Table 6 Manufacturing formula for production runs of 10 mg, 20 mg, 30 mg, and 40 mg paroxetine (as mesylate)

Ingredient	10 mg - tablets (kg)	20 mg - tablets (kg)	30 mg - tablets (kg)	40 mg - tablets (kg)
Paroxetine (as Mesylate)*	_____	_____	_____	_____
Dibasic calcium phosphate	_____	_____	_____	_____
Sodium starch glycolate	_____	_____	_____	_____
Magnesium stearate	_____	_____	_____	_____
Hydroxypropyl methylcellulose**	_____	_____	_____	_____
Hydroxypropyl cellulose**	_____	_____	_____	_____
Titanium dioxide**	_____	_____	_____	_____
Ferric oxide yellow (CI 77492)**	_____	_____	_____	_____
Ferric oxide red (CI 77491)**	_____	_____	_____	_____
Total	_____	_____	_____	_____

For additional information regarding the drug formulation and manufacturing, refer to the Chemistry, Manufacturing, and Controls section of this application.

Analytical Methods

The analytical methods for the determination of paroxetine in human plasma were developed and validated at _____

These two laboratories were responsible for the analysis of plasma samples from Studies 982413, CPR-PA5, 982413B, 009/65/98, and 013/78/99.

A validated high performance liquid chromatographic method using mass spectrometric detection (LC/MS/MS) for the determination of paroxetine in human plasma over concentration ranges as presented in table 1 was developed and utilized for the sample analysis. For additional details on the analytical methods used for these studies, refer to the individual study reports presented in C 3 Exhibits 1 -5.

Table 1 Description of In Vivo Analytical Methods

Study No.	Type of Biological Fluid	Method	Analyte	Precision (% CV) at LOQ		Limit of Quantification	Linear Range
				Intra-assay	Inter-assay		
982413	Plasma	LC/MS/MS	Paroxetine				
CPR-PA5	Plasma	LC/MS/MS	Paroxetine				
982413B	Plasma	LC/MS/MS	Paroxetine				
009/65/98	Plasma	LC/MS/MS	Paroxetine				
			M-Paroxetine				
013/78/99	Plasma	LC/MS/MS	Paroxetine				

Conclusion

Following conclusions were drawn from several studies submitted to this NDA:

1. The highest strength (40 mg) paroxetine mesylate tablets were shown to be bioequivalent to the reference product (40 mg paxil).
2. In two separate BE studies, the 20 mg paroxetine mesylate tablets were shown to be bioequivalent to 20 mg paroxetine HCl tablets (Czech vs Australia and Czech vs Germany).
3. The mean C_{max} and AUC of 10 mg paroxetine mesylate tablets are comparable to the mean C_{max} and AUC of 10 mg paroxetine HCl tablets. The intersubject variability (%CV) on both C_{max} and AUC between test and reference product is comparable.

2x10 mg:

C_{max} = 84% (test); 95% (ref)

AUC = 193% (test); 199%(ref).

The presence of outliers in 2x10 mg tablets study was also investigated. A subject was declared outlier if the difference in AUC between the test and reference product was three times or more (arbitrary selected). There were two subjects (subjects #67 and 84) who met the criteria. The omission of these two subjects from the statistical analysis, though, resulted in decrease in the confidence interval width (108-130 vs 113-139 all subjects included), the 2x10 mg paroxetine tablets manufactured by Synthon failed to meet the bioequivalence criteria.

Based on the power and sample size calculation, it was found that in the 2x10 mg group, 50 (80% power) and 62 (90% power) subjects will be required to successfully demonstrate the bioequivalence. With 37 subjects in the study, the power was only 63%. It should also be noted that the power for 40 mg tablet was 92% (n = 38).

4. The mean C_{max} and AUC of 30 mg paroxetine mesylate tablets are comparable to the mean C_{max} and AUC of 30 mg paroxetine HCl tablets following a single dose. Further, the degree of accumulation based on a cross study comparison showed accumulation to be similar (accumulation ratio = 12)

5. Paroxetine mesylate tablets are compositionally proportional from 10 to 40 mg.

6. Similar dissolution profiles were observed for all tablet strengths (f2> 50 in all cases).

Comments to the Sponsor

Please convey the following Comment to the Sponsor:

1. The FDA's dissolution method and specification for all strengths of paroxetine mesylate tablets is:

Specification: Q = — in 30 minutes.

Labeling Comment

The Sponsor's labeling is similar to SmithKline Beecham's labeling with the exception of multiple dosing pharmacokinetic data. Synthron replaced SmithKline Beecham's multiple dose pharmacokinetic data by its own multiple dose data.

9 Draft Labeling Page(s) Withheld

Recommendation

The 40 mg paroxetine mesylate tablets are bioequivalent to the 40 mg paroxetine hydrochloride tablets. The 20 and 30 mg paroxetine mesylate tablets fulfil the requirements of biowaiver. Therefore, the Sponsor can market 20, 30 and 40 mg paroxetine mesylate tablets.

The 10-mg paroxetine mesylate tablets (dosed as 2 x 10 mg) failed to meet the bioequivalence criteria. Though the mean C_{max} and AUC of 10 mg paroxetine mesylate tablets are comparable to the mean C_{max} and AUC of 10 mg paroxetine HCl tablets, the failure of AUC to meet the bioequivalence criteria may be due to very high intersubject variability (approximately 200% for both test and reference), small sample size and lack of power. Inclusion of more subjects ($n \geq 50$) in the study may have demonstrated bioequivalence between the test and the reference. Furthermore, paroxetine mesylate tablets are compositionally proportional from 10 to 40 mg and they have similar dissolution profiles for all tablet strengths. Since the 10 mg paroxetine mesylate tablets are bioequivalent to the 10 mg paroxetine hydrochloride tablets, the approval of this strength should be based on clinical consideration.

Iftexhar Mahmood, Ph.D. _____

RD/FT initialed by Raman Baweja, Ph.D. _____

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-299, HFD-120, HFD-860 (Mahmood, Baweja, Mehta), HFD-340 (Viswanathan), CDR-Biopharm (for Drug-Files) and FOI (HFD-19) files.

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