Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Comparative bioequivalence studies of tramadol hydrochloride sustained-release 200 mg tablets

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
24 November 2010
Number of times this article has been viewed

Suhas S Khandave[1]
Satish V Sawant[1]
Santosh S Joshi[1]
Yatish K Bansal[2]
Sonal S Kadam[2]

[1]Accutest Research Laboratories (I) Private Limited, Koparkhirne, Navi Mumbai, Maharashtra, India; [2]Ipca Laboratories Limited, Kandivli Mumbai, Maharashtra, India

Background: Tramadol hydrochloride is available as 50 mg immediate-release (IR) and 100 mg, 200 mg, and 300 mg sustained-release (SR) tablets. The recommended dose of tramadol is 50–100 mg IR tablets every 4–6 hours. The tramadol SR 200 mg tablet is a better therapeutic option, with a reduced frequency of dosing, and improved patient compliance and quality of life. The present study evaluated the bioequivalence of a generic tramadol SR 200 mg tablet.

Methods: A comparative in vitro dissolution study was performed on the test and reference products, followed by two separate single-dose bioequivalence studies under fasting and fed conditions and one multiple-dose bioequivalence study under fasting conditions. These bioequivalence studies were conducted in healthy human subjects using an open-label, randomized, two-treatment, two-period, two-sequence, crossover design. The oral administration of the test and reference products was done on day 1 for both the single-dose studies and on days 1–5 for the multiple-dose study in each study period as per the randomization code. Serial blood samples were collected at predefined time points in all the studies. Analysis of plasma concentrations of tramadol and O-desmethyltramadol (the M_1 metabolite) was done by a validated liquid chromatography-mass spectrometry analytical method. The standard acceptance criterion of bioequivalence was applied on log-transformed pharmacokinetic parameters for tramadol and its M_1 metabolite.

Results: The ratios for geometric least-square means and 90% confidence intervals were within the acceptance range of 80%–125% for log-transformed primary pharmacokinetic parameters for tramadol and its M_1 metabolite in all the three studies.

Conclusion: The test product is bioequivalent to the reference product in terms of rate and extent of absorption, as evident from the single-dose and multiple-dose studies. Both the treatments were well tolerated.

Keywords: tramadol, multiple-dose, steady state, bioequivalence

Introduction

Tramadol hydrochloride is a centrally acting, synthetic, opioid analgesic structurally similar to codeine and morphine. It is available in various dosage forms for systemic administration. Tramadol has proven efficacy and safety in a number of acute painful conditions, including trauma, renal or biliary colic, and labor. Chronic pain of malignant or nonmalignant origin, particularly neuropathic pain, is also a common indication for tramadol.[1] Tramadol is available as drops, tablets, and capsules for oral administration. The mean absolute bioavailability of tramadol with all oral formulations is approximately 70%, irrespective of concomitant intake of food. It has a plasma protein binding of about 20%. Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. The relationship between serum concentrations and the

Correspondence: Suhas Sahebrao Khandave
Accutest Research Laboratories (I) Private Limited, A-31, TTC Industrial Area, Khairne MIDC, Koparkhirne, Navi Mumbai, Maharashtra, India
Tel +91 222 778 0718
Fax +91 222 778 0720
Email suhas_khandave@rediffmail.com

analgesic effect is dose-dependent, but varies considerably in individual cases. A serum concentration of 100–300 ng/mL is usually effective.[2] The short elimination half-life of 6 hours necessitates dosing of patients with immediate-release (IR) tramadol preparations every 4–6 hours in order to maintain optimal levels of analgesia in chronic pain. The dose of tramadol is titrated upwards as necessary. The maximum recommended dose of tramadol is 400 mg/day.[3]

Successful long-term treatment of patients with painful conditions requires an appropriate dosage form, optimal dosing, and patient compliance. Sustained-release (SR) formulations are very helpful in achieving treatment objectives. Stable serum levels without marked peak to trough fluctuations and reduced frequency of dosing improve patient compliance, patient satisfaction, and, ultimately, quality of life. Tramadol 100 mg, 200 mg, and 300 mg SR tablets are available commercially to overcome the difficulties associated with the frequent dosing needed for IR tramadol preparations.

