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Cardiac safety with cariprazine treatment

Á. Barabassy[1], B. Sebe[1], I. Laszlovszky[1], B. Szatmári[1], K. Acsai[1] , J. Harsányi[1], M. Patel[2], W. Earley[3], G. Németh[1].

[1]Gedeon Richter Plc., Medical Division, Budapest, Hungary [2]Allergan Plc., Global Medical Affairs, Madison- NJ, USA [3]Allergan Plc., Clinical Development, Madison- NJ, USA.

INTRODUCTION

Long-term treatment with antipsychotic agents are indicated for all patients with schizophrenia. Antipsychotic drugs can be of great benefit for a range of symptoms, but treatment might be associated with unpleasant side effects like cardiac complications.[1] Cardiac arrhythmias, arrest, tachycardia, and prolongation of the QT interval have reported with antipsychotics. The occurrence of cardiovascular side effects complicates the management of mental illness and may contribute to serious, even fatal consequences such as Torsades de Pointes and Sudden Cardiac Death.[2]

STUDY OBJECTIVE

The objective of this analysis is to evaluate the effects of cariprazine on cardiac safety parameters.

METHODS

Data from eight schizophrenia studies - 4 short-term 6-week (Study 1-4),[3–6] 1 long-term 26-week (Study 5),[7] 2 long-term 48-week (Study 6-7)[8,9] and 1 long-term up to 92-week (Study 8)[10] - were analyzed. Pulse rate, QT interval changes, treatment-emergent adverse events (TEAE) and cardiac adverse events associated with drop out (ADO) were examined for placebo (PBO) and cariprazine (CAR) groups. Only patients with baseline and at least one post-baseline measurement were included in the calculations. CAR data is shown in two dose ranges (1.5-3 mg/day and 4.5-6 mg/day). Safety parameters were summarized using descriptive statistics.

RESULTS

Heart rate: A slight increase from baseline in ventricular heart rate (2 bpm) was observed with CAR treatment, which was comparable to PBO treatment (0.7 bpm).

Table 1. Change From Baseline to Endpoint in ventricular heart rate

Mean ventricular heart rate, bpm ± SD			
Study 1-4			
	CAR 1.5-3 mg/day N = 539	CAR 4.5-6 mg/day N = 575	PBO N = 584
Baseline	76.3 ± 14.3	75.7 ± 13.5	75.5 ± 13.2
Cfbl	1.5 ± 15.1	4.5 ± 15.7	0.5 ± 15.2
Study 5			
	-	CAR 4.5 mg/day N = 230	-
Baseline	-	73.8 ± 12.4	-
Cfbl	-	-0.8 ± 13.2	-
Study 6,7			
	CAR 1.5-3.0 mg/day N = 170	CAR 4.5-6.0 mg/day N = 361	-
Baseline	76.2 ± 13.0	–2.0 ± 14.3	-
Cfbl	–2.0 ± 14.3	–0.0 ± 14.7	-
Study 8			
	CAR 3-6 mg/day N = 361		PBO N = 99
Baseline	73.3 ± 12.9		71.1 ± 12.0
Cfbl	2.8 ± 14.6		2.4 / 14.4
Pooled data			
	CAR 1.5-6 mg/day N = 2236		PBO N = 683
Cfbl	2.0 ± 15.0		0.7 ± 15.1

Bpm = beats per minute, SD = standard deviation, Cfbl= change from baseline

QT prolongation

In most of the studies CAR treatment was not associated with QT prolongation. In fact, it led to a shorter QT interval. Incidence of potentially clinically significant (PCS) QT prolongation (QTcF > 500 msec or QTcF increase > 60 msec) was low in both groups (CAR = 0.2%) and (PBO = 0.3%) as measured by the QT interval corrected for heart rate using the Fridericia formula (QTcF), as a significantly better predictor of severe cardiac consequences than the Bazett formula (QTcB)[11]

Taking a conservative approach and looking both at the QTcF and QTcB, QT prolongation was observed in 0.9% of CAR patients vs 1.2% of PBO patients.

CONCLUSIONS

- **Concerning cardiac parameters, cariprazine was generally comparable to placebo.**
- **Changes in heart rate and QT interval were minimal and incidence of cardiac adverse events and discontinuation rates were fairly low.**

Table 2. Changes in QTcF

	CAR 1.5-3 mg/day	CAR 4.5-6 mg/day	PBO
Study 1-4			
	N = 539	N = 575	N = 584
Baseline, msec ± SD	399.6 ± 19.8	399.9 ± 20.8	400.4 ± 21.1
Cfbl, msec ± SD	–1.9 ± 17.8	–2.6 ± 17.2	–3.0 ± 17.9
PCS QtcF, %	0	2 (0.4)	1 (0.2)
Study 5			
	-	N = 230	-
Baseline, msec ± SD	-	407.5 ± 17.6	-
Cfbl, msec ± SD	-	-2.9 ± 14.9	-
PCS Qt prolongation, %	-	0	-
Study 6-7			
	N = 170	N = 361	-
Baseline, msec ± SD	400.2 ± 20.2	402.0 ± 20.5	-
Cfbl, msec ± SD	0.7 ± 16.2	-1.5 ± 18.0	-
PCS QT prolongation, %	2 (1.2)	0	
Study 8			
	N = 361		N = 97
Baseline, msec ± SD	402.3 ± 20.8		403.2 / 23.0
Cfbl, msec ± SD	-1.2 ± 17.7		0.8 ± 19.7
PCS QT prolongation, %	1 (0.3)		0
Pooled data			
	CAR 1.5-6 mg/day N = 2236		PBO N = 683
Cfbl	-2.1 ± 17.0		-1.4 ± 17.8
PCS QT prolongation, %	5 (0.2)		2 (0.3)

Treatment-emergent adverse events and discontinuation rate

The percentage of patients with ECG related TEAEs was similar, 3.9% in the CAR and 3.1% in the PBO group. Discontinuation due to cardiac TEAEs was low in both groups: 0.3% with CAR vs. 0.1% with PBO.

Table 3. Number (%) of Patients With TEAEs and of ADO

Pooled data		
	CAR 1.5-6 mg/day N = 2236	PBO N = 683
TEAE	60 (2.7)	21 (3.1)
ADO	6 (0.3)	1 (0.1)

Occurring TEAEs: Atrial fibrillation, Atrioventricular block first degree, Atrioventricular block second degree, Bundle branch block left, Bundle branch block right, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Electrocardiogram ST-segment depression, Electrocardiogram ST-segment depression, Electrocardiogram T wave abnormal, Electrocardiogram T wave amplitude decreased, Electrocardiogram T wave inversion, Sick sinus syndrome, Sinus arrhythmia, Sinus bradycardia, Supraventricular extrasystoles, Ventricular extrasystoles.

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