Cariprazine Orodispersible Tablet: A New Formulation for Cariprazine

Authors
Viktória Meszár, Gabriella Magyar, Gabriella Mészárosné Pásztor, Balázs Szatmári, Krisztina Péter, Lívia Marton, Zsófia B. Dombi, Ágota Barabássy

Affiliations
Research Directorate, Gedeon Richter Plc, Budapest, Hungary

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Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Zsófia Borbála Dombi
Gyömrői street 19-21
1103 Budapest
Hungary
dombizsb@richter.hu

ABSTRACT

Introduction Cariprazine is an atypical dopamine receptor partial agonist antipsychotic available in the form of capsules. Although capsules are one of the most desirable routes of administration, there are certain situations (e. g., in an acute psychiatric setting, or when swallowing difficulties, or liquid shortages are present) when they cannot be administered. Therefore, alternative solutions like orodispersible tablets are needed. This study aimed to investigate the bioequivalence of a newly developed orodispersible tablet to the commercially available hard gelatine capsule of cariprazine 1.5 mg.

Methods This was a phase I, open-label, randomized, single-dose bioequivalence study. It had a 2-period, 2-sequence, cross-over design, where each subject received one test and one reference product in a randomized sequence, separated by a wash-out period of 55 days. Blood sampling was performed over 72 h after dosing. Cariprazine concentrations were analyzed by a validated HPLC-MS/MS method. Standard bioequivalence statistics was applied to PK parameters calculated by non-compartmental analysis. Safety measures were analyzed descriptively.

Result Pharmacokinetic data of 43 healthy volunteers and safety data of 54 subjects was analyzed. Cariprazine AUC_{0-72h} and C_{max} geometric mean ratios were 117.76 % and 100.88 %, respectively. The 90 % confidence intervals were within the predefined bioequivalence acceptance limits of 80.00 % – 125.00 %. Safety data was in line with the Summary of Product Characteristics of Cariprazine.

Discussion The result of this clinical trial proved the bioequivalence of the new orodispersible tablet formulation when compared to hard gelatine capsules, enabling an alternative option for treatment of those suffering from schizophrenia.

Introduction

Cariprazine is an efficacious and well-tolerated third-generation, partial agonist antipsychotic indicated for the treatment of schizophrenia (EU, US) [1], acute manic or mixed episodes, bipolar I depression and major depression add-on (US) [2]. Consistent with the findings from large comparative clinical trials and observational studies in schizophrenia, cariprazine has been found to be a valuable treatment option, especially in treating negative symptoms of schizophrenia [3–5] and dual schizophrenia (co-occurrence of schizophrenia and substance abuse). In meta-analyses, it showed to have comparable efficacy to other atypical antipsychotics concerning positive symptoms and overall efficacy in schizophrenia [6]. Moreover, cariprazine has a favorable risk/benefit profile [7], which has led to its extensive utilization worldwide. Cariprazine is available in an oral capsule formulation, covering the dose range of 1.5, 3, 4.5, and 6 mg, to be taken once daily with or without food at any time during the day [1]. An orodispersible tablet formulation has

been developed to optimize the utility of cariprazine in patient groups with different needs and preferences.

Orodispersible tablets are solid dosage forms that quickly dissolve or disintegrate in the mouth without requiring water or chewing [8]. Compared to conventional tablets/capsules, orodispersible tablets have several benefits, such as easier administration and better patient adherence [8]. Orodispersible tablets are particularly suitable for pediatric, geriatric, and dysphagic patients who have trouble swallowing conventional solid dosage forms [8]. Although liquid and injectable antipsychotics are alternatives to standard tablets/capsules, in some clinical situations, they have limitations, as patients may spit out the liquid or find injectable medication unacceptable [8]. Orodispersible tablet formulations may have an advantage in patients who are very agitated or have medical conditions that make swallowing difficult, or when there is a need for fluids to take the tablet/capsule, which may not be available and may draw unwanted attention to the condition of the patients [8].