In recent years, generic drug products have become very popular. Bioequivalence studies are the commonly accepted method to demonstrate therapeutic equivalence between two medicinal products. Bioequivalence can be shown either with a single-dose study or a multiple-dose steady-state study. Savings in time and cost are substantial when using bioequivalence as an established surrogate marker of therapeutic equivalence. Ipca Laboratories Limited (Mumbai, India) has developed an SR tablet containing tramadol 200 mg as a generic substitute for the corresponding innovator product. In general, a steady-state study under fasting conditions and two separate single-dose studies under fasting and fed conditions are required to demonstrate bioequivalence for the modified-release dosage forms. Therefore, three bioequivalence studies were undertaken to compare the pharmacokinetic properties of tramadol hydrochloride SR tablets 200 mg (Ipca Laboratories Limited) and Zydol® (tramadol) SR 200 mg prolonged-release tablets (Grunenthal Ltd, High Wycombe, UK) in healthy subjects. Two studies were conducted under fasting and fed conditions using a single-dose approach, and a third study was conducted using a steady-state approach under fasting conditions. All of these studies were conducted after confirming the acceptable results of an in vitro comparative dissolution study.

Materials and methods

In vitro dissolution study

A comparative in vitro dissolution study was conducted ahead of the in vivo bioequivalence studies. It was ensured that the in vitro dissolution data were acceptable as per the regulatory guidelines for conducting bioequivalence studies.[4] The dissolution study was carried out on 12 units each of the test and reference products using the paddle method as per the British Pharmacopoeia monograph. The paddle rotation speed was maintained at 50 rotations per minute at 37 ± 0.5°C. The test was carried out using 900 mL of pH 6.8 phosphate buffer as a dissolution medium. Samples were drawn at hours 1, 4, 8, and 12. Each sample solution was analyzed by high-performance liquid chromatography to determine the dissolution rate. The mean dissolution values at each time interval were used to calculate the difference factor (f_1) and similarity factor (f_2) using the standard mathematical equation.

In vivo bioequivalence studies

In total, 48, 60, and 54 healthy volunteers were enrolled for the single-dose fasting, single-dose fed, and multiple-dose fasting studies, respectively. The ranges for age, weight, and height were 19–41 years, 46–79 kg, and 149–182 cm, respectively. All subjects had an acceptable body mass index (BMI).

The studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines, and the note for guidance on the investigation of bioavailability and bioequivalence laid down by the European Agency for the Evaluation of Medicinal Products.[5–7] The study protocols were approved by the Drushti Independent Ethics Committee, Navi Mumbai, Maharashtra, India. Each subject gave voluntary written informed consent before participation in the study.

All the studies were conducted using an open-label, randomized, two-treatment, two-period, two-sequence, crossover bioequivalence design. The duration of treatment, including the washout period between the two study periods, was 12 days for both the single-dose studies and 21 days for the multiple-dose study.

Healthy adult male subjects were enrolled in the study. The sample size (number of subjects) was calculated on the assumption that there would not be any interaction between formulations and periods, the observations would be log normally distributed, and the variances of test and reference parameters would be the same. Compared with the single-dose fasting studies, the multiple-dose fasting study had more subjects, in anticipation of a higher number of withdrawals due to multiple exposures to the study drugs. Similarly, the number of subjects for the single-dose fed

study was the highest, considering the additional factor of subjects' potential noncompliance with the "morning high-calorie high-fat breakfast" and subsequent withdrawal from the study. The subjects enrolled were expected to produce a probability of greater than 90% for concluding bioequivalence within the normal acceptance limits of 80%–125% for the pharmacokinetic parameters, at a consumer risk of 5%. Subjects with significant diseases or clinically significant abnormal findings were ruled out during screening by obtaining a complete medical history, performing a full physical examination, and laboratory investigations, including hematology, biochemistry, serology, and urine analysis.

The subjects met all the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

- Male gender, with age range 18–55 years, BMI in the range 18.5–24.9 kg/m^2
- Normal baseline medical history, physical examination, and vital signs (blood pressure, pulse rate, respiration rate, and axillary temperature)
- Normal hematology, biochemistry, infectious disease screening (human immunodeficiency virus, hepatitis B, and hepatitis C), urinalysis, electrocardiography, and X-ray
- Willingness not to use any prescription or over the counter medications, including vitamins and minerals, for 14 days prior to and during the course of the study
- Nonsmoking status.

Exclusion criteria

- Any medical or surgical condition which might significantly interfere with the functioning of the gastrointestinal tract, blood-forming organs, etc
- History of cardiovascular, renal, hepatic, ophthalmic, pulmonary, neurologic, metabolic, hematologic, gastrointestinal, endocrine, immunologic, or psychiatric disease
- Participation in a clinical drug study or bioequivalence study 90 days prior to the present study
- Use of xanthine-containing beverages or food (tea, coffee, chocolate, and cola), grapefruit juice, and any alcoholic products for 48 hours prior to dosing until after the last sample collection in each study period
- Blood donation 90 days prior to commencement or during the study
- Known history of hypersensitivity to tramadol hydrochloride or related drugs
- Found positive on urine test for drug abuse done on the day of check-in for each study period
- History of problems with swallowing tablets.

Clinical phase

All the enrolled subjects were confined for at least 12 hours prior to drug administration. After a fast of at least 10 hours, oral administration of the test and reference products was done on day 1 for both the single-dose studies and on days 1–5 for the multiple-dose study in each study period as per the randomization code, with 240 mL of water at ambient temperature. For the single-dose fed study, a high-fat high-calorie breakfast yielding approximately 800–1000 calories was given to the subjects half an hour before dosing in each period.

A total of 22 blood samples for both the single-dose studies and 26 blood samples for the multiple-dose study were collected from the subjects during each study period. Blood samples were collected predose and at 12 hours postdose on days 1, 2, 3, and 4 by fresh venepuncture in the multiple-dose study. Serial blood samples were collected for pharmacokinetic evaluation on day 1 for the single-dose studies and on day 5 for the multiple-dose study until 48 hours postdosing in each period. After collection, the blood samples were centrifuged at 5 ± 3°C and 3500 rotations per minute for 10 minutes to obtain plasma. All plasma samples were stored in the upright position at −20 ± 5°C until analysis of the samples.

The supervising medical officers or nursing staff measured vital signs under the supervision of the principal investigator. Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) were measured before check-in, predosing, after dosing at prescheduled times, and on discontinuation from the study. The subjects were monitored for any adverse events and/or complaints throughout the study. At the end of the study, poststudy evaluation, including physical examination, vital signs, 12-lead electrocardiogram, and clinical laboratory tests (hemogram, biochemistry, and urinalysis) were performed.

Bioanalytical phase

The subjects' plasma samples were analyzed at the bioanalytical facility of Accutest Research Laboratories (I) Private Limited. Samples from periods 1 and 2 for each subject were analyzed together for all the studies. The investigators analyzing the samples did not have access to the randomization schedule and hence were blinded to the order of administration of the study medication.

For all the studies, the analytical method validation included 0.2 mL of plasma samples and solid-phase extraction. Detection was done by the liquid chromatography-mass spectrometry method. Imipramine was used as the internal standard. The linearity range was 7.550–759.994 ng/mL and 1.006–148.710 ng/mL for tramadol and its M_1 metabolite, respectively. The linearity range was enough to quantify the expected concentration range of drug from subject's plasma with the proposed dose of tramadol.

Statistical analysis

All the statistical analyses were performed using SAS software (v. 9.1; SAS Institute, Cary, NC). As per the requirements for single-dose and steady-state studies, the following parameters were calculated individually for each subject from their tramadol and M_1 metabolite plasma concentrations: AUC (area under the plasma concentration-time curve in ng*hr/mL calculated by the linear trapezoidal method); AUC_{Tau} (AUC measured throughout the dosing interval at steady state); C_{max} (maximum plasma concentration observed, in ng/mL); C_{maxss} (C_{max} observed at steady state, in ng/mL); C_{minss} (minimum plasma concentration observed at steady state, in ng/mL); C_{pd} (predose concentration determined immediately before drug was given at steady state); C_{avg} (computed as AUC_{Tau}/T_{au} where T_{au} is dosing interval in hours = 24); % PTF (peak-trough fluctuation calculated as $100 \times (C_{maxss} - C_{minss})/C_{avg}$); and Swing ($[C_{maxss} - C_{minss}]/C_{minss}$).

Tramadol and its M_1 metabolite were considered for establishing bioequivalence between the test and reference products. The pharmacokinetic parameters AUC and C_{max} for the single-dose studies and AUC_{Tau}, C_{maxss}, and C_{minss} for the multiple-dose study were taken as primary efficacy variables. All values below the limit of quantification were considered as zero for the computation of pharmacokinetic parameters and statistical calculations. The actual blood sampling time points were considered for the calculation of pharmacokinetic parameters.

Analysis of variance (ANOVA) was performed (at $\alpha = 0.05$) on the log-transformed primary pharmacokinetic parameters, AUC, C_{max} for the single-dose studies, and AUC_{Tau}, C_{maxss}, and C_{minss} for the multiple-dose study. Effects of period, treatment, and sequence on primary efficacy criteria were analyzed by ANOVA. Each ANOVA also included calculation of least-square means, adjusted differences between formulation means, and the standard error associated with these differences. The 90% confidence intervals for the ratio of geometric means were calculated for the log-transformed primary pharmacokinetic parameters. The confidence interval was expressed as a percentage relative to the least-square means of the reference treatments. Bioequivalence was to be concluded when 90% confidence intervals were within the acceptable range of 80%–125% for log-transformed primary pharmacokinetic parameters.

Results and discussion

In vitro dissolution study

Dissolution curves are shown in Figure 1. From the dissolution profiles, the difference factor (f_1) of 1.39 (acceptable limit 0–15) and the similarity factor (f_2) of 88.07 (acceptable limit 50–100) were obtained. A comparative in vitro dissolution study provides a basis for predicting the likelihood of achieving a successful in vivo bioequivalence performance. This in vitro dissolution study showed that the test and reference products were comparable, indicating essential similarity of both the formulations.

In vivo bioequivalence studies

The subjects completing both the study periods successfully were considered for pharmacokinetic and statistical analysis of both tramadol and its M_1 metabolite. Tramadol was rapidly absorbed after oral administration, with mean peak plasma levels achieved at approximately 4–5 hours postdose for the test as well as reference products in all the studies (Tables 1 and 2, Figure 2). The M_1 metabolite was rapidly absorbed after oral administration, with mean peak plasma levels achieved at approximately 7–8 hours postdose for the test and reference products in all the studies (Tables 1 and 2, Figure 3). The rate and extent of absorption,

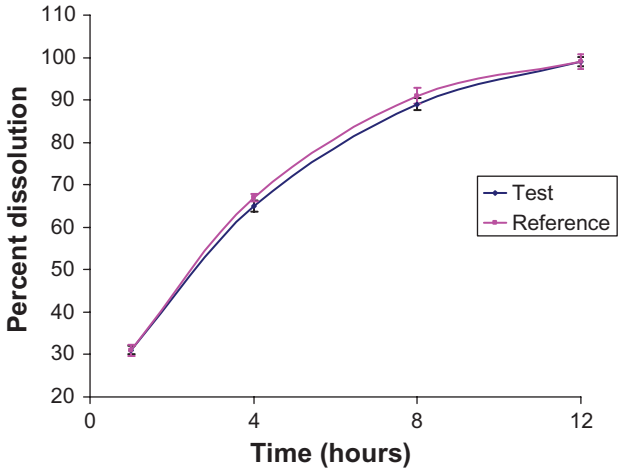

Figure 1 Comparative in vitro dissolution profile of test and reference products in phosphate-buffered saline (pH 6.8).
Note: Error bars indicate standard deviations.
Abbreviations: Test, tramadol 200 mg sustained-release tablet; Reference, Zydol® (tramadol) sustained-release 200 mg tablets.

Table 1 Pharmacokinetic parameters of tramadol and its M_1 metabolite in single-dose fasting and fed studies

Analyte		AUC_{0-t} (ng*hr/mL)		C_{max} (ng/mL)		T_{max} (hours)		$T_{1/2}$ (hours)	
		S1	S2	S1	S2	S1	S2	S1	S2
Tramadol	Test	5340.44 ± 1360.60	6939.69 ± 2122.53	412.00 ± 69.66	542.86 ± 107.32	4.39 ± 1.29	5.20 ± 1.50	7.03 ± 1.16	6.93 ± 1.61
	Ref	5466.38 ± 1323.59	6946.24 ± 2140.58	370.76 ± 74.32	498.45 ± 96.54	4.93 ± 1.33	4.77 ± 0.90	7.17 ± 1.08	7.06 ± 1.65
M_1 metabolite	Test	1217.69 ± 364.19	1272.84 ± 376.21	72.50 ± 26.08	79.35 ± 27.97	5.74 ± 1.72	6.56 ± 1.74	7.75 ± 1.26	7.91 ± 1.56
	Ref	1248.86 ± 408.12	1281.86 ± 385.02	68.24 ± 26.70	72.60 ± 24.51	6.69 ± 1.98	7.15 ± 1.79	7.85 ± 1.02	8.04 ± 1.69

Note: Data are shown as arithmetic mean ± standard deviation for pharmacokinetic parameters.

Abbreviations: AUC_{0-t}, area under curve; C_{max}, peak concentration; T_{max}, time to peak concentration; $T_{½}$, elimination half-life; S1, single-dose fasting study; S2, single-dose fed study; test, test product; ref, reference product.

as evident from the C_{max} and AUC_{0-t} values for tramadol and its M_1 metabolite, was higher for the fed state than for the fasting state (Table 1). In summary, the pharmacokinetic data obtained in all our studies were in accordance with the published data.[1–3,8]

In the multiple-dose steady-state study, it was observed that the mean peak-trough fluctuation for tramadol was 151.75% for the test product and 133.55% for the reference product. Corresponding values for the M_1 metabolite were 104.11% and 93.18% for the test and reference products, respectively (Table 2). We observed the mean peak-trough fluctuations in plasma tramadol concentrations to be significantly higher than those reported in the literature. Grond and Sablotzki reported a fluctuation in tramadol concentrations of approximately 66% with the SR tramadol formulation at steady state.[1] Karhu and Bouchard noted this to be 56%–96%.[8] The occurrence of high mean peak-trough fluctuations in our multiple-dose study could be due to insufficient frequency of drug administration. In all the published studies, the dosing frequency was as per the labeling of the innovator product. In the multiple-dose study, twice-daily administration of the tramadol SR tablet was an ideal way to reach steady state, with less fluctuation. However, once-daily administration of tramadol probably resulted in wide fluctuation in this study.

Overall, the intrasubject variability observed for both the analytes in our studies was low. The highest variability was 13.64%, observed for the C_{minss} with tramadol in our multiple-dose study. As mentioned in the literature, wide variability in the pharmacokinetic parameters of tramadol, which could be partly due to polymorphism in cytochrome P450 isoforms, was not observed in the present studies.[1] The subjects in our studies probably did not have any genetic polymorphisms to account for marked pharmacokinetic variability. It was observed that the ratios for geometric least-square means and 90% confidence intervals were within the acceptance criteria of 80%–125% for log-transformed primary pharmacokinetic parameters for tramadol and its M_1 metabolite in all the studies (Table 3).

A significant period effect for the C_{max} of tramadol and its M_1 metabolite was observed in both the single-dose studies. However, this can be ignored because it was not coupled with any sequence effect. A significant treatment effect for C_{maxss} and C_{minss} for tramadol and C_{minss} for the M_1 metabolite was observed in the multiple-dose study. This effect might reflect the difference in the formulations, but it did not seem to have any impact on the study outcome because the confidence intervals for the log-transformed pharmacokinetic parameters

Table 2 Mean pharmacokinetic parameters for tramadol and its M_1 metabolite at steady state

Formulation	Parameter	Test product	Reference product
Tramadol	AUC_{Tau} (ng*hr/mL)	8368.63 ± 2410.40	8219.91 ± 2198.33
	C_{maxss} (ng/mL)	628.71 ± 137.52	571.96 ± 122.93
	C_{minss} (ng/mL)	122.65 ± 55.44	131.59 ± 53.25
	T_{max} (hours)	4.46 ± 1.09	4.90 ± 1.48
	C_{avg} (ng/mL)	348.69 ± 100.43	342.50 ± 91.60
	PTF (%)	151.75 ± 32.52	133.55 ± 26.64
M_1 metabolite	AUC_{Tau} (ng*hr/mL)	1518.03 ± 543.26	1528.51 ± 519.46
	C_{maxss} (ng/mL)	94.06 ± 32.40	89.70 ± 28.88
	C_{minss} (ng/mL)	29.66 ± 13.58	32.06 ± 12.73
	T_{max} (hours)	6.69 ± 1.75	9.55 ± 2.04
	C_{avg} (ng/mL)	63.25 ± 22.64	63.69 ± 21.64
	PTF (%)	104.11 ± 22.95	93.18 ± 19.89

Note: Data are shown as least square mean ± standard deviation for pharmacokinetic parameters.
Abbreviations: AUC_{Tau}, area under curve at steady state; C_{maxss}, peak concentration at steady state; C_{minss}, minimum concentration at steady state; T_{max}, time to peak concentration; C_{avg}, average concentration computed as $AUC_{Tau}/24$; PTF, peak trough fluctuation computed as $(C_{maxss} - C_{minss})/C_{avg}$.

fell within the acceptance range. Thus, the treatment effect can be ignored.

Safety evaluation

In total, 48, 60, and 54 subjects were exposed to either of the treatments in period 1 of the single-dose fasting, single-dose fed, and multiple-dose fasting studies, respectively, while the corresponding numbers were 48, 46, and 37 in period 2. Successful completion of the clinical phase was done by 40, 44, and 35 subjects in the single-dose fasting, single-dose fed, and multiple-dose fasting studies, respectively. The highest occurrence of adverse events was observed in the multiple-dose fasting study. In this study, a total of 187 adverse events were reported, of which 103 events were observed in subjects given the test product and 84 events were observed in those given the reference product (Table 4). Occurrence of an adverse event was the underlying cause for withdrawal of 8, 14, and 16 subjects in the single-dose fasting, single-dose fed, and multiple-dose fasting studies, respectively. The poststudy laboratory evaluation did not reveal any clinically significant observations requiring further intervention in all the studies.

The majority of the adverse events were expected and related to the study drugs. Dizziness, pruritus, headache, and vomiting were the most common adverse events for both the study treatments, as reported by other investigators.[1,9] Our results are consistent with the published data. The greater occurrence of adverse events in the multiple-dose fasting study could be due to the higher number of exposures of the subjects to the study drugs, with a relatively high dose of tramadol. However, we did not observe any correlation between the occurrence of adverse events and peaking of

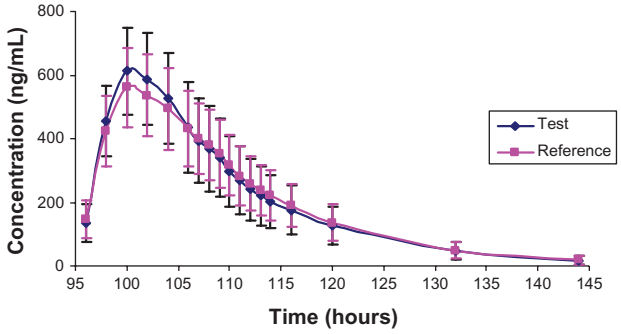

Figure 2 Mean plasma concentration-time profile for tramadol at steady state in multiple-dose fasting study.
Notes: Error bars indicate standard deviations. Plasma samples obtained after tramadol dosing at 96th hour (day 5) are considered for a steady-state profiling.
Abbreviations: Test, tramadol 200 mg sustained-release tablet; Reference, Zydol® (tramadol) sustained release 200 mg sustained-release tablet.

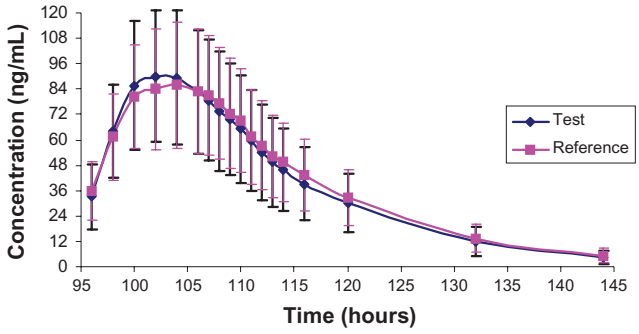

Figure 3 Mean plasma concentration-time profile for M_1 metabolite at steady state in multiple-dose fasting study.
Notes: Error bars indicate standard deviations. Plasma samples obtained after tramadol dosing at 96th hour (day 5) are considered for a steady-state profiling.
Abbreviations: Test, tramadol 200 mg sustained-release tablet; Reference, Zydol® (tramadol) sustained-release 200 mg tablets.

Table 3 Geometric mean ratio, intrasubject variability, and 90% confidence intervals for tramadol and its M_1 metabolite in all studies

Analyte	Study	Parameters	Percent ratio T/R	Percent intra-CV	90% CI for log-transformed data	
					Lower limit	Upper limit
Tramadol	S1	AUC_0 (ng*hr/mL)	97.76	9.22	94.41	101.23
		C_{max} (ng/mL)	111.58	11.30	106.92	116.45
	S2	AUC_{0-t} (ng*hr/mL)	100.08	6.53	97.77	102.45
		C_{max} (ng/mL)	108.73	10.62	104.68	112.95
	S3	AUC_{Tau} (ng*hr/mL)	101.28	7.43	98.28	104.37
		C_{maxss} (ng/mL)	109.88	10.14	105.48	114.47
		C_{minss} (ng/mL)	90.62	13.64	85.78	95.74
M_1 metabolite	S1	AUC_{0-t} (ng*hr/mL)	98.37	7.86	95.49	101.34
		C_{max} (ng/mL)	106.66	10.71	102.43	111.06
	S2	AUC_{0-t} (ng*hr/mL)	99.63	6.96	97.18	102.15
		C_{max} (ng/mL)	108.29	10.11	104.44	112.28
	S3	AUC_{Tau} (ng*hr/mL)	99.23	7.75	96.17	102.39
		C_{maxss} (ng/mL)	104.42	10.12	100.23	108.77
		C_{minss} (ng/mL)	91.29	11.82	87.04	95.75

Abbreviations: AUC_{0-t}, area under curve; AUC_{Tau}, area under curve at steady state; C_{max}, peak concentration; C_{maxss}, peak concentration at steady state; C_{minss}, minimum concentration at steady state; CV, coefficient of variation; T/R, test product/reference product; S1, single-dose fasting study; S2, single-dose fed study; S3, multiple-dose fasting study; CI, confidence interval.

