The Importance of Pharmacovigilance in Overweighing the Benefits and the Risks of Medicinal Products

(Recommendations to Improve Pharmacovigilance Procedures in Egypt)

A Thesis submitted for partial fulfillment of the Doctor of Philosophy (PhD) in Pharmaceutical Sciences (Clinical Pharmacy)

By

Yasmin Gamal Mahran

MSc. Pharm.Sci.

Global Innovation & Operations Manager

Novartis Pharma AG

Under supervision of

Dr. Osama Ahmed Badary, Ph.D.

Head of Clinical Pharmacy Department

Faculty of Pharmacy

Ain Shams University

Dr. Abdel Hamid Abdallah Elshami, Ph.D.

Professor of Pharmaceutics and Idustrial Pharmacy

Faculty of Pharmacy

Ain Shams University

Dr. Mohamed Awad Tag eldin, Ph.D.

Professor of Pneumology

Faculty of Medicine

Ain Shams University

Dr. Nagwa Ali Sabry, PhD

Professor of Clinical Pharmacy

Faculty of Pharmacy

Ain Shams University

Faculty of Pharmacy

Ain Shams University

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

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Disclaimer

- All data available in this study has been obtained with consent and is presented anonymously without any identification of patients.
- The reports presented as international reports have been obtained through public channels in which no confidential information were presented.
- Reporters reporting the information domestically have confirmed that all materials have been already reported to both marketing authorization holder and regulatory bodies for follow up and inclusion in their databases.
- The views and opinions expressed in the following thesis are those of the individual author and should not be attributed to any organization with which the author is employed or affiliated.
- The materials provided in this thesis and under appendix are the intellectual property of the individual presenter and are protected under the copyright laws of Egypt and other countries.
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Abstract

Introduction

Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines. Generally, pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbal medicine and traditional medicines with a view to identifying new information about hazards associated with medicines and preventing harm to patients.

Pharmacovigilance is particularly concerned with Adverse Drug Reactions which are officially described as: "A response to a drug which is noxious and unintended, and which occurs at doses normally used… for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function" as defined by the Council for International Organization for Medical Sciences (CIOMS).

Pharmacovigilance is gaining importance for physicians and scientists as the number of stories in the mass media of drug recalls increases. Because clinical trials involve several thousand patients at most; less common side effects and ADRs are often unknown at the time a drug enters the market. Even very severe adverse drug reactions, such as liver damage, are often undetected because study populations are small. Post marketing pharmacovigilance uses tools such as data mining and investigation of case reports to identify the relationships between drugs and adverse drug reactions.

Aim of work:

This study aimed to assess the reported adverse events for the study drugs during the review period and evaluate the benefit risk analysis in order to reach scientific recommendations for the regulatory bodies. Additionally, the study aimed to evaluate the challenges in operation Pharmacovigilance procedures in Egypt and reach recommendation to ensure proper pharmacovigilance procedures.

Subjects and Methods:

Five to ten physicians were recruited and trained on a simulated pharmacovigilance reported environment and collected adverse events for the study drugs in Egypt. Internationonally,

published reports during the review period were evaluated. The review period was determined to be from 01 June 2008-30 June 2012.

Results

Very low number of domestic reports were received in comparison to internationally received reports, however the researcher have analysed these reports and presented a proper benefit risk analysis plan which was in favor of having the drug in market and highlighted some risk in using the drug that should be communicate dto the patients before hand. Challenges faced during the collection of these reports were analysed and recommendations were presented to improve drug safety procedures in Egypt.

Recommendation & Conclusion

Recommendation to improve decision making and evaluate Egypt-specific findings in a benefit risk analysis of study drugs in the Egyptian market is provided in details in this study.

In addition, a frequency analysis of reported events in Egypt and worldwide against time of exposure, underlying disease and number of reports is provided and a detailed comparison of reported events in Egypt with those reported worldwide.

In conclusion, to improve the drug safety system and as corporate culture shifts to a greater emphasis on public health and members of a qualified workforce, the study has suggested some senior management responsibilities in the local pharmacovigilance department that would help identify serious problems with drugs. In addition, companies should be able to field well trained teams to process pharmacovigilance data from numerous data streams (e.g., pre-market data, post-marketing surveillance, safety reporting, pharmacoepidemiology data, etc.) and take appropriate action as needed. Such a team will depend on sophisticated safety signal identification and interpretation mechanisms and an effective risk communication strategy.