One of the main challenges in treating patients with mental illnesses such as schizophrenia is treatment non-adherence. Here, the average for poor adherence to antipsychotic medication is around 50 % but ranges between 20 % and 90 % [9–11]. Non-adherence is more common when patients disagree with treatment, medication regimens are difficult, and when side effects are unacceptable [11–14]. Up to 80 % of patients with schizophrenia are at least partially nonadherent to antipsychotic treatment at some point during their illness, which, in turn, can lead to treatment failure, relapse, and hospitalization [8]. Furthermore, since many patients have poor insight into their illness, any measures that can improve the acceptance of the medication can help them stick to their treatment and improve their long-term outcomes [8]. As oral treatments are less invasive than injections, using oral formulations can help build a good initial therapeutic relationship that predicts a positive attitude towards medication, which in turn predicts adherence [8].

A recent study on patient's acceptance of medication formulations for acute agitation found that there was a clear preference for oral formulations over intramuscular or inhaled formulations [15]. This finding is particularly important, as treatment guidelines now recommend that patient preferences are considered in treatment choices (shared decision-making or informed choice) [15]. A survey of hospitalized patients with schizophrenia in 2010 showed that 42 % wanted to be involved in treatment decisions [15]. Patients involved in their treatment decisions had a better therapeutic relationship, more positive attitudes towards their medication, and better insight than patients who were not involved [15]. So, although some doctors may prefer injectable formulations for adherence, patients still prefer oral formulations. Hence, having various oral formulations (e. g., tablet, capsule, orodispersible tablet, liquid) to treat mental disorders still has value in psychiatric treatment.

The purpose of this article is to present the outcome of a bioequivalence study comparing a newly developed cariprazine orodispersible tablet formulation (1.5 mg) to the standard cariprazine capsule 1.5 mg. The primary objective was the assessment of bioequivalence between these two formulations in healthy adult volunteers after a single dose administration under fasting conditions in a cross-over design.

Methods

Study design and participants

This was a phase I open-label, randomized, single-dose bioequivalence study. It was conducted at one clinical study center in Germany. Only healthy Caucasian males and females of non-childbearing potential (permanently sterile or postmenopausal) aged 18 to 55 years (inclusive) were enrolled in the clinical trial. Participants had to be healthy non-smokers with a body mass index (BMI) between 18.5 and 30 kg/m^2 (inclusive). Regular treatment with any systemically available medication and intake of strong or moderate CYP3A4 inhibitors or inducers, or strong or moderate CYP2D6 inhibitors within 30 days prior to treatment administration was excluded.

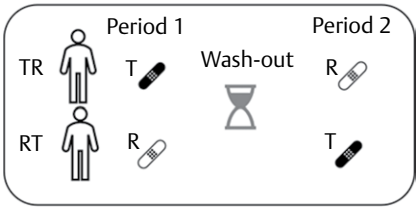
A schematic diagram of the trial is presented in ▶ **Fig. 1**. This trial was performed in a 2-period, 2-sequence, cross-over design, where each subject was planned to receive one test and one reference product in a randomized sequence, separated by a wash-out period of 55 days to avoid any carry-over effects. This type of design makes it possible to have an intra-individual comparison between treatments and is the standard design for bioequivalence studies [16].

The study consisted of a 3-week screening period, during which the volunteers were assessed if they fulfilled all inclusion criteria and none of the exclusion criteria. Eligible subjects were then hospitalized from 24 h before study drug administration (Day 1 and Day 56) until 72 h post dose (last PK sampling). An end-of-study examination was performed within 14 to 21 days after the last administration of treatment, followed by a follow-up call at 6 weeks post-dose.

Blood sampling was performed over 72 h post-dose to characterize pharmacokinetic parameters. A truncated approach was considered adequate in accordance with the Guideline on the Investigation of Bioequivalence [16] for substances with a long half-life and administered as immediate release formulations [16]. Blood samples were withdrawn at the following time points: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48, 60, 72 h post-dose (23 samples per subject and period).

Treatments

This trial was performed with the lowest dose strength of cariprazine (1.5 mg). The EMEA BE guideline [16] allows for the selection of lower strengths if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. As shown previously, healthy volunteers do not tolerate cariprazine doses high-



▶ **Fig. 1** Schematic presentation of the trial.

er than 1.5 mg [1]. Moreover, cariprazine has linear pharmacokinetics in the dose-range of 1.5–6 mg, so what is seen for 1.5 mg is also valid for higher doses.

The subjects were randomly assigned to one of the two possible sequences, TR or RT, where the test compound (T) was the cariprazine 1.5 mg orodispersible tablet, and the reference compound (R) was cariprazine 1.5 mg hard capsule, both developed and manufactured by Gedeon Richter Plc.

The investigational products were administered at the trial site under the supervision of the study team. Both treatments were followed by an inspection of the oral cavity and of the hands. In case of T, subjects wetted their mouth by swallowing 20 mL of water (room temperature) prior to administration. Afterwards, one orodispersible tablet was taken orally without further fluid intake in an upright position by placing it on the tongue, where it disintegrated. The orodispersible tablet was not chewed or swallowed whole. Subjects were instructed to let the orodispersible tablet disintegrate in their mouth. Once the tablet was dispersed or the latest up to 90 s after being placed on the tongue, in case some residues were not dispersed completely, the subjects swallowed the saliva. In the case of R, one hard capsule was taken orally with 240 mL water (room temperature) in an upright position.

Analytical methods

Cariprazine concentrations in plasma samples were analyzed using a validated HPLC-MS/MS method developed by Gedeon Richter Plc. (LLOQ for cariprazine was 10 pg/mL). Metabolite concentrations of desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR) in plasma samples were analyzed by the same validated HPLC-MS/MS method (LLOQ for DCAR and DDCAR was 20 pg/mL) and were presented in the bioanalytical report as supportive data only. No PK parameters were calculated for the metabolites as the chosen study design does not allow accurate determination of metabolite PK parameters.

Pharmacokinetic and statistical analysis

Pharmacokinetic parameters for cariprazine were derived by noncompartmental analysis. In accordance with the requirements of the EMEA BE Guideline [16], AUC_{0-72h} and C_{max} of cariprazine were considered as primary variables and decision criteria for bioequivalence assessment. Analysis of variance (ANOVA) was performed on ln-transformed AUC_{0-72h} and C_{max} at the alpha level of 0.05. Fixed factors incorporated in the model included Sequence, Subject (Sequence), Period, and Formulation. The ratio of means (T/R) and 90 % confidence interval for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, were calculated. Acceptance limits of 80.00 % – 125.00 % were applied for AUC_{0-72h} and C_{max} 90 % confidence intervals. T_{max} of cariprazine was a secondary variable evaluated descriptively.

Analysis populations

For the current clinical trial, two populations were analyzed: full analysis set (FAS) and per-protocol set (PPS). The per-protocol set, defined as all randomized subjects who finished the clinical trial without any major protocol deviations, was used to assess cariprazine pharmacokinetics. Descriptive statistics were used for the plasma concentrations and pharmacokinetic parameters of cariprazine. The full analysis set comprised all subjects randomized. The incidence of adverse events (AEs), adverse drug reactions (ADRs), and serious adverse events (SAEs) were calculated for each treatment group. All safety measures were analyzed using descriptive statistics.

Monitoring and ethics

Monitoring in the clinical trial was performed in accordance with the requirements of the GCP guideline [17] and based on the monitoring plan. Source data verification was performed for 100 % of data obtained during the clinical trial on-site. This study was performed in compliance with European Union Directive 2001/20/EC, applicable national statutory requirements, the Declaration of Helsinki, and ICH Good Clinical Practice (GCP), including the archiving of essential documents and the requirements of the German Medicinal Product Act (Arzneimittelgesetz, AMG). The clinical trial was only initiated after receiving positive opinion from the Independent Ethics Committee and approval from the national health authority (BfArM) was received for clinical trial protocol, subject information, including the ICF, as well as any subsequent amendments.

Informed consent was obtained from all subjects involved in the study, prior to the first measures and activities. Every subject had the right to refuse further participation in the clinical trial at any time and without giving reasons. Subjects were informed in the ICF that they would not receive any medical benefit from their participation since they were healthy and did not need treatment with this medical substance.