Table 4 Occurrence of adverse events in all the studies

Adverse event	Reported (n)					
	Test product			Reference product		
	S1	S2	S3	S1	S2	S3
Lightheadedness	00	00	01	00	00	00
Giddiness	17	13	28	09	14	27
Drowsiness	00	00	01	00	00	01
Headache	10	07	12	05	07	09
Cold	00	01	01	02	01	00
Bradycardia	01	03	00	00	05	01
Hypotension	00	02	00	00	00	02
High blood pressure	00	00	01	00	00	01
Vomiting	05	09	07	04	08	10
Nausea	04	10	9	02	03	03
General abdominal pain	00	00	03	00	00	05
Burning epigastric pain	00	01	03	00	01	00
Constipation	00	00	01	00	00	03
Itching	03	03	19	01	00	19
Body ache	02	01	01	01	01	01
Dry skin (both feet)	00	00	01	00	00	00
Fever	01	00	04	00	02	00
Shivering	00	00	01	00	00	00
Burning micturition	00	00	02	0	00	00
Difficulty in micturition	00	00	03	00	00	01
Retention of urine	00	00	01	00	00	00
Bilateral shoulder pain	00	00	00	00	00	01
Bilateral knee joint pain	00	00	01	00	00	00
Pain in arm	01	00	01	00	00	00
Burning sensation in back	00	00	01	00	00	00
Backache	00	01	01	00	00	00
Total	**44**	**51**	**103**	**24**	**42**	**84**

Note: Adverse events either spontaneously reported by the subject or observed by the medical personnel.

Abbreviations: S1, single-dose fasting study; S2, single-dose fed study; S3, multiple-dose fasting study.

plasma tramadol concentrations in either of the studies. All the adverse events were mild to moderate in severity, and resolved during the clinical phase. No serious adverse event was observed in either of the studies.

Conclusion

The in vitro dissolution study indicated suitability of the test product for use in the in vivo bioequivalence studies. All of the in vivo studies in healthy human subjects demonstrated that the generic test tablet, tramadol hydrochloride SR 200 mg, is bioequivalent to the reference product, Zydol SR 200 mg, in terms of rate and extent of absorption. The highest number of adverse events and dropouts/withdrawals was observed in the multiple-dose fasting study. The longer study duration, multiple drug administration, and relatively high total dose of tramadol probably contributed to the findings of this study. Overall, both the study treatments were well tolerated.

Disclosure

This study was conducted by Accutest Research Laboratories Limited, Navi Mumbai, India, and was sponsored by Ipca Laboratories Limited, Mumbai, India. The authors report no conflicts of interest in this work.

References

1. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet*. 2004;43(13):879–923.
2. Zydol® SR [Prescribing information]. Wycombe, Buckinghamshire: Grunenthal Ltd; 2010.

3. Ultram® ER [Prescribing information]. Steinbach, Manitoba: Biovail Corporation; 2010.
4. Prior A, Frutos P, Correa CP. Comparison of dissolution profiles: Current guidelines. Docencia 507. Available at: http://www.sefig.com/doc/Congreso%20Granada/013_DOC.pdf. Accessed Nov 1 2010.
5. World Medical Association. Declaration of Helsinki; Ethical Principles for Medical Research Involving Human Subjects. Seoul: 59th World Medical Association General Assembly; 2008. Available at: http://www.wma.net/en/30publications/10policies/b3/17c.pdf. Accessed Nov 1 2010.
6. ICH Harmonized Tripartite Guideline for GCP, 1996. Available at: http://www.ich.org/cache/compo/475-272-1.html. Accessed Nov 1 2010.
7. The European Agency for the Evaluation of Medicinal Products, Evaluation of Medicines for Human Use. Note for guidance on the investigation of bioavailability and bioequivalence, 2001. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003519.pdf. Accessed Nov 1 2010.
8. Karhu D, Bouchard S. Comparative bioavailability of tramadol Contramid® once-a-day and tramadol immediate-release tablets. Abstract presented at the 23rd Annual Meeting of the American Academy of Pain Medicine, 2007 February 7–10, New Orleans, LA.
9. Ryzolt® [Prescribing information]. Stamford, CT: Purdue Pharma Ltd; 2010.