بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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MONA MAGHRABY

Therapeutic Equivalence of Generic Product Versus Reference Product of Ivabradine in patients with Chronic Heart Failure: A Comparative Study

A thesis Submitted for the partial fulfillment of the Master's Degree in Pharmaceutical Sciences (Clinical Pharmacy)

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2019

Acknowledgements

I am deeply thankful to "Allah" by the grace of whom, this work was possible. I would like to express my deep appreciation to ***Prof. Dr. Nagwa Ali Sabri,*** *Prof and Head of Clinical Pharmacy Department – Faculty of Pharmacy - Ain Shams University, for her sincere help, valuable guidance and continuous support in completing this work. I am very grateful to* ***Prof. Dr. Ebtissam Abdel Ghaffar Metwally Darwesh,*** *Prof. of Pharmacology and Head of Pharmacy Practice and Clinical Pharmacy Department -Faculty of Pharmaceutical sciences and Pharmaceutical Industries-Future University in Egypt, for her great assistance, precious advice and valuable guidance in completing this work. I am greatly thankful to* ***Dr. Naglaa Samir Bazan,*** *Fellow and Head of Clinical Pharmacy-Critical Care Medicine Department-Cairo University Hospitals, for her close supervision, valuable efforts and continuous encouragement during the progress of this work.*

I am greatly indebted to ***Prof. Dr. Ahmed Alsherif,*** *professor of Critical Care Medicicine-Faculty of Medicine-Cairo University and* ***Dr. Hazem Khorshid****, Lecturer of Cardiology-Cardiology Department - Ain Shams University, for their great and valuable help in the clinical aspects of the study. I would like to thank all members of Clinical Pharmacy Department, Faculty of Pharmacy - Future University in Egypt, for their support. I am very grateful to* ***Future University in Egypt*** *for its great assistant and Fund my research. I dedicate my thesis to the soul of my father who always live in my heart and mind forever, to my beloved mother. And to all my family and best friends for their kind and sincere help, love and support during the progress of this work.*

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List of Abbreviations

ACC/AHA	**American College of Cardiology/American Heart Association**
ACEI	**Angiotensin Converting Enzyme Inhibitor**
AHF	**Acute Heart Failure**
ALT	**Alanine Transaminase Enzyme**
ARBs	**Angiotensin Receptor Blockers**
AST	**Aspartate Transaminase Enzyme**
AV node	**Atrioventricular Node**
BEAUTIFUL	**Morbidity-mortality evaluation of the If-inhibitors ivabradine in patients with CAD and left ventricular dysfunction**
BUN	**Blood Urea Nitrogen**
CAD	**Coronary artery disease**
cAMP	**Cyclic adenosine monophosphate**
CARVIVA	**Carvedilol, ivabradine or their combination on exercise capacity in patients with HF**
cGMP	**Cyclic guanosine monophosphate**
CHF	**Chronic Heart Failure**
CO	**Cardiac Output**
COMET	**Carvedilol or Metoprolol European Trial**
CVD	**Cardiovascular disease**
DCM	**Dilated cardiomyopathy**
DIG	**Digitalis intervention Group**
ESC	**European society of cardiology**
FDA	**Food and Drug Administration**
HCN	**Hyperpolarization activated cyclic nucleotide-gated**
HF	**Heart Failure**
HFpEF	**Heart Failure with preservative Ejection Fraction**
HFrEF	**Heart Failure with reduced Ejection Fraction**
HTN	**Hypertension**
IHF	**Ischemic heart failure**
LVEF	**Left Ventricular Ejection Fraction**

MI	**Myocardial infarction**
NIHF	**Non-ischemic heart failure**
NYHA FC	**New York Heart Association Functional Classification**
RAAS	**Renin- angiotensin -aldosterone system**
RHR	**Resting heart rate**
SAN	**Sino-atrial node**
SHIFT	**Systolic HF treatment with the If inhibitor ivabradine trial**
SNS	**Sympathetic nervous system**
Sr.cr	**Serum Creatinine**

Abstract

Background:

Generic substitution of brand ivabradine prescriptions can reduce drug expenditures and improve adherence. However, the distrust of generic medicines by practitioners and patients due to doubts regarding their quality and fear of counterfeiting compromise the acceptance of this practice.

Aim of the Work:

The current study was designed to compare the therapeutic equivalence of brand product versus generic product of ivabradine in adult patients with chronic heart failure with reduced ejection fraction (≤40%) (HFrEF).

Patients and Methods:

The study was carried out on 32 Egyptian patients with HFrEF who were randomized to one of the two groups: Group A received branded ivabradine (Procrolan ©) for 12 weeks followed by another 12 weeks of receiving generic (Bradipect ©), while Group B received the same intervention with opposite order without washout period. All patients received their guideline directed medical therapy throughout the study period. The following parameters were evaluated at the end of the 12^{th} week and 24^{th} week of either receiving branded or generic ivabradine: Primary outcomes were resting heart rate (HR), New York Heart Association NYHA FC, Quality of life (QoL) using Minnesota Living with Heart Failure (MLWHF) and EF. Secondary outcomes were number of hospitalizations for worsening HFrEF and adverse effects. Washout period was not allowed for ethical reasons.

Results:

At the 12^{th} week, the reduction in HR was comparable in the two groups (90.13±7.11 to 69±11.41 vs 96.13±17.58 to 67.31±8.68 bpm in group A and group B, respectively). Also, the increase in EF was comparable in the two groups (27.44 ±4.59 to 33.38±5.62 vs 32±5.96 to 39.31±8.95 in group A and group B, respectively). The improvement in NYHA FC was comparable in both groups (87.5% in group A vs 93.8% in group B). The mean value of the QOL improved from 31.63±15.8 to 19.6±14.7 vs 35.68±17.63 to 22.9±15.1 for the group A and group B, respectively. Similarly, at end of 24^{th} week, no significant changes were observed from data observed at 12^{th} week regarding HR, EF, QoL and NYHA FC. Only

minor side effects, mainly phosphenes, and a comparable number of hospitalizations were observed in both groups.

Conclusion:

The study revealed no statistically significant differences in the therapeutic effect and safety between generic and branded ivabradine. Study results supports the assumption that practitioners can safely switch to generic ivabradine for economic reasons.

Key words:

Heart Failure, Ivabradine, Bradipect ©, Procoralan ©, Therapeutic Equivalence, Crossover study

1. Introduction

European Society of Cardiology (ESC) defined heart failure (HF) as a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress **(Ponikowski et al., 2016).**

1.1 Types of Heart Failure

The main terminology used to describe HF is historical and is based on measurement of the left ventricular ejection fraction (LVEF). HF comprises a wide range of patients, from those with normal LVEF [typically considered as ≥50%; HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as ≤ 40%; HF with reduced EF (HFrEF)] **(Ponikowski et al., 2016).** Differentiation of patients with HF based on LVEF is important due to different underlying a etiologies, demographics, co-morbidities and response to therapies **(Butler J et al., 2012).**

1.1.1. Heart Failure with Preserved EF (HFpEF) (diastolic dysfunction)

Definition of HFpEF based on American Colleague of Cardiology/American Heart Association American Heart Association (ACC/AHA) and ESC is LVEF ≥50% (**Yancy et al., 2013; Ponikowski et al., 2016; Yancy et al., 2017)**. It has been suggested that the incidence of HFpEF is increasing and that a greater portion of patients hospitalized with HF have HFpEF **(Steinberg et al., 2012).**

HFpEF is sub classified into a) HFpEF, borderline with LVEF 41% to 49%. These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF. b) HFpEF, improved with LVEF >40%. It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF (**Yancy et al., 2013)**.