Results

Subject disposition and demographic characteristics

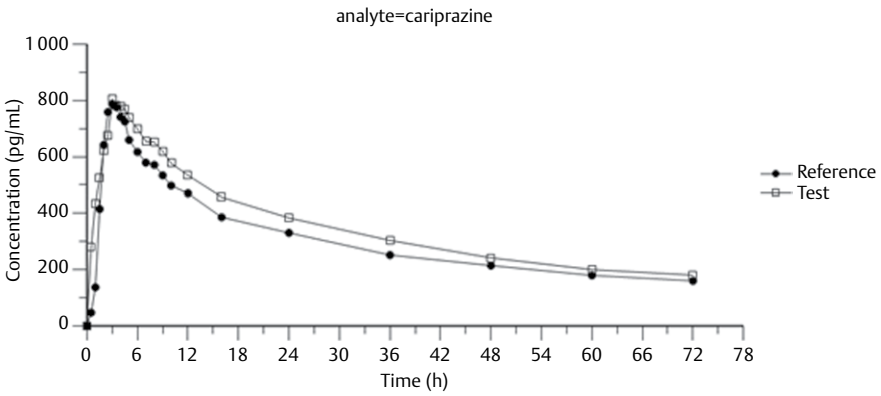
Fifty-four healthy male and female subjects of non-childbearing potential were randomized and included in the FAS, while 53 subjects received the investigational compound at least once. One subject who was randomized but did not receive the investigational compound was still included in the FAS following the protocol.

Ten subjects dropped out before completion of PK blood sampling: two subjects withdrew their consents, five subjects were withdrawn due to vomiting, and three subjects were withdrawn due to other AEs (see ▶ **Table 3**). In addition, one subject was excluded from PPS due to minimal exposure under the reference product (AUC < 5 % mean AUC_R); thus, the PPS consisted of 43 subjects.

Out of the 43 subjects included in the PPS 1 was female and 42 were male. Subjects were aged 20 to 55 years with a BMI between 18.7 and 29.9 kg/m². All subjects were Caucasian as given in the inclusion criteria of the trial.

Pharmacokinetic analyses

▶ **Fig. 2** presents the mean plasma concentration vs. time profiles of cariprazine after single oral administration of cariprazine 1.5 mg orodispersible tablet (T) and cariprazine 1.5 mg capsules, hard (R) under fasting conditions to subjects of the PPS.



▶ **Fig. 2** Mean plasma concentration vs. time profiles of cariprazine after single oral administration of Cariprazine 1.5 mg orodispersible tablets (T) and Cariprazine 1.5 mg capsules, hard (R) under fasting conditions.

The mean curves of cariprazine obtained after a single oral administration of cariprazine 1.5 mg orodispersible tablets (T) and cariprazine 1.5 mg capsules, hard (R) increased without any lag-time, reaching their comparable maximum values of about 800 pg/mL at 3 h post-dose.

In the present clinical trial, pre-dose values in period II were observed in 9 cases in a range of 11.1 to 15.9 pg/mL (LLOQ: 10 pg/mL) despite the already long wash-out phase of 55 days, with 6 cases prior to administration of T and 3 cases prior to the administration of R. Overall, these values were below 5 % of the respective C_{max} value in all cases, so subject's data were included in pharmacokinetic measurements and calculations without any adjustments.

Pharmacokinetic parameters obtained after administration of the two formulations are summarized in ▶ **Table 1**. Parametric point estimates and 90 % confidence intervals determined for the primary pharmacokinetic parameters of cariprazine; comparison of Test vs. Reference (T/R) are shown in ▶ **Table 2**.

For the primary pharmacokinetic parameter AUC_{0-72h} of cariprazine, a point estimate of 117.76 % with an affiliated 90 % confidence interval of 111.86 % – 123.96 % was calculated, representing a result within the pre-defined acceptance limits for demonstration of bioequivalence of the Test and Reference product [16]. For the primary pharmacokinetic parameter C_{max} of cariprazine, a point estimate of 100.88 % with an affiliated 90 % confidence interval of 93.33 % – 109.04 % was calculated. The confidence interval was completely within the pre-defined acceptance limits of 80.00 % – 125.00 %. Thus, the bioequivalence of Test and Reference products was clearly demonstrated for both PK parameters of cariprazine.

Safety and tolerability outcomes

Safety data is summarized in ▶ **Table 3**. Fifty-three subjects received the investigational products at least once. In total, 98 treatment-emergent adverse events (TEAEs) were reported by 41 subjects. Fifty-four TEAEs in 29 subjects occurred after Test treatment and 44 TEAEs in 26 subjects after Reference treatment. Therefore, the number of subjects who experienced TEAEs after Test treatment was nearly similar to the number of subjects who experienced TEAEs after Reference treatment.

▶ **Table 1** Geometric mean (GeoCV %) pharmacokinetic parameters of cariprazine after single oral administration of (T) and (R) under fasting conditions, n = 43.

PK parameter	ODT (test)	Capsule (reference)
AUC_{0-72h} (h · pg/mL)	23800 (33.22)	20200 (43.44)
C_{max} (pg/mL)	890 (38.23)	882 (49.93)
t_{max} * (h)	3.50 (1.00–6.00)	3.50 (1.52–8.02)

*For t_{max} median (min-max) is presented, ODT = orodispersible tablet.

▶ **Table 2** Point estimates and 90 % confidence intervals of pharmacokinetic parameters of cariprazine: comparison of Test vs. Reference (T/R).

Parameter	Point Estimate [%]	Lower Limit CI [%]	Upper Limit CI [%]	CV_{intra} [%]
AUC_{0-72h}	117.76	111.86	123.96	14.22
C_{max}	100.88	93.33	109.04	21.67

CI = confidence interval.

The most frequently reported TEAEs were: fatigue (n = 18), nausea (n = 13) and headache (n = 12). In total, 83 TEAEs were classified as study drug-related (Test: 45, Reference: 38) and 15 TEAEs were classified as not related to the drug (Test: 9, Reference: 6).

Discussion

The primary objective of this study was to evaluate the bioequivalence of a newly developed orodispersible tablet containing 1.5 mg cariprazine in comparison to cariprazine 1.5 mg hard capsules and to show that the new formulation is just as safe and tolerable as the original hard capsule formulation. Both trial objectives were met: bioequivalence of the Test and the Reference product was demonstrated based on AUC_{0-72h} and C_{max} values of cariprazine. Data on safety and tolerability showed a comparable risk profile for both formulations and a tolerability in line with the SmPC of cariprazine as well as the substance class of atypical antipsychotics.

▶ **Table 3** Treatment-Emergent Adverse Events with at least 5 % occurrence.

	Period 1		Period 2	
	Test	**Reference**	**Test**	**Reference**
Death	0	0	0	0
SAE	0	0	0	0
ADO	4 (+ 1 PTAE)	1	1	1
TEAE	32	20	22	24
from this:				
Fatigue	6	3	2	7
Nausea	5	3	3	2
Headache	3	3	3	3
Abdominal discomfort	1	0	0	2
Blood pressure increased	4	1	2	2
Nasopharyngitis	0	2	1	0
Dizziness	3	1	2	0
Myalgia	1	1	1	0
Presyncope	0	2	1	0

ADO = Adverse Events Leading to Drop-Out, SAE = Serious Adverse Events, PTAE = Pre-Treatment Adverse Events, TEAE = Treatment-Emergent Adverse Events.

With this positive clinical trial, another opportunity opens up for dosing of patients treated with cariprazine: dosing with the new cariprazine formulation, the cariprazine orodispersible tablet. It disperses quickly in the mouth, has a pleasant taste, and can be used without any liquid. With its advantages, the cariprazine orodispersible tablet is an awaited treatment formulation.

Disclosure

Author Contributions

All authors participated in the writing, editing, and critical revision of intellectual content, and approved the final version of this manuscript. Specific roles: Viktória Meszár (Clinical Project Manager and manuscript first draft), Gabriella Magyar (Pharmacokineticist), Gabriella Pásztor Mészáros (Principal Analyst), Krisztina Péter (study design), Balázs Szatmári (data interpretation), Lívia Marton (Clinical Project Manager), Zsófia Dombi (writing assistance), Ágota Barabássy (data interpretation and writing assistance).

Data Availability Statement

The study data is owned by Gedeon Richter Plc (Budapest, Hungary). Parts of data can be made available upon request.

Previous communication

Data of this study was not published previously.

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Conflict of Interest

Authors are employed by the company Gedeon Richter Plc. The authors declare that study received funding from Gedeon Richter Plc.

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