Key words:

Pharmacovigilance, drug safety, benefit-risk analysis, challenges, domestic adverse events, adverse drug reactions, Individual case safety reports.

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List of Abbreviations

Abbreviation	Meaning
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ANDA	Abbreviated New Drug Application
BPR	Bosentan Patient Registry
CA	Competent Authority
CIOMS	Council for International Organizations of Medical Sciences
CRO	Country Research Organization
CT	Clinical Trial
CTC	Common Toxicity Criteria
DHPC	Dear Healthcare Professional Communication
DSMB	Drug & Safety Monitoring Board
EC	Ethics Committee
EEA	European Economic Area
EEG	Electroencephalography
EMA/ EMEA	European Medicinal Agency
EPVC	Egyptian Pharmacovigilance Center
EU	European Union
EV	Eudravigilance
EVCTM	Eudravigilance Clinical Trial Module
EVPM	Eudravigilance Post-Authorization Module
FDA	Food & Drug Administration
HA	Health Authority
HCP	Health Care Professionals
HIV	Human Immuno-deficiency Virus
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IKS	Interkantonale Kontrollstelle für Heilmittel /Intercantonal Control Station for medicines
INDA	Investigational New Drug Application
Inv.	Investigator
JMO	Japanese Maintenance Organization
LD50 level	Median Lethal Dose
M&S	Marketing & Sales

MAH	Marketing Authorization Holder
MB	Management Board
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare Products Regulatory Agency
MR	Market Research
MSSO	Maintenance & Support Service Organization
NDA	New Drug Application
NHS	National Health System
NIH	National Institute of Health
Non-HCP	Non-Health Care Professionals
NORCB	National Organization for Research & Control of biologics
NSAID	Non Steroidal Anti-inflammatory drugs
PAH	Pulmonary Artery Hypertension
PASS	Post-Authorization Safety Studies
PBS	Pharmaceutical Benefits Scheme
PMS	Post Marketing Studies
PV	Pharmacovigilance
RSI	Relative Strength Index
SAE	Serious Adverse Event
SANZ	Schweizerische Arzneimittelnebenwirkungszentrale/Swiss Drug Adverse Event Monitoring Center
SAR	Serious Adverse Reaction
SME	Small & Medium Sized Enterprises
SMQ	Standard MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SR	Spontaneous Report
SUSAR	Suspected Unlisted Serious Adverse Reactions
UAE	United Arab Emirates
UK	United Kingdom
UMC	Uppsala Monitoring Center
USA	United States of America
VAERS	Vaccine Adverse Event Reporting System
WG	Working Group
WHO	World Health Organization
WHOART	World Health Organization Adverse Reaction Terminology

Introduction
&
Review of Literature

Introduction and Review of Literature

The decision to approve a new drug is based on having a satisfactory balance of benefits and risks on the basis of the information available on this drug at that time. Once a product is marketed, new information will be generated, which may have an impact on the benefit-risk profile of the product. The detailed evaluation of the new information generated through pharmacovigilance activities is important for all products to ensure their safe use. No degree of care and caution at the pre-clinical and clinical testing stages can guarantee an absolute safety when a product is marketed and prescribed in large populations with settings different from the clinical trials. Thus, a strong pharmacovigilance system is required to ensure the continuous monitoring and evaluation of the new safety data generated under the real-world conditions on the effects, side effects, contraindications, drug interactions, new indications and use in new populations of all drugs **(EMEA, 2005)**.

Pharmacovigilance

What is pharmacovigilance?

The word pharmacovigilance is derived from the Greek 'Pharmaco' (medicine) and the Latin 'Vigilantia' (vigilance, watchfulness). It is the process of monitoring, evaluating and improving the safety of medicines in use. It is carried out by pharmaceutical companies on their products and by government agencies on all medicinal products. Healthcare professionals (e.g. Doctors and Pharmacists) have a role too, in reporting suspected side effects of medicines to government agencies or pharmaceutical companies **(EMEA homepage, 2013).**

Basics and definitions

Adverse Event

Adverse Event Definition: An adverse event (AE) is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated